Integrase strand transfer inhibitor (INSTI) use and cancer incidence in a large cohort setting

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Background

- Since the introduction of highly effective antiretroviral therapy (ART), the life expectancy of people living with HIV is approaching that of the general population [1,2].
- With an aging population there has also been an increase in the burden of comorbidities, such as non-AIDS-defining cancer (NADC) [3,4].
- As ART use is lifelong, it is crucial to identify any associations between ART use and the risk of comorbidities.
- INSTIs are a relatively new drug class, and so there is limited data assessing long-term clinical outcomes associated with INSTI use, such as cancers.

Methods

- Participants from RESPOND were followed from baseline (latest of local cohort enrolment and 1 Jan 2012) until earliest of first cancer event (excluding pre cancers, relapse of a primary cancer, non-melanoma skin cancers), final follow-up, or 31 Dec 2019.
- INSTI exposure was lagged by 6 months to:
  - reduce potential confounding by indication where individuals at higher cancer risk or with symptoms indicative of cancer but no clinical diagnosis, may be preferentially prescribed INSTIs;
  - account for the fact that cancer development is a slow process, and so current cancer risk is unlikely to be attributable to recent ART-exposure.
- Generalised estimating equations with negative binomial regression was used to assess the association between cancer incidence and lagged cumulative INSTI exposure, adjusting for potential confounders (Figure 1 footnote).
- Analyses were repeated for NADCs and AIDS-defining cancers (ADCs) separately.

Table 1: Baseline characteristics

		Overall n	Overall (%)
		29340	(100)
Gender	Male	21818	(74.4)
Ethnicity	White	20419	(69.6)
	Black	2983	(10.2)
BMI (kg/m²)	<18.5	873	(3.0)
	≥25	6706	(22.9)
HIV risk group	MSM	13229	(45.1)
ART history at baseline	ART Naive	7172	(24.4)
	ART Experienced, VL<200 cps/mL	19951	(68.0)
Smoking status	Current	8196	(27.9)
	Previous	2261	(7.7)
Prior AIDS event		5785	(19.7)
Prior cancer		1742	(5.9)
Prior comorbidity		19172	(65.3)
		Median	**Interquartile Range**
Baseline date, month/year		01/12	(01/12, 02/13)
Age, years		44	(36, 51)
CD4 cell count at baseline, cells/mm³		524	(357, 715)
CD4 cell nadir, cells/mm³		241	(120, 384)
Total duration of previous ART, years		7.7	(3.0-13.9)

Abbreviations: BMI-body mass index; MSM-men who have sex with men; ART-antiretroviral; VL-viral load. Comorbidities include hypertension, diabetes, non-AIDS defining cancer, end-stage liver and renal disease, cardiovascular disease, chronic kidney disease, and dyslipidemia. Percentage of unknown variable: Ethnicity 15.9, body mass index 35.6, HIV risk 4.1, smoking status 36.4, prior AIDS 5.4, prior cancer 2.1, prior comorbidity 25.7

Table 2: Association between INSTI exposure and NADCs and ADCs

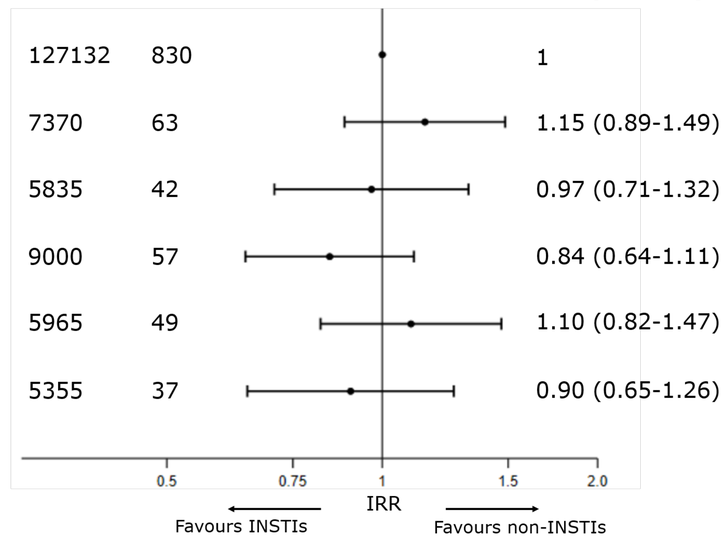
INSTI exposure, months	All NADCs N events (PYFU)	All NADCs Adjusted IRR (95% CI)	All ADCs N events (PYFU)	All ADCs Adjusted IRR (95% CI)
0	625 (127132)	1	205 (127132)	1
<6	46 (7370)	1.22 (0.90, 1.65)	17 (7370)	0.86 (0.52, 1.43)
6-<12	37 (5835)	1.25 (0.89, 1.74)	5 (5835)	0.31 (0.13, 0.77)
12-<24	52 (9000)	1.11 (0.84, 1.48)	5 (9000)	0.22 (0.09, 0.53)
24-<36	41 (5965)	1.31 (0.95,1.80)	8 (5965)	0.56 (0.28, 1.15)
36+	34 (5355)	1.16 (0.82, 1.65)	3 (5355)	0.25 (0.08, 0.78)
Global P-value		0.32		0.0002

