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

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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 with current Centers for Disease Control and Prevention (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.

Methods: We applied parametric survival models among 2423 WLHIV with negative or atypical squamous cell of undetermined significance (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. 'rescreening threshold'), a 6–12-month return (after ASC-US), and immediate colposcopy [after low-grade squamous intraepithelial lesion (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 with $CD4^+$ greater than 500 cells/μl and after either three negative cytology tests or a negative cytology/oncogenic human papillomavirus cotest (all 3-year risks≤1.3%); a 1-year return after negative cytology with either positive oncogenic human papillomavirus cotest (1-year risk = 1.0%) or $CD4^+$ cell count less than 500 cells/μl (1-year risk = 1.1%); and a 6–12-month return after ASC-US (3-year risk = 8.2% if $CD4^+$ cell count at least 500 cells/μl; 10.4% if $CD4^+$ cell count = 350–499 cells/μl). Other suggestions differed modestly from current guidelines, including colposcopy (vs. 6–12 month return) for WLHIV with ASC-US and $CD4^+$ cell count less than 350 cells/μl (3-year risk = 16.4%) and a lengthened 2-year (vs. 1-year) interval after negative cytology with $CD4^+$ cell count at least 500 cells/μl (2-year risk = 0.98%).

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Conclusions: Current cervical cancer screening guidelines for WLHIV are largely appropriate. $CD4^+$ cell count may inform risk-tailored strategies.

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Keywords: benchmarking, $CD4^+$, cervical cancer, cervical intraepithelial neoplasia, HIV, high-grade squamous intraepithelial neoplasia, precancer, risk, screening guidelines

Introduction

Women living with HIV (WLHIV) are at elevated risk of cervical cancer and precancer [1–3]. This risk has declined in recent years, possibly because of 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 US 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 cotesting [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 cotest [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, whereas the CDC recommends that WLHIV return for rescreening after 3 years [12–14]. After negative cytology alone, suggested intervals are 3 years for HIV-uninfected women compared with 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 with a parallel group of HIV-uninfected women who are at high risk of acquiring HIV [20]. Although 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, as 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 $CD4^+$ cell 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 with 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 rescreening (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 cotesting, 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, as 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 rescreening. Therefore, we estimated risk benchmarks at 3 years, and defined the 3-year return benchmark as the rescreening 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 3-year return benchmark. For consistency, we also estimated risk benchmarks at 3 years for a 6–12 month 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 substudy [7,18]. Conventional single-slide testing [26] and noncommercial type-specific HPV DNA L1 degenerate primer MY09/MY11/HMB01 PCR 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].

The 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, http://links.lww.com/QAD/B58).

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 and 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+ (if any) 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, http://links.lww.com/QAD/B58).

For risk following combined cytology and oncHPV (cotesting) 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 cotesting [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+ end point, 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 end point. 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 cotest], we stratified by $CD4^{+}$ cell count at the time of cytology using a standard threshold that was near the median ($\geq$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.

Role of the funding source

The 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, http://links.lww.com/QAD/B58) based on four estimates of risk after negative cytology among general population women [22,31,32] and HIV-uninfected WIHS women. The benchmarks warranting a 6–12 month return and immediate colposcopy were 8.8% (based on four studies of risk after ASC-US) and 14.4% (based on two studies of risk after LSIL), respectively.

For the cytology only analysis, we analyzed 2423 WLHIV in the WIHS, including 2049 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$^+$ cell count at least 500 cells/μl at the time of cytology, compared with only 29% of women with ASC-US cytology ($P < 0.001$). Most women contributed at least 5 years of follow-up. For risk following cotest results, we analyzed 1439 WLHIV, including 1070 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 oncogenic human papillomavirus testing

We compared $_b$HSIL+ risk among WLHIV with negative cytology with the general population

Table 1. Descriptive characteristics of 2423 women living with HIV in the Women's Interagency HIV Study with negative or atypical squamous cell of undetermined significance (ASC-US) cytology at their first visit in 2000 or later.

