Optimizing Anal Cancer Screening in PWH: The Role of ADAR1 mRNA in Predicting High-Grade Lesions

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BACKGROUND

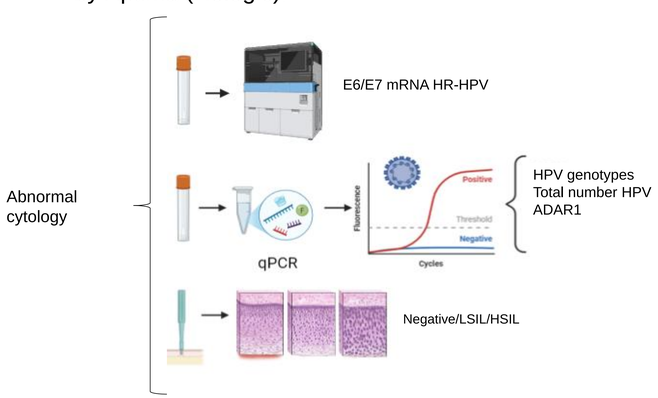
The incidence of anal squamous cell carcinoma is significantly increased in people with HIV (PWH). Early detection of high-grade squamous intraepithelial lesions (HSIL) through high-resolution anoscopy (HRA) in individuals with abnormal anal cytology can prevent over half of these cases. However, the poor specificity of anal cytology leads to a high number of unnecessary HRAs. This poses significant challenges to anal cancer screening, considering the scarce availability of HRA. Overexpression of adenosine deaminase acting on RNA 1 (ADAR1) has been reported in several cancers, including cervical cancer.

OBJECTIVE

This study aimed to determine whether quantifying ADAR1 mRNA levels could improve the selection of candidates for HRA.

METHODS

- **DESIGN:** Prospective cohort single-center study of HIV-positive adults with abnormal anal cytology (ASCUS, LSIL or HSIL).
- **SAMPLES:** 171 patients underwent HRA. Sample collection: anal swabs and biopsies.
- **DATA ANALYSIS**: HPV genotypes and ADAR1 were quantified by qPCR. E6/E7 mRNA HPV were detected by Aptima (Hologic).



ADAR1 mRNA levels show high predictive accuracy for HSIL in PWH with abnormal cytology and may reduce a substantial number of unnecessary HRAs

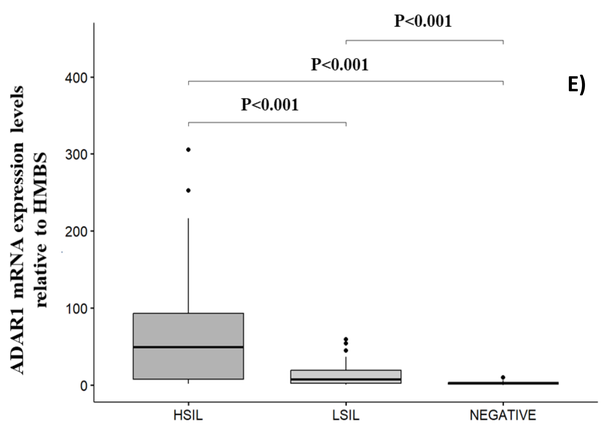
RESULTS

Participants with HSIL had a higher median number of HPV genotypes compared to those without HSIL (5 [4-8] vs 3 [1-5], p<0.001). ADAR1 mRNA levels were significantly higher in the HSIL group compared to the non-HSIL group (49.4 vs 4.1, p<0.001). The ROC curve for ADAR1 mRNA showed an area under the curve of 0.83 (95% CI: 0.75-0.92). Using a threshold of ≥24.8 relative units to endogenous control, the test achieved 73% sensitivity, 92% specificity, 74% positive predictive value and 92% negative predictive value. This threshold would reduce the need for HRA to 22.8% of participants with abnormal anal cytology. Among the 132 (73%) participants with ADAR1 levels <24.8, incorporating HPV genotype quantification with a threshold of >4 improved HSIL detection rates to 95%, though it would require 40 (23%) additional HRAs. Compared to E6/E7 mRNA, ADAR1 mRNA led to a greater reduction of HRA referrals (77.2% to 48.8%).

