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Long-Term ART Is Not Associated With Reduced Anogenital Cancer Risk: A Case-Cohort Study

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BACKGROUND

- People with HIV (PWH) are elevated risk of virally associated anogenital cancers due to immunodeficiency, chronic HPV carriage, and behavioral risk factors.
- No study has assessed the time-varying impact of antiretroviral therapy (ART) on cancer risk reduction in anogenital cancers affecting women living with HIV
- Botswana has a generalized HIV epidemic, primarily affecting women living with HIV, with high public ART coverage

OBJECTIVE

- Our aim was to assess whether sustained ART reduces risk of HPV-associated anogenital cancers in PWH

METHODS

- **Design:** Prospective Case-Cohort Study
- Target trial emulation framework below

	Target Trial	Emulated Trial
Eligibility Criteria	• Born between Jan 1947 and Dec 1998 • Baseline (time zero) is defined at age 10 • No history of cancer or HIV infection at baseline • Citizen of Botswana	Same as target trial • Eligible individuals from four principal oncology centers were enrolled (Thabatse) • Eligible individuals from population-based random sample were enrolled (BCPP)
Exposure	Four categories of HIV infection and ART treatment: • No HIV infection • HIV infection with no ART • HIV infection with ART < 5 years • HIV infection with ART for ≥ 5 years	Same as target trial
Treatment Assignment	Random assignment	Assumed random assignment using inverse probability weighting (IPTW) on a priori selected factors: five-year age strata, region, sex*, education level, and AIDS and smoking history
Blinding	No blinding (open-label)	Same as target trial
Outcomes	Cervical, anal, vulvar, and penile cancer confirmed via histology	Same as target trial
Follow-up	Starts at baseline and ends at date of anogenital cancer diagnosis, last contact by study team, or April 2020	Same as target trial
Causal contrasts	Intention-to-treat	Same as target trial
Statistical Analysis	Incident rate ratio analysis comparing risk to people without HIV infection.	Same as target trial while accounting for the weighted design

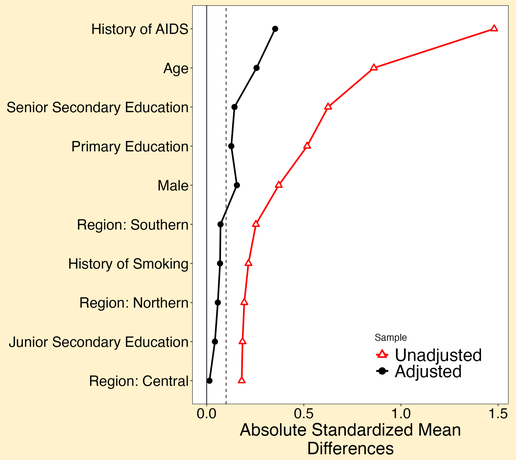
RESULTS

- A total of 17,321 participants were enrolled, including 1,377 cancer cases
  - Only 0.1% (11) of cases and 1.0% (138) of controls were excluded due to missing data.

Table 1. Patient Baseline Characteristics

Treatment category	Less than 5 years of ART	5 or more years of ART
Age, year	38.0 [32.0, 46.0]	44.0 [38.0, 51.0]
Geographic Region		
Northern	911 (38.1)	1480 (43.2)
Central	691 (28.9)	1017 (29.7)
Southern	788 (33.0)	925 (27.0)
Primary school or less education	904 (37.8)	1780 (52.0)
Smoking History	235 (10.9)	329 (10.3)
CD4 Nadir		
Less than 200	479 (20.0)	964 (28.2)
200 to 349	684 (28.6)	851 (24.9)
350 to 499	509 (21.3)	598 (17.5)
500 or greater	477 (20.0)	785 (22.9)
Not available	241 (10.1)	224 (6.5)
Most Recent Viral Load		
<1000 copies mL	2273 (95.1)	3283 (95.9)
≥1000 copies mL	67 (2.8)	76 (2.2)
Not available	50 (2.1)	63 (1.8)