Characteristic	Negative cytology *N* (%)	ASC-US cytology *N* (%)	*P* value
Total	2049 (100)	374 (100)	
oncHPV status			<0.001
Negative	1247 (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	1254 (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$^+$ cell count (cells/μl)[a]			<0.001
≥500	1042 (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[b]			0.07
Current smoker	1118 (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

Percentages may not sum exactly to 100 because of rounding. ART, antiretroviral therapy; ASC-US, atypical squamous cell of undetermined significance; IQR, interquartile range; oncHPV, oncogenic human papillomavirus; WIHS, Women's Interagency HIV Study.
[a]If CD4$^+$ cell count was missing, we used the most recent CD4$^+$ cell count measured prior to the time of cytology ($N = 36$, 1.5%), allowing a gap of up to 2 years.
[b]Missing for one woman.

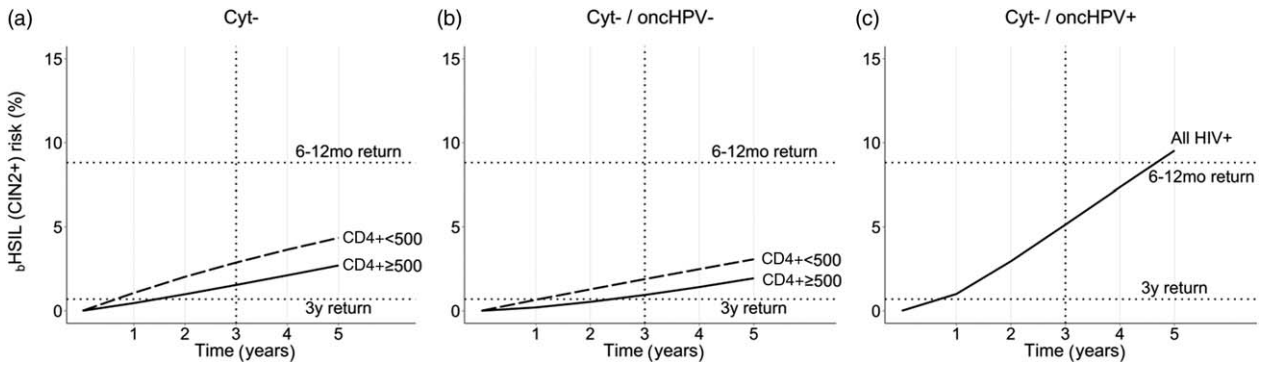

Fig. 1. Risk of cervical $_b$HSIL+ (CIN2+) among 2049 WLHIV following negative cytology (Cyt-), by CD4$^+$ cell count at the time of cytology and oncogenic HPV status, compared with general population risk benchmarks for recommending women be rescreened in 3 years (3-year return) or 6–12 months (6–12-month return). The figure includes panels for: (a) any oncogenic HPV result (positive, negative, or unknown), (b) oncHPV negative, or (c) oncHPV positive. Calculation of risks following a cotest result (panels b and c) was restricted to 1194 women aged 30 years and older. $_b$HSIL+, biopsy-confirmed cervical high-grade squamous intraepithelial neoplasia or worse; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; oncHPV, oncogenic human papillomavirus; WLHIV, women living with HIV. Among WLHIV with negative cytology, there were 20 $_b$HSIL+ (CIN2+) events over 5 years among 1042 women with CD4$^+$ cell count at least 500 cells/μl and 33 events among 985 women with CD4$^+$ cell count less than 500 cells/μl. Among women with negative cytology and a negative oncHPV cotest, there were nine $_b$HSIL+ events among 511 women with CD4$^+$ cell count at least 500 cells/μl and 15 events among 553 women with CD4$^+$ cell count less than 500 cells/μl. Among women with negative cytology and a positive oncHPV cotest, 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.

benchmarks. After a single negative cytology result (Fig. 1a), WLHIV with CD4$^+$cell count at least 500 cells/μl (measured concurrently with cytology) first exceeded the 3-year 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$^+$ cell count less than 500 cells/μl, 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$^+$ cell count at least 500 cells/μl may be able to safely return for rescreening in 2 years, whereas risk among women with CD4$^+$ cell count less than 500 cells/μl warrants a 1-year return.

