Anal HPV infection & disease
Common and preventable, but hard to treat
Marra, E.
CHAPTER 4

Detection rate of high-grade squamous intraepithelial lesions as a quality assurance metric for high-resolution anoscopy in HIV-positive

Matthijs L. Siegenbeek van Heukelom, Elske Marra, Irina Cairo, Arne Van Eeden, Maarten F. Schim van der Loeff, Henry J.C. De Vries, Jan M. Prins

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Abstract

Objective
High-resolution anoscopy (HRA)-guided biopsies are the gold standard for identifying anal intraepithelial neoplasia, but diagnosing high-grade squamous intraepithelial lesions (HSIL) is dependent on the skills of the anoscopist. To validate the HSIL detection rate as a quality assurance (QA) metric for HRA in HIV-positive men.

Design & setting
Retrospective study; Three HIV outpatient clinics in Amsterdam, The Netherlands.

Patients
HIV-positive men-who-have-sex-with-men (MSM)

Main outcome measures
We analyzed the HSIL detection rate per HRA, the mean number of biopsies taken and the mean HSIL rate per biopsy in time-subsequent groups (TSGs) for seven anoscopists performing HRA in HIV-positive MSM.

Results
Seven anoscopists (5 MDs and 2 RNs) performed HRA in 1340 HIV-positive MSM. The overall HSIL detection rate for all seven anoscopists combined increased significantly over time, from 27% to 40% (p<0.001; OR 1.15 [95%CI 1.08-1.23] per 50 HRAs). The mean number of biopsies increased significantly from 1.4 (22% HSIL per biopsy) to 2.0 biopsies per patient (29% HSIL per biopsy) (p<0.001). Three anoscopists showed a significant increase in proportion of HSIL per biopsy with increasing experience.

Limitations
There were statistically significant differences, with limited clinical significance, in characteristics of patient populations between anoscopists and clinics.

Conclusions
We found significant variations in HSIL detection rate among anoscopists performing HRA in HIV-positive MSM. HSIL detection rate and mean HSIL rate per biopsy can be used as QA metric to follow-up the learning curve of high-resolution anoscopists.
**Introduction**

HIV-positive men who have sex with men (MSM) are at increased risk for developing anal squamous cell carcinoma (aSCC) \(^1\). The precursor stage of aSCC is anal intraepithelial neoplasia (AIN). High-resolution anoscopy (HRA)-guided biopsies are the gold standard for identifying AIN and the level of dysplasia is histopathologically graded as AIN 1, 2 or 3 and categorized as low-grade squamous intraepithelial lesions (LSIL; AIN1) or high-grade squamous intraepithelial lesions (HSIL; AIN 2 and 3).

The reported prevalence of HSIL in HIV-positive MSM ranges from 2.7% to 54% \(^2-4\). Although diagnosing HSIL is dependent on the skills of the anoscopist, the ability of the anoscopist to identify HSIL is usually not taken into account in reports on HSIL prevalence and treatment success \(^5-7\). Missing HSIL leads to an underestimation of HSIL prevalence, an overestimation of treatment success and a misunderstanding of the natural history of AIN. In the worst case, it could lead to interval carcinomas \(^8\).

To assess the quality of care is common practice in many medical areas. For HRA, several quality assurance (QA) metrics have been proposed \(^9\). These QA metrics are based on quality indicators (QI) used in similar medical procedures, like colonoscopy or colposcopy, but before using those for HRA, they first need to be validated. Assessing the individual anoscopist’s HSIL detection rate might be a relevant QA metric for HRA and may help to improve HRA quality and the likelihood of identifying HSIL \(^10\).

In this study, we assessed the HSIL detection rate in HIV-positive MSM over time for seven anoscopists in Amsterdam, the Netherlands, and we propose to use a standardized learning curve as a quality standard for performing HRA.

**Methods**

**Subjects**

At three HIV outpatient clinics in Amsterdam, the Netherlands, HRA is routinely offered to MSM. From a database containing data on all 1681 HIV-positive MSM that underwent HRA screening between 12 February 2008 and 24 November 2015 at one of these three clinics, we selected the data of the first HRA of each patient. Data on HRAs by anoscopists who had performed less than 100 HRAs were excluded from the analyses. None of the anoscopists received training for, or practiced, colposcopy or similar procedures prior to performing HRA. One anoscopist, a dermatologist, had previous experience in taking skin biopsies and performing electrocautery. Prior to performing unsupervised HRA, all anoscopists received identical, hands-on HRA training from an expert that has performed HRA in >300 unique patients. Nurses who
Characteristics of the patients included in the learning curve study of the 7 anoscopists (N=1340).