Figure 1. Covariate Balance Pre- and Post-Adjustment



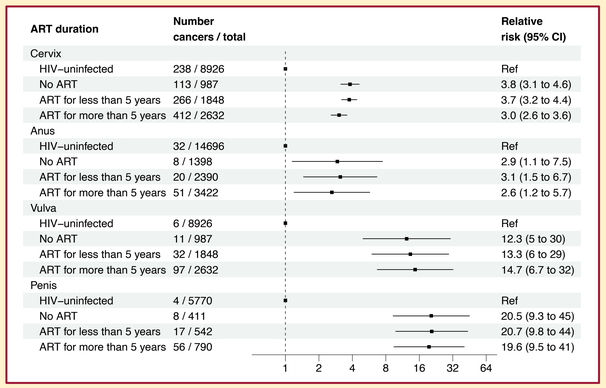


Figure 2. Risk of Cervical, Anal, Vulvar, and Penile Cancer by HIV status and ART duration. Marginal risk ratio estimates from G-computation of logistic regression models. Denominator is sex-specific, aside from anal cancers.

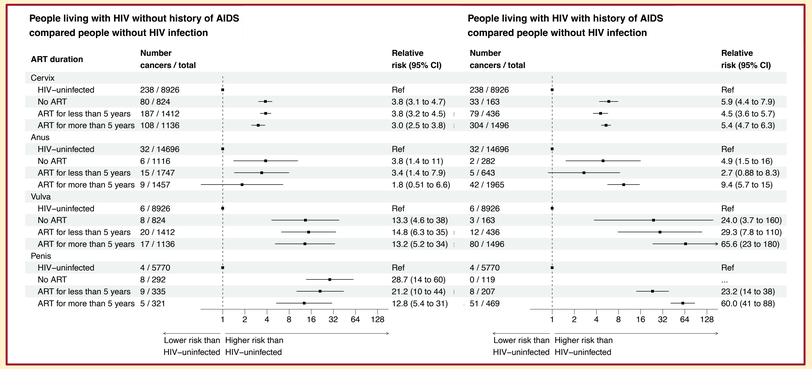
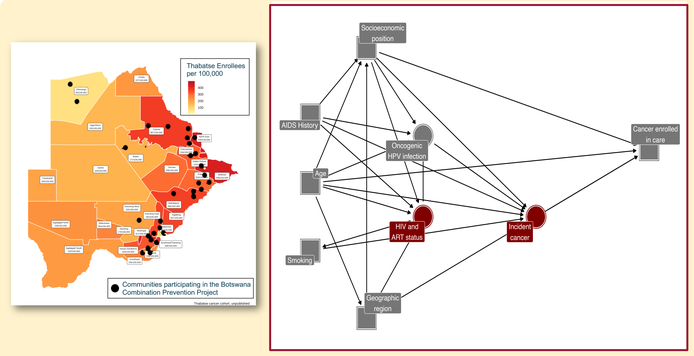


Figure 3. Anogenital Cancer Risk by AIDS History and ART duration. IPTW and logistic regression models fitted on datasets stratified by prior AIDS history.



CONCLUSIONS

- In all categories of ART duration, HIV infection was associated with a large increase in risk for each cancer studied.
- There was no protective effect observed with long-term ART. In fact, risk for vulvar and penile cancer increased with longer durations of ART.
- Although prior AIDS history increases risk of cancer incidence by 79%, long-term HIV infection heightens cancer risk, even after accounting for confounding factors
- There is a great need for anogenital cancer screening and treatment programs globally to address excess cancer burden

LIMITATIONS

- Lack of temporal resolution on HIV vs. HPV infection
- Sub-cohort is not geographically representative of cancer cohort
- Unable to account for competing mortality, so may underestimate cancer risk in PWH on no ART
- Shifting ART treatment guidelines over time
  - 2002-2007: ZDV/3TC/NVP or EFV (CD4 count ≤250)
  - 2008-2011: TDF/FTC/NVP or EFV (CD4 count ≤250)
  - 2012-2015: TDF/FTC/EFV (CD4 count ≤350)
  - 2016-present: DF/FTC/DTG (no CD4 count requirement)

ADDITIONAL KEY INFORMATION

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