Risks were lower among women with a concurrent negative cytology and oncHPV test (negative cotest; Fig. 1b). For WLHIV with CD4$^+$ cell count at least 500 cells/μl, risk first exceeded the 0.69% 3-year return benchmark at 3 years [3-year risk = 0.94 (95% CI 0.21–1.7%)]. Among WLHIV with CD4$^+$ cell count less than 500 cells/μl, 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$^+$ cell count less than 200 cells/μl (1-year risk = 1.6%), but more moderate among the larger group with CD4$^+$ cell count 200–499 cells/μl (1 and 2-year risks = 0.33% and 0.90%, respectively). These data thus suggest that risk is low following a negative cotest, consistent with a suggested 3-year return in WLHIV with CD4$^+$ cell count more than 500 cells/μl and possibly a 2-year return in WLHIV with CD4$^+$ cell count less than 500 cells/μl.

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

Atypical squamous cell of undetermined significance cytology with or without oncogenic human papillomavirus testing

After ASC-US cytology (Fig. 2a), the 3-year $_b$HSIL+ risk among WLHIV with CD4$^+$ cell count at least 500 cells/μl was 8.2% (95% CI 3.3–13.2%), approximating the 6–12-month return benchmark of 8.8%. Women with CD4$^+$ cell count less than 500 cells/μl 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$^+$ cell count less than 350 cells/μl (3-year risk = 16.4% [95% CI 11.1–21.7%], Supplemental Figure 2, http://links.lww.com/QAD/B58). This suggests that appropriate management strategies for women with ASC-US and unknown oncHPV status are repeat cytology in 6–12-months for women with current CD4$^+$ cell count at least 350 cells/μl, as currently recommended. For

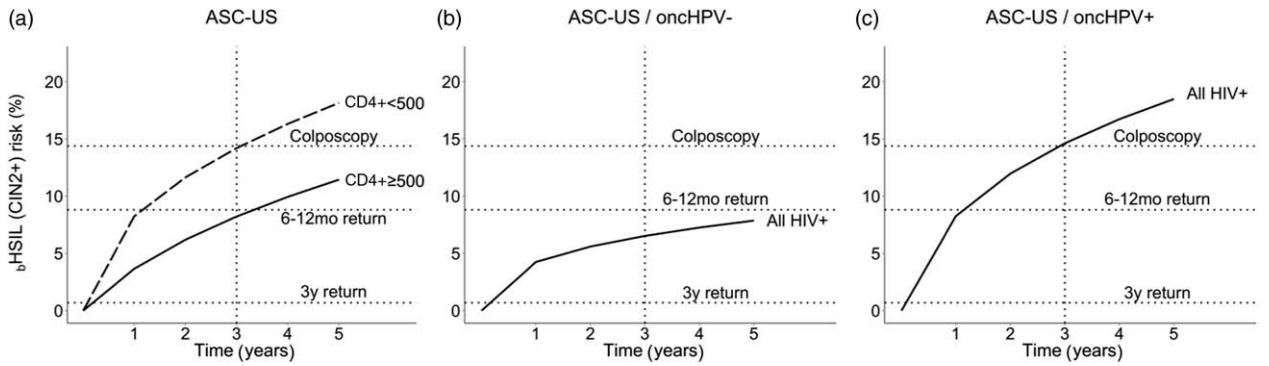

Fig. 2. Risk of cervical $_b$HSIL+ (CIN2+) among 374 WLHIV following ASC-US cytology, by CD4$^+$ cell count at the time of cytology and oncogenic HPV cotest status, compared with general population risk benchmarks for recommending women be rescreened in 3 years (3-year return), 6–12 months (6–12-month return), or referred for immediate colposcopy. The figure includes panels for: (a) any oncogenic HPV result (positive, negative, or unknown), (b) oncHPV negative, or (c) oncHPV positive. Calculation of risks following a cotest result (panels b and c) was restricted to 245 women aged 30 years and older. ASC-US, atypical squamous cell of undetermined significance; $_b$HSIL+, biopsy-confirmed cervical high-grade squamous intraepithelial neoplasia or worse; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; oncHPV, oncogenic human papillomavirus; WLHIV, women living with HIV. Among WLHIV with ASC-US cytology, there were 10 $_b$HSIL+ (CIN2+) events over 5 years among 108 women with CD4$^+$cell count at least 500 cells/μl. and 41 events among 265 women with CD4$^+$ cell count less than 500 cells/μl. Among women with ASC-US cytology and a negative HPV cotest, there were 12 $_b$HSIL+ events among 163 women. Among women with ASC-US cytology and a positive HPV cotest, there were 14 $_b$HSIL+ events among 82 women. CD4$^+$ cell count was measured at the time of cytology and was unknown for one woman.