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<tbody>
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<td>50 (10.3)</td>
<td>48 (9.3)</td>
<td>50 (9.7)</td>
<td>50 (9.5)</td>
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<tr>
<td>Never smoked</td>
<td>101 (37%)</td>
<td>37 (33%)</td>
<td>33 (35%)</td>
<td>49 (43%)</td>
<td>55 (32%)</td>
<td>71 (52%)</td>
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<tr>
<td>Currently smoking</td>
<td>102 (37%)</td>
<td>48 (48%)</td>
<td>39 (42%)</td>
<td>31 (27%)</td>
<td>55 (32%)</td>
<td>47 (35%)</td>
<td>125 (38%)</td>
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<td>HIV-related variables</td>
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<td>&lt;0.001</td>
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<tr>
<td>Currently using cART</td>
<td>304 (91%)</td>
<td>113 (97%)</td>
<td>94 (93%)</td>
<td>120 (99%)</td>
<td>169 (99%)</td>
<td>136 (100%)</td>
<td>327 (99%)</td>
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<tr>
<td>CD4 count cells/µl (median/IQR)</td>
<td>550 (420-710)</td>
<td>705 (530-890)</td>
<td>640 (480-800)</td>
<td>665 (500-840)</td>
<td>685 (470-855)</td>
<td>590 (460-790)</td>
<td>630 (470-810)</td>
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<tr>
<td>Nadir CD4 count cells/µl (median/IQR)</td>
<td>180 (70-270)</td>
<td>220 (130-340)</td>
<td>240 (120-320)</td>
<td>230 (150-310)</td>
<td>220 (150-310)</td>
<td>230 (120-320)</td>
<td>220 (130-320)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV plasma viral load, copies/ml (n/%)</td>
<td>207 (79%)</td>
<td>104 (95%)</td>
<td>84 (90%)</td>
<td>113 (97%)</td>
<td>157 (96%)</td>
<td>116 (97%)</td>
<td>311 (92%)</td>
<td>&lt;0.001</td>
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</table>

Abbreviations: SD: standard deviation; HIV: human immunodeficiency virus; cART: combination antiretroviral therapy; IQR: interquartile range; a: total - 6 missing; A1 - 4 missing; A2 - 1 missing; A3 - 0 missing; A4 - 1 missing; A5 - 0 missing; A6 - 0 missing; A7 - 0 missing; b: total - 112 missing; A1 - 83 missing; A2 - 5 missing; A3 - 9 missing; A4 - 7 missing; A5 - 0 missing; A6 - 3 missing; A7 - 5 missing; c: total - 413 missing; A1 - 359 missing; A2 - 12 missing; A3 - 4 missing; A4 - 26 missing; A5 - 3 missing; A6 - 1 missing; A7 - 8 missing; d: total - 30 missing; A1 - 24 missing; A2 - 1 missing; A3 - 1 missing; A4 - 1 missing; A5 - 0 missing; A6 - 2 missing; A7 - 1 missing; e: total - 195 missing; A1 - 16 missing; A2 - 11 missing; A3 - 14 missing; A4 - 24 missing; A5 - 27 missing; A6 - 39 missing; A7 - 64 missing; f: total - 49 missing; A1 - 20 missing; A2 - 8 missing; A3 - 3 missing; A4 - 3 missing; A5 - 1 missing; A6 - 2 missing; A7 - 12 missing; g: total - 156 missing; A1 - 96 missing; A2 - 8 missing; A3 - 9 missing; A4 - 5 missing; A5 - 7 missing; A6 - 18 missing; A7 - 13 missing

* = this anoscopist did not collect data on the number of sex partners in the preceding 6 months.
performed HRA had access to direct supervision from an MD at all times.