Results

- Overall, 29,340 individuals were included in the analysis (Table 1).
- By the end of follow-up (FU), 13,950 (48%) individuals had been exposed to ≥1 INSTI: 8607 dolutegravir, 3328 cobicistat-boosted elvitegravir, 3266 raltegravir, and 845 bictegravir.
- For those exposed to INSTIs, median cumulative exposure was 32 months (IQR 16-47).
- During 160,657 person-years of FU (PYFU, median 6.18 years [IQR 3.86-7.52]), there were 1078 cancer events (incidence rate [IR] 6.7/1000 PYFU [95% CI: 6.3-7.1]): 243 ADCs and 835 NADCs.
- The most common incident cancers were non-Hodgkin lymphoma (n=113, 10.5%), lung cancer (112, 10.4%), Kaposi's sarcoma (106, 9.8%), and anal cancer (103, 9.6%).
- After adjustment for potential confounders, the incidence of any cancer was similar for those with and without exposure to INSTIs (Figure 1).

Figure 1: Association between any cancer risk and cumulative exposure to INSTIs, adjusted for potential confounders

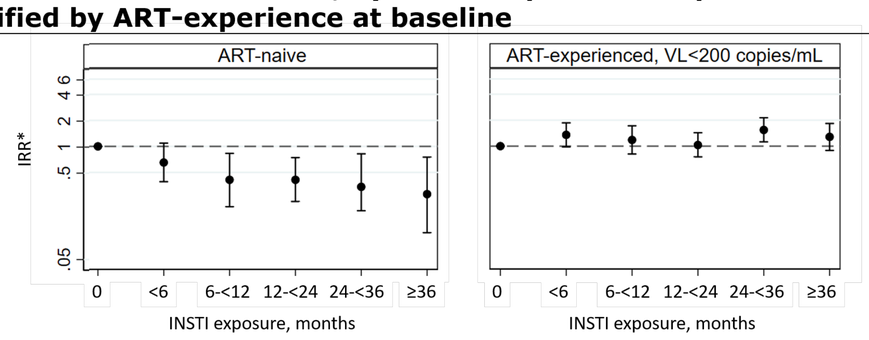
Cumulative INSTI exposure	n persons	PYFU	n events	Adjusted IRR (95% CI)
0 months	29340	127132	830	1
<6 months	12508	7370	63	1.15 (0.89-1.49)
6 - <12 months	11061	5835	42	0.97 (0.71-1.32)
12 - <24 months	9770	9000	57	0.84 (0.64-1.11)
24 - <36 months	7110	5965	49	1.10 (0.82-1.47)
≥ 36 months	4480	5355	37	0.90 (0.65-1.26)



Abbreviations: INSTI-integrase strand transfer inhibitor; PYFU-person years of follow-up; IRR-incidence rate ratio; CI-confidence interval
IRR adjusted for age, sex, ethnicity, HIV risk group, antiretroviral treatment experience, CD4 cell count, CD4 nadir, BMI, geographical region, hepatitis B, prior diabetes, prior AIDS, prior cancer, prior chronic kidney disease, prior cardiovascular disease, prior end stage liver disease (all fixed at baseline), smoking status (time updated). Note, INSTI exposure is lagged by 6 months.

- There was a significant interaction between INSTI exposure and baseline ART-experience (interaction p<0.0001; Figure 2). For ART-naïve participants, cancer incidence decreased with increasing INSTI exposure, mainly driven by a decreasing incidence of ADCs. For ART-experienced, cancer incidence was similar across all INSTI exposure categories.
- There was no interaction between INSTI exposure and other subgroups (age group, smoking status, CD4 nadir; interaction p>0.1 for all).
- There was no association between INSTI exposure and NADCs, while the incidence of ADCs decreased as exposure to INSTIs increased (Table 2).

Figure 2: Adjusted incidence of cancer, by INSTI exposure compared to no exposure, stratified by ART-experience at baseline



n individuals at risk	7172	3796	3318	2867	1998	1167	19951	7936	7068	6309	4694	3040
n cancers	181	16	8	12	7	4	590	41	28	39	40	32
n NADCs	68	6	7	12	7	4	518	37	26	37	32	30
n ADCs	113	10	1	0	0	0	72	4	2	2	8	2

*IRR calculated from a negative binomial regression model, adjusted for the same confounders as the main analysis, and including an interaction term between INSTI exposure and ART-experience at baseline (p-value for interaction <0.0001)

Limitations

- Despite the large study size, we had too few events to reliably assess associations between cancer risk and individual INSTIs or to assess individual cancers.
- Median exposure to INSTIs may have been too short to detect an association with cancer risk, given cancers can take years to develop.
- We cannot exclude the possibility of unmeasured confounding or confounding by indication.

Conclusion

- There was no association between INSTI exposure and cancer risk in ART-experienced individuals.
- There was a decreasing cancer incidence with increasing exposure in those starting INSTIs from ART-naïve, driven by a fast decline in ADCs, likely due to improvements in immune function.

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

References: [1] Trickey A, et al. Lancet HIV. 2017 [2] Marcus JL, et al. JAMA. 2020 [3] Dubrow R, et al. Curr Opin Oncol. 2012 [4] Weber R, et al. HIV Med. 2013