WLHIV with CD4$^+$ cell count less than 350 cells/μl, it may be appropriate to consider immediate colposcopy.

Following ASC-US cytology combined with a negative oncHPV test (Fig. 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 3-year 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 (Fig. 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 6–12-month return following an ASC-US/oncHPV-negative cotest, but immediate colposcopy following an ASC-US/oncHPV-positive cotest.

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 3-year return risk benchmark. After three consecutive negative cytology results, for WLHIV with CD4$^+$ cell count at least 500 cells/μl (measured at the third cytology), the 3-year return benchmark (0.69%) was first exceeded at 3 years [3-year risk = 0.96% (95% CI 0.31–1.6%); Fig. 3a]. For WLHIV with CD4$^+$ cell count less than 500 cells/μl, risk appeared slightly higher, matching the benchmark at 2 years [2-year risk = 0.68% (95% CI 0.12–1.2%), Fig. 3b]; however, CIs were wide and also included the benchmark at 3 years. This suggests that risk after three consecutive negative cytology results is low for all women, consistent with a suggested return after 3 years in women with CD4$^+$ cell count at least 500 cells/μl. For women with CD4$^+$ cell count less than 500 cells/μl, a return after 2 years might be considered. Of note, among women with CD4$^+$ cell count at least 500 cells/μl, each additional negative cytology result suggested reduced risk (Fig. 3a), whereas among women with CD4$^+$ cell count less than 500 cells/μl, risks after two and three negative results were equivalent (Fig. 3b).

Results based on outcome of cervical intraepithelial neoplasia grade 3 or higher

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, http://links.lww.com/QAD/B58). The risk benchmarks for CIN3+ included the same studies as for CIN2+ (Supplemental Table 1, http://links.lww.com/QAD/B58) and were 0.36% (3-year return), 3.4% (6–12-month return), and 4.7% (colposcopy; Supplemental Figure 2, http://links.lww.com/QAD/B58). CIs 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 cotest), where benchmarks were reached more quickly using CIN3+. Apart from this, strategies suggested by CIN3+ were the same as for CIN2+.

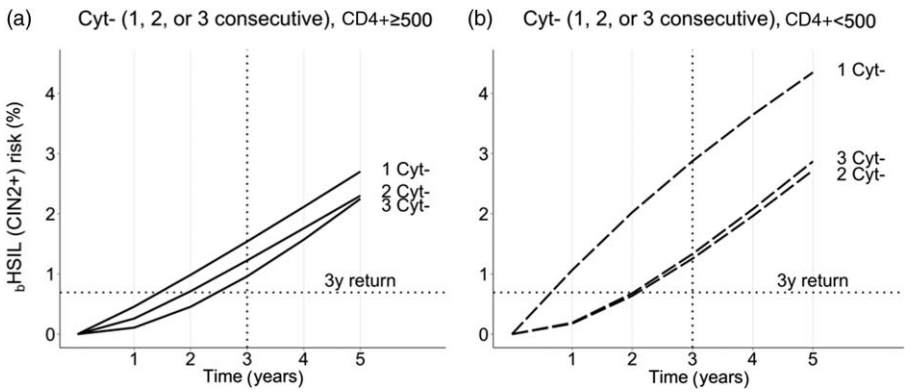

Fig. 3. Risk of cervical $_b$HSIL+ (CIN2+) among WLHIV following one, two, or three consecutive negative cytology results (Cyt-), by CD4$^+$ cell count at final cytology: (a) at least 500 cells/μl; (b) less than 500 cells/μl, compared with the general population risk benchmark for recommending women be rescreened in 3 years (3-year return). $_b$HSIL+, biopsy-confirmed cervical high-grade squamous intraepithelial neoplasia or worse; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; WLHIV, women living with HIV. Among WLHIV with CD4$^+$ cell count at least 500 cells/μl, there were 1042, 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$^+$ cell count less than 500 cells/μl, there were 985, 785, and 620 women with 33, 16, and 14 $_b$HSIL+ (CIN2+) events, respectively, for analysis of 1, 2, and 3 consecutive negative cytology results.