The HRA screening routine was identical for all anoscopists: a digital anal rectal exam followed by peri- and intra-anal inspection using a colposcope (ZEISS opmi pico surgical microscope) with repeated application of acetic acid (3% or 5%) and staining with Lugol's iodine when indicated. Anal cytology was not performed. All lesions with clinical suspicion of AIN \(^{11,12}\) were biopsied and histopathologically graded by AIN-experienced pathologists. When multiple biopsies were taken, the highest AIN grade defined the final diagnosis.

The Ethics review board of the Academic Medical Center in Amsterdam reviewed and approved this study (reference nr. W15_047 # 15.0058). All anoscopists gave consent for studying and anonymously publishing their individual HRA learning curves.

### Study design

Baseline characteristics (age, smoking, number of sex partners in the past six months, use of combination antiretroviral therapy (cART), nadir CD4+ cell count, CD4+ cell count at time of HRA, and plasma HIV-RNA) were collected for each patient.

To evaluate the HSIL detection rate per anoscopist over time, we analyzed time-subsequent groups (TSGs), each containing a maximum of 50 patients. The first TSG of an anoscopist contained the first 50 HRAs performed and the last TSG contained the last HRAs performed by the anoscopist. If the last TSG of an anoscopist contained less than 20 patients, it was excluded from the analysis. For each anoscopist, the HSIL detection rate per HRA, the mean number of biopsies taken and the mean HSIL rate per biopsy was assessed per TSG. This way, we evaluated the rate of progress of anoscopists for identifying HSIL. Also, we measured HRA exposure by calculating for each anoscopist the median time per TSG: the number of months required for screening 50 patients. We created an average learning curve by combining data of all anoscopists.

### Statistical analysis

Differences between anoscopists, between clinics and between median time per TSG per anoscopist were explored using X2-test and Fisher-exact test for categorical data, and ANOVA and Kruskal-Wallis test for continuous data. For each anoscopist the HSIL detection rate over time was analyzed using a nonparametric test for trend across TSGs. We also assessed the associations between the number of biopsies taken per patient and the proportion of HSIL per biopsy, and the number of HRAs per anoscopist.

### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(N=359)</th>
<th>(N=117)</th>
<th>(N=102)</th>
<th>(N=171)</th>
<th>(N=138)</th>
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<td>Age in years (mean/SD)</td>
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<td>49 (43%)</td>
<td>55 (32%)</td>
<td>71 (52%)</td>
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<tr>
<td>Previously smoking</td>
<td>27 (24%)</td>
<td>24 (25%)</td>
<td>21 (22%)</td>
<td>17 (13%)</td>
<td>7 (7%)</td>
<td>42 (25%)</td>
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<tr>
<td>Currently smoking</td>
<td>102 (37%)</td>
<td>48 (48%)</td>
<td>39 (42%)</td>
<td>31 (27%)</td>
<td>55 (32%)</td>
<td>47 (35%)</td>
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<tr>
<td>Number of sex partners</td>
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<td>in the preceding 6 months</td>
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<td>HIV-variables</td>
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<td>Currently using cART (n/%)</td>
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<td>220 (150-310)</td>
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<td>HIV plasma viral load</td>
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<td>&lt;50</td>
<td>≥50</td>
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Abbreviations: SD: standard deviation; HIV: human immunodeficiency virus; cART: combination antiretroviral therapy; IQR: interquartile range; a: total - 6 missing; A1 - 4 missing; A2 - 1 missing; A3 - 0 missing; A4 - 1 missing; A5 - 0 missing; A6 - 0 missing; A7 - 0 missing; b: total - 112 missing; A1 - 83 missing; A2 - 5 missing; A3 - 9 missing; A4 - 7 missing; A5 - 0 missing; A6 - 3 missing; A7 - 5 missing; c: total - 413 missing; A1 - 359 missing; A2 - 12 missing; A3 - 4 missing; A4 - 26 missing; A5 - 3 missing; A6 - 1 missing; A7 - 8 missing; d: total - 49 missing; A1 - 20 missing; A2 - 8 missing; A3 - 3 missing; A4 - 3 missing; A5 - 1 missing; A6 - 2 missing; A7 - 12 missing; g: total - 156 missing; A1 - 96 missing; A2 - 8 missing; A3 - 9 missing; A4 - 5 missing; A5 - 7 missing; A6 - 18 missing; A7 - 13 missing.

* = this anoscopist did not collect data on the number of sex partners in the preceding 6 months.
Detection rate of anal HSIL

Statistical analyses was performed using Stata Statistics/Analysis software (IC version 14.2). α was set at P<0.05.

