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Cervical cancer screening intervals and management for women living with HIV: A risk benchmarking approach

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Abstract

Objective—We suggested cervical cancer screening strategies for women living with HIV (WLHIV) by comparing their precancer risks to general population women, and then compared our suggestions to current CDC guidelines.

Design—We compared risks of biopsy-confirmed cervical high-grade squamous intraepithelial neoplasia or worse ($_b$HSIL+), calculated among WLHIV in the Women's Interagency HIV Study, to "risk benchmarks" for specific management strategies in the general population.

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Disclosures: Some authors have been members of guidelines committees as follows: Teresa Darragh was a member of one of the working groups for the ACS/ASCCP/ASCP cervical cancer screening guidelines. Stewart Massad was on the panel that developed the 2012 ACS/ASCCP/ASCP cervical cancer screening guidelines. Stewart Massad, Joel Palefsky, and Howard Strickler were on the panel that developed the CDC management of opportunistic infections (OI) guidelines (section for management of HPV, including cervical cancer screening, in Adults/Adolescents with HIV). Howard Minkoff serves on the panel that writes perinatal guidelines for HIV (AIDSinfo.nih.gov). In addition, a study of Howard Strickler involves free blinded testing using HPV E6/E7 protein assays by Arbor Vita, p16/Ki67 cytology by MTM Laboratories/Ventura–Roche, and MCM-2/TOP2A cytology by BD Diagnostics; no financial payments to Dr. Strickler or his home institution were received.

Methods—We applied parametric survival models among 2,423 WLHIV with negative or ASC-US cytology during 2000–2015. Separately, we synthesized published general population $_{b}$HSIL+ risks to generate 3-year risk benchmarks for a 3-year return (after negative cytology, i.e., "re-screening threshold"), 6–12-month return (ASC-US), and immediate colposcopy (LSIL).

Results—Average 3-year $_{b}$HSIL+ risks among general population women ("risk benchmarks") were 0.69% for a 3-year return (after negative cytology), 8.8% for a 6–12-month return (after ASC-US), and 14.4% for colposcopy (after LSIL). Most CDC guidelines for WLHIV were supported by comparing risks in WLHIV to these benchmarks, including: a 3-year return after three negative cytology tests or a negative cytology/oncHPV co-test with CD4≥500 (all 3y-risks≤1.3%); a 1-year return after negative cytology with either positive oncHPV co-test (1y-risk=1.0%) or CD4<500 (1y-risk=1.1%); and a 6–12-month return after ASC-US (3y-risk=8.2% if CD4≥500; 10.4% if CD4=350–499). Other suggestions differed modestly from current guidelines, including colposcopy (vs. 6–12mo return) for WLHIV with ASC-US and CD4<350 (3y-risk=16.4%) and a lengthened 2-year (vs. 1-year) interval for WLHIV with CD4≥500 after negative cytology (2y-risk=0.98%).

Conclusions—Current cervical cancer screening guidelines for WLHIV are largely appropriate. CD4 count may inform risk-tailored strategies.

Keywords

cervical cancer; HSIL; CIN; precancer; risk; benchmarking; HIV; CD4; screening guidelines

Introduction

Women living with human immunodeficiency virus (WLHIV) are at elevated risk of cervical cancer and precancer [1–3]. This risk has declined in recent years, possibly due to improvements in effective antiretroviral therapy (eART) or cervical cancer screening [4–6]. Cervical cancer/precancer risks increase with diminishing immune status among WLHIV, even when comparing women with the same result from a cytology or oncogenic human papillomavirus (oncHPV) test [2,3,7–11].

To prevent cervical cancer in the general population, the U.S. Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS) recommend screening by cytology alone or, in women ages 30 years and above, screening either by cytology alone or with oncHPV co-testing [12,13]. For WLHIV, the Centers for Disease Control and Prevention (CDC) issues screening and management guidelines that employ the same modalities in the same age groups, but reflect that WLHIV are at higher cervical cancer risk [14]. For example, after a negative co-test (i.e., a concurrent cytologic diagnosis within normal limits [negative cytology] and negative oncHPV test), the USPSTF and ACS recommendation for HIV-uninfected women is a 5-year return, while the CDC recommends that WLHIV return for re-screening after 3 years [12–14]. After negative cytology alone, suggested intervals are 3 years for HIV-uninfected women compared to 1 year for WLHIV.

The CDC guidelines were influenced by data from the Women's Interagency HIV Study (WIHS) [3,6–8,11,15–19]. In WIHS studies, WLHIV have been compared to a parallel

group of HIV-uninfected women who are at high risk of acquiring HIV [20]. While these women are an appropriate reference for exploring causal effects of HIV, their cervical precancer risks may be higher than risks in the general population, since HIV and cervical HPV have shared risk factors. Thus, from these studies, it is difficult to determine whether screening strategies for the general population can be applied to WLHIV.

