North American AIDS Cohort Collaboration on Research and Design

JOHNS HOPKINS MEDICINE SCHOOL OF MEDICINE

898

Incident Diabetes Among People with HIV After Switching to Integrase Strand Transfer Inhibitors

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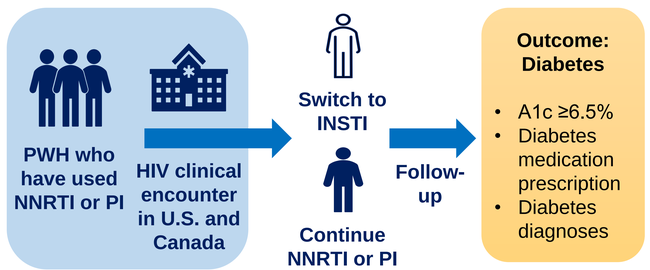
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BACKGROUND

- Initiating integrase strand transfer inhibitors (INSTI) has been associated with weight gain and new-onset diabetes in antiretroviral therapy (ART)-naïve people with HIV (PWH)
- The effect of switching to INSTI on diabetes risk is unclear for ART-experienced PWH
- **Aim:** estimate the effect of switching to INSTI from non-nucleoside reverse-transcriptase inhibitors (NNRTI) or protease inhibitors (PI) on the risk of incident diabetes

METHODS

- Collaborative cohorts of PWH across the U.S. and Canada (January 2016–December 2022)
- PWH aged ≥18 years without history of diabetes who have used NNRTI or PI for ≥180 days and attended ≥1 HIV clinical encounters
- Nested clinical trials method used to emulate a target trial where PWH are randomized to switching to INSTI vs. continuing NNRTI or PI at clinical encounters



- PWH were followed from the day of eligible clinical encounter (unit of observation = clinical encounter) until the first of: outcome, loss to follow-up, death, end-of-study, or administrative closure or end of observation window for diabetes for the corresponding cohort
- Inverse probability weights used to mitigate confounding from non-random treatment assignment and informative censoring
- Weighted Cox regression used to estimate the risk of diabetes, accounting for repeated observations

There was a 22% increase in the 5-year risk of incident diabetes among PWH who switched INSTI *vs.* those who continued NNRTI or PI; the risk was concentrated in the first 2 years. When weight gain in the first year was considered as a mediator, the risk attenuated only slightly to 18%.

RESULTS

- 13,071 PWH followed from 81,365 encounters where they continued NNRTI or PI and 4,416 encounters where they switched to INSTI (median follow-up: 2.5 years)
- Median age 56 years; 90% male at birth; 40% identified as Black; 63% had BMI ≥25
- At clinical encounters where a switch to INSTI was made, 50% was also initiated on TAF *vs.* where NNRTI or PI was continued, 11% was initiated on TAF
- Key covariates including demographics, BMI, tenofovir formulations, viral suppression, and duration of NNRTI or PI at study entry were adjusted.

Table 1. The risk of incident diabetes associated with switching from NNRTI or PI to INSTI between 2016 and 2022

Comparison groups	N of events/ N of encounters (%)	Adjusted incidence rate, per 1,000 PY (95% CI)	Adjusted hazard ratio (95% CI)
Continued NNRTI or PI	5,041/81,365 (6.2)	23.9 (23.2–24.5)	Reference
Switched to any INSTI	400/4,416 (9.1)	29.3 (26.3–32.5)	1.22 (1.03–1.45)
Specific INSTI			
Bictegravir	87/1,097 (7.9)	29.6 (18.9–44.0)	1.13 (0.79–1.62)
Dolutegravir	182/1,953 (9.3)	27.8 (23.6–32.7)	1.11 (0.87–1.41)
Elvitegravir	127/1,322 (9.6)	30.4 (23.1–39.3)	1.22 (0.85–1.77)
Raltegravir	4/44 (9.1)	21.6 (5.9–55.4)	1.05 (0.26–4.17)

- HR diabetes for the first two years after switching to INSTI was 1.47 (95% CI, 1.19–1.81) *vs.* 0.95 (95% CI, 0.74–1.23) for the latter three years (interaction *P* <0.01)
- HR diabetes for switching to INSTI was similar when the first-year weight gain was accounted for as a potential mediator (HR, 1.18; 95% CI, 0.97–1.43)

Figure 1. Adjusted cumulative incidence of diabetes after switching to INSTI compared to continuing NNRTI or PI

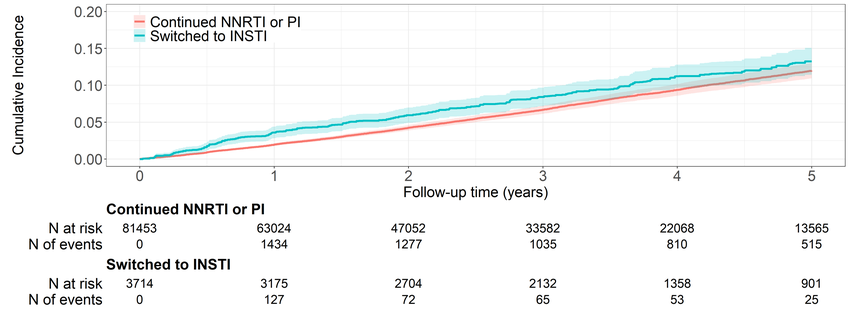


Table 2. Risk of incident diabetes associated with switching to INSTI from (i) NNRTI and (ii) PI

Comparison groups	N of events/ N of encounters (%)	Adjusted incidence rate, per 1,000 PY (95% CI)	Adjusted hazard ratio (95% CI)
Continued NNRTI	3,459/54,766 (6.3)	24.5 (23.7–25.3)	Reference
Switched to INSTI	250/2,702 (9.3)	27.7 (23.9–32.0)	1.09 (0.86–1.37)
Continued PI	1,509/26,599 (5.7)	22.7 (21.6–23.9)	Reference
Switched to INSTI	150/1,714 (8.8)	30.5 (25.8–35.8)	1.38 (1.06–1.80)

CONCLUSIONS

- Switching to INSTI from NNRTI or PI was associated with a modest, but statistically significant risk of incident diabetes in multi-site cohorts of PWH across the U.S. and Canada
- Diabetes risk was concentrated in the the first two years after switch and those switching from PI
- The effect of switching to INSTI on diabetes was not meaningfully mediated by weight gain in the first year following the switch

ADDITIONAL KEY INFORMATION

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