Results

In total 1340 men underwent a first-time HRA by an anoscopist who performed >100 HRAs (range 102-359 first HRAs per anoscopist). These anoscopists were five medical doctors (MD) and two registered nurses (RN), ranging in age from 30-58 years old and working at clinic A, B or C at either the department of Dermatology or the department of Internal Medicine.

Patient populations differed statistically significant between anoscopists (Table 1) and clinics (Table 2) on all included characteristics. Patient populations of the anoscopists differed statistically significant between TSGs for anoscopist 7 with regard to age and for anoscopists 1, 6 and 7 with regard to nadir CD4+ cell count (data not shown).

During 1340 first HRAs, 2236 biopsies were taken, of which 418 (19%) were categorized as HSIL, leading to 389 HSIL diagnoses (29% of HRAs). The overall HSIL detection rate for all seven anoscopists combined increased significantly over time, from 27% in the first TSG to 40% in the seventh TSG (p<0.001; OR 1.15 [95%CI 1.08-1.23] per 50 HRAs)(Fig. 1A-B). The mean number of biopsies increased significantly from 1.4 (22% HSIL per biopsy) in the first TSG to 2.0 biopsies per patient (29% HSIL per biopsy) in the seventh TSG (p<0.001)(Fig. 1C).

The HSIL detection rate per outpatient clinic increased significantly over time for clinics B and C, from 20% and 26% in the first TSG to 40% (p=0.002) in the fourth TSG and 48% (p<0.001) in the seventh TSG, respectively. The HSIL detection rate in clinic A increased non-significantly, from 33% in the first TSG to 40% (p=0.15) in the eighth TSG.

The individual HSIL detection rate increased significantly over time for anoscopists 1, 5 and 7, from 32%, 20% and 36% in the first TSG to 40%, 48% and 45% in the last TSG (p=0.045, p=0.008, and p=0.02) respectively (Fig. 1B). All anoscopists had an increasing mean number of biopsies taken per HRA, and this was significant for anoscopists 1,5, 6 and 7. The mean number of biopsies taken ranged between anoscopists in the first TSG from 0.9 to 2.1 per patient, with 22% (range 14% to 41%) of their biopsies being HSIL. In the last TSG, the mean number of biopsies ranged from 1.6 to 2.6 per patient, with 23% (range 10% to 28%) of biopsies being HSIL (Fig. 1C). Anoscopists 5, 6 and 7 showed
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| Table 2 - Characteristics of the patients included in the learning curve study of 7 anoscopists by clinic (N=1340). |
|-------------------------------------------------|---------------------------------|-----------------|-----------------|-----------------|
|                                                 | Clinic A (N=578)                | Clinic B (N=293) | Clinic C (N=469) | P-value         |
| **Demographic variables**                       |                                 |                 |                 |                 |
| Age in years (mean/SD) (a)                       | 48 (9.7)                        | 50 (9.6)        | 50 (9.2)        | 0.019           |
| Smoking status (n/%) (b)                        |                                 |                 |                 | 0.001           |
| Never smoked                                    | 171 (36%)                       | 104 (36%)       | 195 (42%)       |                 |
| Previously smoking                              | 121 (25%)                       | 96 (34%)        | 94 (20%)        |                 |
| Currently smoking                               | 189 (39%)                       | 86 (30%)        | 172 (37%)       |                 |
| Number of sex partners in the preceding 6 months (median/IQR) (c) | 1 (1-5)*                      | 1 (1-4)         | 2 (1-6)         | 0.006           |
| Number of sex partners in the preceding 6 months (n/%) (c) |                                 |                 |                 | 0.002           |
| 0-1                                              | 108 (53%)*                      | 144 (55%)       | 218 (47%)       |                 |
| 2-5                                              | 49 (24%)*                       | 71 (27%)        | 118 (26%)       |                 |
| ≥6                                               | 46 (23%)*                       | 49 (19%)        | 124 (27%)       |                 |
| **HIV-related variables**                       |                                 |                 |                 | <0.001          |
| Currently using cART (n/%) (d)                  |                                 |                 |                 |                 |
| No                                               | 41 (7%)                         | 3 (1%)          | 3 (1%)          |                 |
| Yes                                              | 511 (93%)                       | 289 (99%)       | 463 (99%)       |                 |
| CD4 count cells/µl (median/IQR) (e)              | 590 (440-760)                   | 670 (490-850)   | 620 (470-810)   | <0.001          |
| Nadir CD4 count cells/µl (median/IQR) (f)       | 200 (90-280)                    | 220 (150-310)   | 230 (130-320)   | <0.001          |
| HIV plasma viral load, copies/ml (n/%) (g)      |                                 |                 |                 | 0.020           |
| <50                                              | 395 (85%)                       | 270 (96%)       | 427 (97%)       |                 |
| ≥50                                              | 70 (15%)                        | 11 (4%)         | 11 (3%)         |                 |