In this study, we aimed to describe the cervical cancer screening strategies suggested for WLHIV by an explicit comparison of their cervical precancer risks to true general population risks to which USPSTF and ACS guidelines are applied. To draw these comparisons, we used the framework of risk benchmarking, which was adopted during a 2012 conference to establish consensus management guidelines for abnormal cervical cancer screening tests in the general population [21–23]. In addition, because immunosuppression is strongly associated with cervical cancer/precancer risk in WLHIV [2,3,7–11], we considered CD4 count as a stratifying factor to explore potential opportunities for risk-tailored screening strategies.

Methods

Overall Approach

Risk benchmarking is used to ensure consistent management of individuals who are at similar risk of disease [21,22]. In brief, a management strategy for a particular test result is chosen by calculating disease risk among patients with the test result, then comparing this to risks following other test results with well-established management guidelines (“risk benchmarks”). Then, the guideline associated with a similar risk is applied to the test result in question. For cervical cancer screening, guidelines in the general population are well established, based on large clinical trials and extensive observational or clinical cohort data. Appropriate data are less available in WLHIV, with the WIHS being one of few cohorts with adequate sample size and follow-up. Therefore, we first estimated risk benchmarks of biopsy-confirmed cervical high-grade squamous intraepithelial neoplasia or worse ($_{b}$HSIL+) in the general population, and then assessed risks in the WIHS.

Consistent with the approach used to incorporate oncHPV testing into current guidelines, we generated benchmarks for the levels of risk that have historically triggered each of the following management strategies in the general population: a 3-year return for re-screening (this is the recommendation after negative cytology), a 6–12-month return (after atypical squamous cell of undetermined significance [ASC-US]), and immediate colposcopy (after low-grade squamous intraepithelial lesion [LSIL]) [22,23]. Then, for each result defined by cytology alone or cytology/oncHPV co-testing, we applied the strategy whose corresponding benchmark closely approximated the risk among WLHIV.

To address questions regarding the interval between negative screens, we extended the existing framework of risk benchmarking. Specifically, since USPSTF and ACS guidelines recommend a 3-year return following negative cytology, we reasoned that the risk accumulated at 3 years after negative cytology in the general population represents the threshold that triggers re-screening. Therefore, we estimated risk benchmarks at 3 years, and defined the 3y-return benchmark as the re-screening threshold. Then, to identify the

suggested return interval for WLHIV following a negative screen, we chose the annual time-point at which risk very closely approximated, or first exceeded, the 3y-return benchmark. For consistency, we also estimated risk benchmarks at 3 years for a 6–12mo return (after ASC-US) or immediate colposcopy (LSIL).

Study Population

We calculated risks among WLHIV in the WIHS, an observational cohort of women with and at risk for HIV (https://statepi.jhsph.edu/wihs/wordpress/). Enrollment occurred during 1994–95, 2001–02, 2011–12, and 2013–15 at 11 study sites across the United States [20,24,25]. Participants are screened every 6 months with cytology and are referred to colposcopy for ASC-US cytology or worse. HPV DNA testing of cervicovaginal lavage samples is also available at many visits from a previous HPV sub-study [7,18]. Conventional single-slide testing [26] and noncommercial type-specific HPV DNA L1 degenerate primer MY09/MY11/HMB01 polymerase chain reaction assays [18] are used for cytology and HPV testing, respectively. We defined oncHPV positivity as the presence of any of the 13 oncogenic HPV types included in the Hybrid Capture II assay, which is commonly used in cervical cancer screening [27].

This analysis was restricted to the years 2000–2015 (to represent the current HIV treatment era) and to WLHIV aged 21–65 years old (ages when screening is recommended). We analyzed all participants from the different enrollment waves collectively, although $_{b}$HSIL+ risk decreases with time in study [3]. We excluded women with a history of hysterectomy prior to entry. We made no exclusions based on history of cervical precancer or its treatment, as we aimed to mimic a clinical care setting representing all WLHIV. Our study updates previous WIHS analyses [3,6–8,11,15–19] by including new sites in the southern United States. The WIHS protocol was approved by institutional review boards at participating study sites.

Calculation of Benchmarks and Risks

To generate risk benchmarks, we identified large published studies describing risks of $_{b}$HSIL+ after negative, ASC-US, or LSIL cytology among general population women in usual care in the United States, and also included risks among WIHS HIV-uninfected women. We synthesized estimates across studies using unweighted linear regression models with random (study-specific) intercepts. For each cytology result, we calculated the corresponding risk benchmark by using the overall mean intercept and slope to predict risk at 3 years (further details in Supplemental Methods).