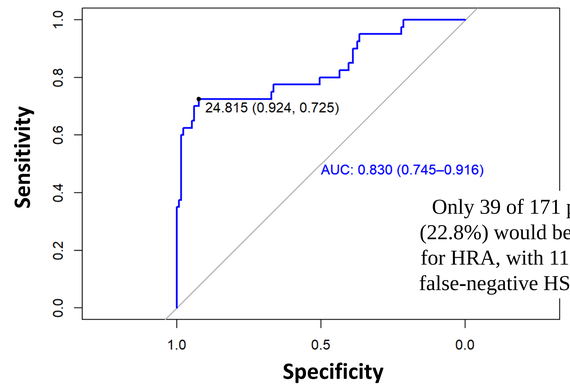
A) Baseline characteristics

Characteristics	Participants with HSIL (n=40)	Participants without HSIL (n= 131)	All participants (n=171)	P-value
Age, years, median (IQR)	52.0 (38.8-58.2)	50.0 (43.0-57.0)	50.0 (43.0-57.5)	0.943
Sex at birth, n (%) Female Male	 3 (7.5) 37 (92.5)	 25 (19.1) 106 (80.9)	 28 (16.4) 143 (83.6)	0.137
Origin, n (%) Caucasian Other	 31 (77.5) 9 (22.5)	 113 (86.3) 18 (13.7)	 144 (84.2) 27 (15.8)	0.216
HIV-1 viral load, n (%) <50 copies/mL ≥50 copies/mL	 37 (92.5) 3 (7.5)	 123 (93.9) 8 (6.1)	 160 (93.6) 11 (6.4)	0.720
Nadir CD4 T cell count, cell/µL, median (IQR)	258 (134-350)	270 (135-402)	267 (134- 372)	0.334
HPV vaccination, n (%)	14 (35.0)	40 (30.5)	54 (31.6)	0.736

B) ADAR1 is a predictor for anal HSIL

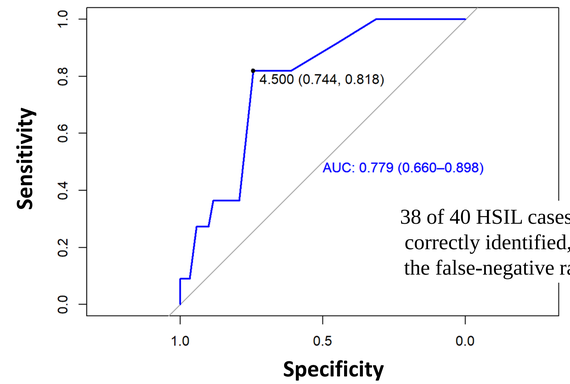


C) Predictive model for anal HSIL based on ADAR1 mRNA levels in all participants (n=171)



Only 39 of 171 patients (22.8%) would be referred for HRA, with 11 (27.5%) false-negative HSIL cases.

D) Predictive model for anal HSIL based on total HPV counts in participants with ADAR1 under the cut-off (n=132)



38 of 40 HSIL cases would be correctly identified, reducing the false-negative rate to 5%.

E) Comparison of the diagnostic metrics between methods

Diagnostic performance	ADAR1 mRNA quantification	E6/E7 mRNA HR-HPV detection
Sensitivity	0.73	0.80
Specificity	0.92	0.58
DOR	31.9	5.6
HRA reduction	77.2 %	48.8 %

ADDITIONAL KEY INFORMATION

- Author contact information: melissa.bello@fisabio.es
- This work was supported by Instituto de Salud Carlos III: PI22/01949; CD23/00136

CONCLUSION

ADAR1 mRNA quantification helps mitigate the limited availability of HRA by more accurately identifying PWH who need the procedure.