abbreviations: SD: standard deviation; HIV: human immunodeficiency virus; cART: combination antiretroviral therapy; IQR: interquartile range

a: total - 6 missing; Clinic A - 5 missing; Clinic B - 1 missing; Clinic C - 0 missing; b: total - 112 missing; Clinic A - 97 missing; Clinic B - 7 missing; Clinic C - 8 missing; c: total - 413 missing; Clinic A - 375 missing; Clinic B - 29 missing; Clinic C - 9 missing; d: total - 30 missing; Clinic A - 26 missing; Clinic B - 1 missing; Clinic C - 3 missing; e: total - 195 missing; Clinic A - 41 missing; Clinic B - 51 missing; Clinic C - 103 missing; f: total - 49 missing; Clinic A - 31 missing; Clinic B - 4 missing; Clinic C - 14 missing; g: total - 156 missing; Clinic A - 113 missing; Clinic B - 12 missing; Clinic C - 31 missing

* = excluding anoscopist 1 who did not collect data on the number of sex partners in the preceding 6 months
a significant increase in the proportion of HSIL per biopsy with increasing experience, while this proportion significantly decreased for anoscopists 1, 2, 3 and 4 (data not shown). The median time per TSG ranged between anoscopists from 1.7 to 21.7 months. Anoscopists 1, 5 and 7 required a median of 4.5, 4.7 and 1.7 months per 50 HRAs, anoscopists 2, 3, 4 and 6 required a median of 10.3, 21.7, 7.2 and 7.1 months. Therefore, the anoscopists who showed a significant increase in HSIL detection rate over time were also the ones with the shortest TSG.

**Discussion and Conclusion**

In this study we analyzed HSIL detection rates of seven anoscopists performing HRA in HIV-positive MSM and found a wide variation between anoscopists in HSIL detection rate, mean number of biopsies taken, and percentage of HSIL per biopsy. Over time the number of biopsies per HRA increased and the percentage of biopsies with HSIL detected remained stable, resulting in an overall increasing HSIL detection rate.

A minimum of 50 HRAs per year and identifying at least 20 cases of anal HSIL have been proposed as QA metrics for HRA. This study validates the HSIL detection rate and mean HSIL rate per biopsy as QA metric for HRA. The highest achievable HSIL detection rate equals the true prevalence of HSIL in a population. It has not been established what the true prevalence of anal HSIL is in HIV-positive MSM in the Netherlands. Therefore, it is difficult to set benchmark values for HRA competence. However, our study showed that three anoscopists (1, 5 and 7) achieved a significant increase in HSIL detection rate over time, to at least 40% in their last TSG (Fig. 1B). Following their HSIL detection rates, anoscopists in Amsterdam should strive for an HSIL detection rate of at least 40%, which is comparable to that of experienced clinics. Anoscopists 1, 5 and 7 performed their HRAs in a relatively short time period and showed a significant increase in HSIL detection rate over time. Other anoscopists required more time for screening 50 patients and did not have a significant increase in HSIL detection rate over time. This suggests that performing many HRAs in a short amount of time might help to increase HSIL detection rates.

Mean HSIL percentage per biopsy reflects the accuracy of the anoscopist in recognizing HSIL and is most useful as a QA metric when combined with HSIL detection rate. A low accuracy rate (≤20% HSIL biopsies) reflects too many normal tissue biopsies and implicates an unnecessary increase in HRA time and cost and potentially leads to
increased comorbidity and discomfort for the patient, whereas high accuracy rates (>80%) accompanied by low to moderate HSIL detection rates (10-30%) suggests that not all lesions with characteristics of HSIL are being biopsied and therefore HHSIL diagnosis might be missed.