Among WLHIV in the WIHS, we first analyzed $_{b}$HSIL+ risk following a single cytology result, disregarding oncHPV results. We identified each eligible woman's first cytology in 2000 onward, then restricted to women with a negative or ASC-US result. We did not consider results of LSIL or worse. We identified each woman's first occurrence of $_{b}$HSIL+ following her entry cytology, then calculated follow-up time from cytology to the earliest of $_{b}$HSIL+, age 66, or last screening follow-up (cytology or colposcopy). We used parametric survival models to estimate annual cumulative incidence of $_{b}$HSIL+ from 1 to 5

years. We truncated follow-up at 5 years to improve the fit of parametric models to nonparametric estimates (further details in Supplemental Methods).

For risk following combined cytology and oncHPV (co-testing) results, after restricting to women with a concurrent oncHPV test result, we also restricted to WLHIV aged 30–65 years to maintain consistency with age guidelines for co-testing [12–14]. Where possible, for women without a concurrent oncHPV result, we analyzed the next visit with both cytology and oncHPV results available (N=93).

We also analyzed risk following multiple consecutive negative cytology results, which by design were obtained every 6 months. Among women with negative cytology, we further restricted to women whose second, and then third, cytology was negative. We did not consider pre-2000 results. In each case, we calculated follow-up from the final cytology, excluding women with a gap of 4 or more years between consecutive results (N=8 and N=6 after 2 and 3 negative results, respectively).

We used biopsy-confirmed cervical intraepithelial neoplasia grade 2 or higher [CIN2+] [28] as our primary $_{b}$HSIL+ endpoint, given the more limited number of CIN grade 3 or higher (CIN3+). However, we repeated all analyses using CIN3+, as this is a more specific precancer endpoint. For analyses with larger numbers of women, and thus better power to evaluate the effect of CD4 cell count (analyses based on cytology only [disregarding oncHPV], and women with a cytology-negative/oncHPV-negative co-test), we stratified by CD4 cell count at the time of cytology using a standard threshold that was near the median (≥500 or <500 cells/μL). Consistent with other benchmarking studies, we considered risk benchmarks to be measured without error [22,29,30], but estimated 95% confidence intervals [CIs] for relevant $_{b}$HSIL+ risks among WLHIV. We calculated two-sided Wald p-values for selected statistical comparisons.

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This study was funded by the National Institutes of Health. The funding source had no role in data collection, analysis, or interpretation.

Results

The 3-year $_{b}$HSIL+ (CIN2+) risk benchmark for a suggested 3-year return to screening was 0.69% (Supplemental Figure 1, Supplemental Table 1) based on 4 estimates of risk after negative cytology among general population women [22,31,32] and HIV-uninfected WIHS women. The benchmarks warranting a 6–12mo return and immediate colposcopy were 8.8% (based on 4 studies of risk after ASC-US) and 14.4% (based on 2 studies of risk after LSIL), respectively.

For the cytology-only analysis, we analyzed 2,423 WLHIV in the WIHS, including 2,049 with negative cytology and 374 with ASC-US cytology (Table 1). Most women with negative cytology were non-Hispanic Black (61%), had taken ART (80%), and were aged 30–49 years (74%) at the time of cytology. Approximately half (51%) of women with negative cytology had a CD4≥500 at the time of cytology, compared to only 29% of women

with ASC-US cytology (p<0.001). Most women contributed at least 5 years of follow-up. For risk following co-test results, we analyzed 1,439 WLHIV including: 1,070 cytology-negative/oncHPV-negative, 124 cytology-negative/oncHPV-positive, 163 ASC-US/oncHPV-negative, and 82 ASC-US/oncHPV-positive.

Negative cytology, with or without oncHPV testing

We compared $_{b}$HSIL+ risk among WLHIV with negative cytology to the general population benchmarks. After a single negative cytology result (Figure 1A), WLHIV with CD4≥500 (measured concurrently with cytology) first exceeded the 3y-return benchmark (0.69%) at 2 years (2-year risk=0.98% [95%CI 0.44–1.5%]). The 3-year risk among these women (1.5%) was statistically significantly higher than the benchmark (p=0.019). Among WLHIV with a CD4<500, risk first exceeded the benchmark at 1 year (1-year risk=1.1% [95%CI 0.51–1.6%]), and the 2-year risk (2.0%) was statistically significantly higher than the benchmark (p<0.001). This suggests that after a single negative cytology, WLHIV with CD4≥500 may be able to safely return for re-screening in 2 years, whereas risk among women with CD4<500 warrants a 1-year return.