The average learning curve developed in this study could be used as a reference for anoscopists performing HRA in HIV-positive MSM (Fig. 1A). In case of a lower than expected HSIL detection rate for the number of HRAs performed, identifying barriers for HSIL detection and overcoming these barriers could increase the likelihood of detecting HSIL. Such benefits of analyzing learning curves have been observed in other, comparable procedures 14.

Both nurses and doctors in this study showed similar learning curves for identifying HSIL. Neither doctors nor nurses had prior experience with HRA or similar procedures. In Figure 1B we observed that 5 out of 7 anoscopists had a lower HSIL detection rate in the second TSG than in the first. This could partly be explained by the fact that the anoscopists had, on average, their first 10 HRAs supervised by a more experienced anoscopist. For anoscopist 3 we observed the lowest HSIL detection rate of all anoscopists, for all TSG’s. This anoscopist had also the longest median time in months per TSG: 21.7 months. The long median time in months per TSG of this anoscopist and anoscopists 2, 4 and 6 supports the notion that performing only 1-2 HRAs weekly is not sufficient for achieving acceptable HSIL detection rates. Anoscopists 1, 5 and 7 performed many HRAs in a short amount of time and significantly improved their performance.

Anoscopists 5, 6 and 7 increased the percent of HSIL per biopsy, but only anoscopists 1, 5 and 7 diagnosed more HSIL over time (Figure 1B and C). This shows that anoscopist 6 improved her accuracy in distinguishing HSIL from LSIL and nondysplastic lesions, without identifying more patients with HSIL. Vice versa, anoscopist 1 improved in identifying patients with HSIL, but did not improve her accuracy in distinguishing HSIL from LSIL and non-dysplastic lesions. There is no clear explanation as to why A5 and A7 became more accurate in identifying HSIL per lesion and overall, while A6 only became more accurate on a lesion level, and A1 on a population level. Anoscopists 1, 5 and 7 could have increased their HSIL detection rate due to having a high HRA exposure, as shown by relatively short median time per TSG when compared
Detection rate of anal HSIL

Figure 1. HSIL detection rate and number of biopsies taken by seven high-resolution anoscopists performing HRA in HIV-positive MSM

A) Mean proportion of HRAs during which HSIL was detected, data of all anoscopists combined per time-subsequent group of at most 50 patients per anoscopist.

B) Proportion of HRAs during which HSIL was detected, for each anoscopist per time-subsequent group of at most 50 patients.

C) Mean number of biopsies per HRA taken by each anoscopist, and by all anoscopists combined, in time-subsequent groups of at most 50 patients.

*p-value of non-parametric trend test comparing indicated time-subsequent groups

A = anoscopist; M = male; F = female; MD = medical doctor; RN = registered nurse; HSIL = high-grade squamous intraepithelial lesions

Future studies should prospectively investigate the characteristics of anoscopists, and their learning curves, to help identify facilitators and barriers for increasing HSIL detection rates.

This study is the first to propose a quality standard for HRA. This proposition is strong as it reflects the learning curves of seven anoscopists who screened 1340 patients. We recommend anoscopists who perform HRA in HIV-positive MSM to assess and aggregate their learning curves, to allow the development of benchmark values.

As HSIL prevalence may vary per risk group, learning curves need to be assembled for each separate patient population.

A weakness of this study might be the statistically significant differences in patient populations between anoscopists and clinics, which could however be explained by the large study population, easily leading to statistically
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significant but not clinically important differences. As no consistent risk factors for HSIL have been identified, the variation between anoscopists cannot be explained by these population differences \(^{15}\). The difference in median nadir CD4+ cell count between TSG in one anoscopist is explained by the fact that she started screening patients with the lowest cell count first, as this is a risk factor for aSCC \(^{16}\).

In conclusion, we demonstrate significant variations in HSIL detection rate among anoscopists performing HRA in HIV-positive MSM. We recommend performing sufficient HRAs per week for achieving an acceptable HSIL detection rate and to use the individual HSIL detection rate and mean HSIL percentage per biopsy as QA metric for HRA. We recommend clinics to evaluate their anoscopists, to ensure that every anoscopist performs according to the average learning curve, and to explore the causes of substandard performance.
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References

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