Risks were lower among women with a concurrent negative cytology and oncHPV test (negative co-test, Figure 1B). For WLHIV with CD4≥500, risk first exceeded the 0.69% 3y-return benchmark at 3 years (3-year risk=0.94 [95%CI 0.21–1.7%]). Among WLHIV with CD4<500, 1- and 2-year risks were 0.66% (95%CI 0.08–1.2%) and 1.3% (95% CI 0.47–2.1%), respectively, with 3-year risk (1.9% [95%CI 0.87–2.9%]) remaining substantially below the threshold for a 6–12 month return (8.8%). In further analysis, we identified that risk was strongly elevated among the small group of WLHIV with CD4<200 (1-year risk=1.6%), but more moderate among the larger group with CD4 200–499 (1- and 2-year risks=0.33% and 0.90%, respectively). These data thus suggest that risk is low following a negative co-test, consistent with a suggested 3-year return in WLHIV with CD4>500 and possibly a 2-year return in WLHIV with CD4<500.

Finally, when negative cytology was combined with a positive oncHPV co-test (Figure 1C), risk among all WLHIV exceeded the 3y-return benchmark at 1 year (1-year risk=1.0% [95%CI 0–2.4%]), suggesting a 1-year return.

ASC-US cytology, with or without oncHPV testing

After ASC-US cytology (Figure 2A), the 3-year $_{b}$HSIL+ risk among WLHIV with CD4≥500 was 8.2% (95%CI 3.3–13.2%), approximating the 6–12mo return benchmark of 8.8%. Women with CD4<500 appeared to have a higher 3-year risk of 14.2% (95%CI 10.2–18.2%), approximating the colposcopy benchmark of 14.4%, but this was driven by high risk among WLHIV with CD4<350 (3-year risk=16.4% [95%CI 11.1–21.7%], Supplemental Figure 2). This suggests that appropriate management strategies for women with ASC-US and unknown oncHPV status are repeat cytology in 6–12mo for women with current CD4≥350, as currently recommended. For WLHIV with CD4<350, it may be appropriate to consider immediate colposcopy.

Following ASC-US cytology combined with a negative oncHPV test (Figure 2B), 3-year risk among all WLHIV was 6.5% (95%CI 2.9–10.1%). Although this is below the 8.8%

benchmark for a 6–12mo return, the 1-year risk was much higher than the 3y-return benchmark (1-year risk=4.3% [95%CI 1.6–6.9%] vs. 0.69% benchmark). When ASC-US cytology occurred instead with a positive oncHPV test (Figure 2C), the 3-year risk among all WLHIV was 14.6% (95%CI 7.4–21.8%), approximating the benchmark for colposcopy (14.4%). Taken together, this supports a 6–12mo return following an ASC-US/oncHPV-negative co-test, but immediate colposcopy following an ASC-US/oncHPV-positive co-test.

Consecutive negative cytology results

When oncHPV testing is not employed, guidelines have used consecutive negative cytology results to identify women at low risk [14]. Therefore, we compared $_{b}$HSIL+ risk after multiple negative cytology results (spaced by approximately 6 months) to the 3y-return risk benchmark. After 3 consecutive negative cytology results, for WLHIV with CD4≥500 (measured at the third cytology), the 3y-return benchmark (0.69%) was first exceeded at 3 years (3y risk=0.96% [95%CI 0.31–1.6%], Figure 3A). For WLHIV with CD4<500, risk appeared slightly higher, matching the benchmark at 2 years (2y risk=0.68% [95%CI 0.12–1.2%], Figure 3B); however, confidence intervals were wide and also included the benchmark at 3 years. This suggests that risk after 3 consecutive negative cytology results is low for all women, consistent with a suggested return after 3 years in women with CD4≥500. For women with CD4<500, a return after 2 years might be considered. Of note, among women with CD4≥500, each additional negative cytology result suggested reduced risk (Figure 3A), while among women with CD4<500, risks after 2 and 3 negative results were equivalent (Figure 3B).

Results based on outcome of CIN3+

We assessed the sensitivity of our results to our definition of $_{b}$HSIL+ by repeating our analysis using CIN3+ instead of CIN2+ (Supplemental Figures 3–6, Supplemental Table 2). The risk benchmarks for CIN3+ included the same studies as for CIN2+ (Supplemental Table 1) and were 0.36% (3y return), 3.4% (6–12mo return), and 4.7% (colposcopy) (Supplemental Figure 2). Confidence intervals around CIN3+ risk estimates were very wide, and we disregarded them to identify suggested strategies. One analysis had modestly different inferences (concurrent negative cytology and oncHPV co-test), where benchmarks were reached more quickly using CIN3+. Apart from this, strategies suggested by CIN3+ were the same as for CIN2+.

Discussion

In this study, we explored the cervical cancer screening strategies suggested by an explicit comparison of precancer risks between WLHIV and general population women. Although our approach differed from prior studies in multiple ways, including restriction to the current era of HIV treatment (2000 or later), our results largely supported existing cervical cancer screening guidelines for WLHIV [14] (Table 2). We also explored the utility of CD4 cell count for stratifying $_{b}$HSIL+ risks among WLHIV. Although we could not always estimate risks with sufficient precision to rule out alternative strategies, we identified some scenarios in which CD4 count could be further explored for tailoring screening intervals or management strategies.

Our analysis identified that some WLHIV have low $_b$HSIL+ risks. For WLHIV with negative cytology, a negative oncHPV co-test, and a CD4≥500, as well as for WLHIV with 3 consecutive negative cytology results and a CD4≥500, risks of precancer were low (<1% at 3 years). While these risks were still modestly above the benchmark for a 3-year return (0.69%), their confidence intervals included this benchmark while definitively excluding the 6–12mo return benchmark of 8.8% (upper bounds≤1.7%). A previous study of co-test-negative WLHIV in the WIHS did not identify any cases of $_b$HSIL+ over 5 years, but did suggest higher risk of low-grade SIL among WLHIV with lower CD4 counts [18]. Our study, which includes larger numbers of WLHIV, suggests that some portion of these low-grade SIL will progress to high-grade SIL.

Further, our results suggested that WLHIV with lower CD4 counts may benefit from more frequent screening than those with higher CD4 counts. Even when co-testing is used, our approach suggested WLHIV with a CD4<500 may have higher $_b$HSIL risk than WLHIV with CD4≥500. The small group of WLHIV with CD4<200 had particularly high risk, but it is unlikely that frequent screening would be beneficial in these women, who may have multiple medical problems and/or short life expectancy. When negative cytology was found concurrently with oncHPV, we found that a 1-year return is appropriate, consistent with current guidelines [14]. A previous WIHS study supports the additional guideline for colposcopy if HPV16 or HPV18 is present [7]; however, we did not have sufficient post-2000 data to confirm this strategy. Following ASC-US cytology, which is common among WLHIV [33], guidelines currently recommend colposcopy only if oncHPV is concurrently detected. Our analysis suggested that when oncHPV is unknown, a CD4<350 indicates similarly high risk, whereas women with higher CD4 counts can safely return for repeated screening within 1 year.

In the United States and other high-resource settings, the proportion of women with low CD4 counts has decreased as more WLHIV are on eART [34]. However, in low-resource settings, any recommendation for more aggressive screening among WLHIV with low CD4 counts could affect a large proportion of WLHIV [35,36]. It is unclear whether eART itself (independent of its effect on CD4 count) directly impacts $_b$HSIL+ incidence [14,19,37], and our study did not stratify by eART status. However, our findings do support guidelines recommending that all WLHIV be offered eART [38], which increases CD4 counts and thus may reduce $_b$HSIL+ risks [19]. As in the general population, HPV vaccination will also continue to influence the balance of benefits and harms for cervical cancer screening in WLHIV [39].

WLHIV constitute a special population that is at elevated risk for cervical cancer, but is also subject to a high burden of medical screening and tests. We explored screening strategies for WLHIV using an approach based on risk benchmarking, which provides a framework for ensuring that similar management is applied to similar risks. We used the best available data from a large and established cohort study to evaluate risks among WLHIV, and applied parametric survival models so that risk estimates did not change sharply when outcomes were sparse. Though many studies have examined cervical cancer screening in the WIHS, our study complements prior work by including additional data from new WIHS cohorts, restricting to the current eART era, and employing benchmarks that reflect true general

population risks. Our selection of CD4 cell count as an *a priori* factor for stratification of $_{b}$HSIL+ risks is supported by extensive research in the WIHS and other studies [2,3,7–11].

Our approach required that we apply risk benchmarking in two novel ways. First, we compared risks across populations (the WIHS and general population studies) that differ with regard to frequency of screening, $_{b}$HSIL+ outcome ascertainment, data quality, and statistical methods. Second, the time-to-benchmark approach that we used to suggest screening intervals is a novel application that was not previously established. Consistent with other benchmarking studies, we considered risk benchmarks to be measured without error [22,29,30], and we set screening intervals according to when these benchmarks were met or exceeded. However, with the first benchmark at 0.69% (3-year return), it could be argued that a higher threshold should be used before shortening the screening interval from 3 years, as the second benchmark was much higher (8.8% for 6–12mo return) – a matter for guideline committees to consider. Our risk benchmark estimates may be sensitive to the inclusion or exclusion of studies (e.g., non-U.S. studies were excluded). However, we believe that our approach of synthesizing risks from robust studies yielded the best available benchmarks to reflect the risk levels associated with general population screening guidelines in the United States. Finally, while we have identified some opportunities for tailoring screening by CD4 count at the time of cytology/HPV testing, there are other potential stratification factors that we did not consider. For example, $_{b}$HSIL+ risk is likely affected by a woman's cumulative history of immunosuppression (including the nadir CD4 value and duration of immunosuppression), and women with a previous history of $_{b}$HSIL+ (with or without treatment) may have higher risks and thus require more individualized management. Further, risk may also vary by age, particularly in unscreened women.

Considerable research has evaluated cervical HPV infection and abnormalities among WLHIV, but few studies have explicitly compared risks between WLHIV and general population women within a systematic framework oriented toward screening guidelines. Despite major differences from prior work, our analysis largely supported existing screening guidelines for WLHIV. We additionally found that CD4 cell count, measured at the time of a cervical cancer screening test, may have utility to inform some decisions about screening intervals and management. The impetus to include additional strata to refine screening practices, though, must be balanced against the goal to simplify and harmonize clinical guidelines. As HIV therapies and cervical cancer screening continue to evolve, optimal management will require ongoing evaluation of appropriate screening strategies in this population. The novel benchmarking approach used in this study could be a helpful new tool in this process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Author Contributions

HAR and GD conceived of and designed the study. HDS, LSM, CBP, TMD, HM, MJK, MF, JP, LF, LR, JM, SS, CC, and GD collected and/or managed the data. HAR analyzed the data with supervision by GD and additional input from HDS, LSM, and CBP. HAR and GD drafted the manuscript with input from HDS and LSM. All authors revised the manuscript and gave final approval.

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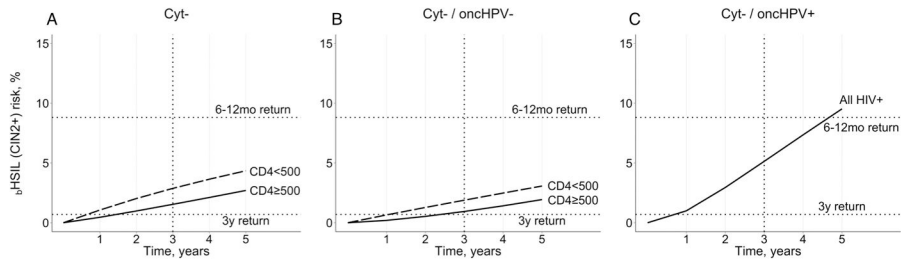

Figure 1.

Risk of cervical $_{b}$HSIL+ (CIN2+) among 2,049 women living with HIV (WLHIV) following negative cytology, by CD4 cell count at the time of cytology and oncogenic HPV status, compared to general population risk benchmarks for recommending women be re-screened in 3 years (3y return) or 6–12 months (6–12mo return). The Figure includes panels for: any oncogenic HPV result (positive, negative or unknown) (Fig 1A), oncHPV-negative (Fig 1B), or oncHPV-positive (Fig 1C). Calculation of risks following a co-test result (panels B and C) was restricted to 1,194 women aged 30 years and older.

Among WLHIV with negative cytology, there were 20 $_{b}$HSIL+ (CIN2+) events over 5 years among 1,042 women with CD4≥500 and 33 events among 985 women with CD4<500.

Among women with negative cytology and a negative oncHPV co-test, there were 9 $_{b}$HSIL+ events among 511 women with CD4≥500 and 15 events among 553 women with CD4<500.

Among women with negative cytology and a positive oncHPV co-test, there were 10 $_{b}$HSIL + events among 124 women. CD4 cell count was measured at the time of cytology and was unknown for 22 women.

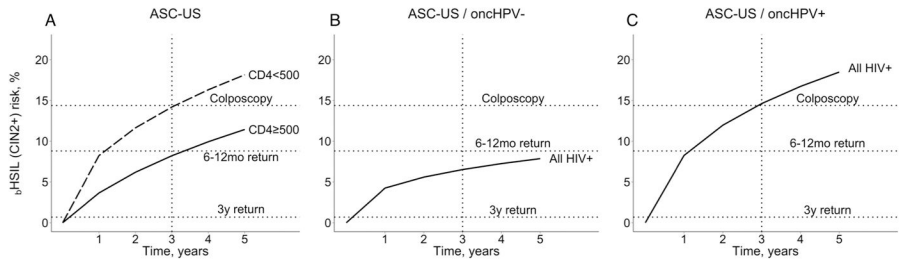

Figure 2.

Risk of cervical $_{b}$HSIL+ (CIN2+) among 374 women living with HIV (WLHIV) following ASC-US cytology, by CD4 cell count at the time of cytology and oncogenic HPV co-test status, compared to general population risk benchmarks for recommending women be re-screened in 3 years (3y return), 6–12 months (6–12mo return), or referred for immediate colposcopy. The Figure includes panels for: any oncogenic HPV result (positive, negative or unknown) (Fig 2A), oncHPV-negative (Fig 2B), or oncHPV-positive (Fig 2C). Calculation of risks following a co-test result (panels B and C) was restricted to 245 women aged 30 years and older.

Among WLHIV with ASC-US cytology, there were 10 $_{b}$HSIL+ (CIN2+) events over 5 years among 108 women with CD4≥500 and 41 events among 265 women with CD4<500.

Among women with ASC-US cytology and a negative HPV co-test, there were 12 $_{b}$HSIL+ events among 163 women. Among women with ASC-US cytology and a positive HPV co-test, there were 14 $_{b}$HSIL+ events among 82 women. CD4 cell count was measured at the time of cytology and was unknown for 1 woman.

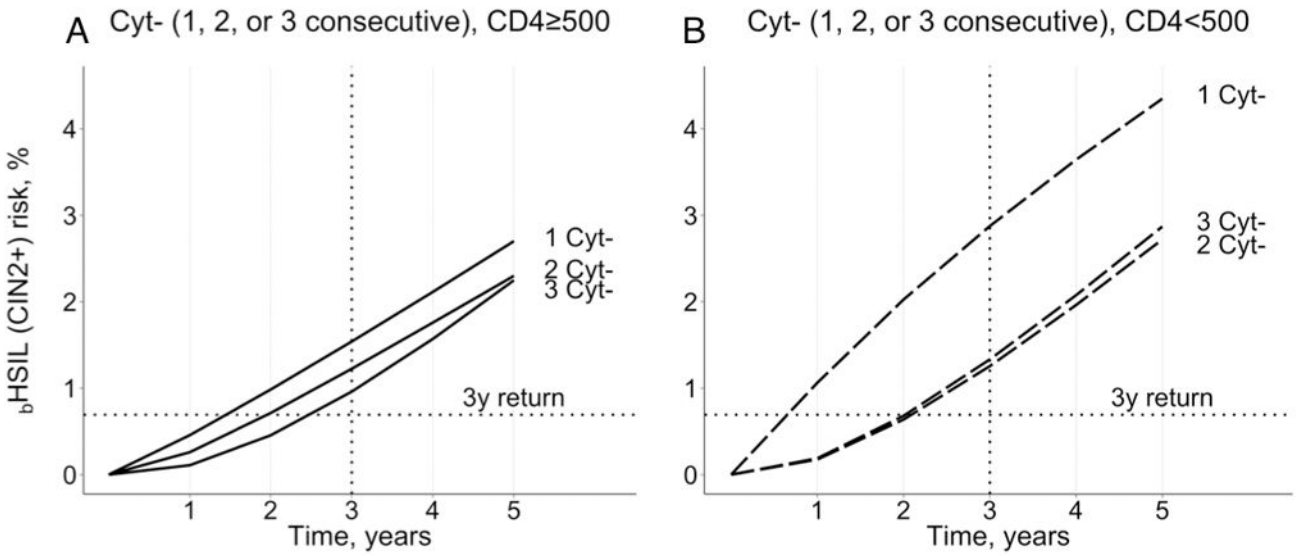

Figure 3.

Risk of cervical $_b$HSIL+ (CIN2+) among women living with HIV (WLHIV) following 1, 2, or 3 consecutive negative cytology results, by CD4 cell count at final cytology (≥500 Fig 3A, <500 Fig 3B), compared to a general population risk benchmark for recommending women be re-screened in 3 years (3y return).

Among WLHIV with CD4≥500, there were 1,042, 846, and 716 women with 20, 14, and 12 $_b$HSIL+ (CIN2+) events, respectively, for the analysis of 1, 2, and 3 consecutive negative cytology results. Among WLHIV with CD4<500, there were 985, 785, and 620 women with 33, 16, and 14 $_b$HSIL+ events, respectively, for analysis of 1, 2, and 3 consecutive negative cytology results.

Table 1

Descriptive characteristics of 2,423 women living with HIV in the Women's Interagency HIV Study with negative or ASC-US cytology at their first visit in 2000 or later

Characteristic	Negative cytology N (%)	ASC-US cytology N (%)	p-value
Total	2,049 (100)	374 (100)	
oncHPV status			<0.001
Negative	1,247 (60.9)	191 (51.1)	
Positive	159 (7.8)	103 (27.5)	
Unknown	643 (31.4)	80 (21.4)	
Age, years			0.046
20–29	243 (11.9)	62 (16.6)	
30–39	773 (37.7)	145 (38.8)	
40–49	744 (36.3)	123 (32.9)	
50 or older	289 (14.1)	44 (11.8)	
Race/ethnicity			0.66
Non-Hispanic Black	1,254 (61.2)	238 (63.6)	
Non-Hispanic White	259 (12.6)	39 (10.4)	
Hispanic	467 (22.8)	85 (22.7)	
Other	69 (3.4)	12 (3.2)	
WIHS enrollment cohort			<0.001
1994–95	932 (45.5)	189 (50.5)	
2001–02	509 (24.8)	116 (31.0)	
2011–12	215 (10.5)	34 (9.1)	
2013–15	393 (19.2)	35 (9.4)	
Current CD4 count (cells/μL) *			<0.001
≥500	1,042 (50.9)	108 (28.9)	
350–499	423 (20.6)	90 (24.1)	
200–349	359 (17.5)	88 (23.5)	
<200	203 (9.9)	87 (23.3)	
Missing	22 (1.1)	1 (0.3)	
Smoking status †			0.07
Current smoker	1,118 (54.6)	184 (49.3)	
Not a current smoker	930 (45.4)	189 (50.7)	
Ever ART			0.16
No	409 (20.0)	63 (16.8)	
Yes	1,640 (80.0)	311 (83.2)	
Length of follow-up, years (median, IQR)	6.9 (1.6–12.9)	5.0 (1.6–12.8)	0.12

ART, antiretroviral therapy; IQR, interquartile range. Percentages may not sum exactly to 100 due to rounding.

* If CD4 count was missing, we used the most recent CD4 count measured prior to the time of cytology (N=36, 1.5%), allowing a gap of up to 2 years.

[†]Missing for one woman.

Table 2

Summary of $_b$HSIL+ (CIN2+) risks among women living with HIV and the cervical cancer screening strategies suggested by this risk benchmarking approach.

Cytology	HPV	CD4	Observed $_b$HSIL+ (CIN2+) risk, % (95% CI) at: 1 year	2 years	3 years	Risk-based strategy	CDC guideline [14]
3 Negative	Unknown	≥500	0.11 (0–0.30)	0.45 (0.02–0.89)	0.96 (0.31–1.6)	3y return	3y return
		<500	0.19 (0–0.46)	0.68 (0.12–1.2)	1.3 (0.52–2.1)	2–3y return	
Negative	Negative	≥500	0.20 (0–0.51)	0.53 (0–1.1)	0.94 (0.21–1.7)	3y return	3y return
		<500	0.66 (0.08–1.2)	1.3 (0.47–2.1)	1.9 (0.87–2.9)	2y return *	
	Unknown	≥500	0.46 (0.10–0.81)	0.98 (0.44–1.5)	1.5 (0.83–2.3)	2y return	1y return
		<500	1.1 (0.51–1.6)	2.0 (1.2–2.8)	2.9 (1.9–3.9)	1y return	
	Positive	Any	1.0 (0–2.4)	3.0 (0.40–5.5)	5.1 (1.7–8.6)	1y return	1y return. Colposcopy if HPV16+ or HPV16/18+ †
ASC-US	Negative	Any	4.3 (1.6–6.9)	5.6 (2.4–8.8)	6.5 (2.9–10.1)	6–12mo return	(Not stated)
	Unknown	≥500	3.7 (0.62–6.7)	6.2 (2.2–10.2)	8.2 (3.3–13.2)	6–12mo return	6–12mo return
		350–499	6.9 (2.4–11.4)	9.0 (3.4–14.4)	10.4 (4.3–16.5)	6–12mo return	
		<350	8.9 (5.3–12.6)	13.1 (8.6–17.7)	16.4 (11.1–21.7)	Colposcopy	
	Positive	Any	8.3 (3.2–13.3)	12.0 (5.7–18.2)	14.6 (7.4–21.8)	Colposcopy	Colposcopy

Three-year risk benchmarks based on general population risks were 0.69% (3y return), 8.8% (6–12mo return), and 14.4% (colposcopy). Risks after combined cytology/HPV testing (co-testing) were calculated only among women aged 30 years and older, consistent with U.S. Preventive Services Task Force, American Cancer Society, and Centers for Disease Control and Prevention (CDC) guidelines. CD4 count was measured at the time of cytology/HPV testing.

$_b$HSIL+, biopsy-confirmed high grade squamous intraepithelial lesion or worse; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; WLHIV, women living with HIV; CDC, Centers for Disease Control and Prevention.

* We found that a 2-year return was more appropriate than a 1-year return for most women in this group (see Results).

† We did not have sufficient data to evaluate whether HPV16/18-specific results warrant colposcopy, as currently recommended in the CDC guidelines.