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$^+$ cell count could be further explored for tailoring screening intervals or management strategies.

Table 2. Summary of biopsy-confirmed cervical high-grade squamous intraepithelial neoplasia or worse (cervical intraepithelial neoplasia grade 2 or higher) risks among women living with HIV and the cervical cancer screening strategies suggested by this risk benchmarking approach.

Cytology	oncHPV	CD4$^+$ cell count	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)	3-year return	3-year return
		<500	0.19 (0–0.46)	0.68 (0.12–1.2)	1.3 (0.52–2.1)	2–3-year return	
Negative	Negative	≥500	0.20 (0–0.51)	0.53 (0–1.1)	0.94 (0.21–1.7)	3-year return	3-year return
		<500	0.66 (0.08–1.2)	1.3 (0.47–2.1)	1.9 (0.87–2.9)	2-year return[a]	
	Unknown	≥500	0.46 (0.10–0.81)	0.98 (0.44–1.5)	1.5 (0.83–2.3)	2-year return	1-year return
		<500	1.1 (0.51–1.6)	2.0 (1.2–2.8)	2.9 (1.9–3.9)	1-year return	
	Positive	Any	1.0 (0–2.4)	3.0 (0.40–5.5)	5.1 (1.7–8.6)	1-year return	1-year return[b]
ASC-US	Negative	Any	4.3 (1.6–6.9)	5.6 (2.4–8.8)	6.5 (2.9–10.1)	6–12-month return	(Not stated)
	Unknown	≥500	3.7 (0.62–6.7)	6.2 (2.2–10.2)	8.2 (3.3–13.2)	6–12-month return	6–12-month return
		350–499	6.9 (2.4–11.4)	9.0 (3.4–14.4)	10.4 (4.3–16.5)	6–12-month 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% (3-year return), 8.8% (6–12-month return), and 14.4% (colposcopy). Risks after combined cytology/HPV testing (cotesting) were calculated only among women aged 30 years and older, consistent with US Preventive Services Task Force, American Cancer Society, and CDC guidelines. CD4$^+$ cell count was measured at the time of cytology/HPV testing. $_b$HSIL+, biopsy-confirmed high grade squamous intraepithelial lesion or worse; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; CDC, Centers for Disease Control and Prevention; oncHPV, oncogenic human papillomavirus.
[a]We found that a 2-year return was more appropriate than a 1-year return for most women in this group (see results section).
[b]Colposcopy if HPV16+ or HPV16/18+ suggested. We did not have sufficient data to evaluate this portion of the guideline.

Our analysis identified that some WLHIV have low $_b$HSIL+ risks. For WLHIV with negative cytology, a negative oncHPV cotest, and a $CD4^+$ cell count at least 500 cells/μl, as well as for WLHIV with three consecutive negative cytology results and a $CD4^+$ cell count at least 500 cells/μl, risks of precancer were low (<1% at 3 years). Although these risks were still modestly above the benchmark for a 3-year return (0.69%), their CIs included this benchmark, whereas they definitively excluded the 6–12-month return benchmark of 8.8% (upper bounds≤1.7%). A previous study of cotest-negative WLHIV in the WIHS identified only one case of $_b$HSIL+ over 5 years, but did suggest higher risk of LSIL among WLHIV with lower $CD4^+$ cell counts [18]. Our study, which includes a larger number of WLHIV, suggests that some portion of these LSIL will lead to $_b$HSIL.

Further, our results suggested that WLHIV with lower $CD4^+$ cell counts may benefit from more frequent screening than those with higher $CD4^+$ cell counts. Even when cotesting is used, our approach suggested WLHIV with a $CD4^+$ cell count less than 500 cells/μl may have higher $_b$HSIL risk than WLHIV with $CD4^+$ cell count at least 500 cells/μl. The small group of WLHIV with $CD4^+$ cell count less than 200 cells/μl 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 $CD4^+$ cell count less than 350 cells/μl indicates similarly high risk, whereas women with higher $CD4^+$ cell 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 $CD4^+$ cell 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 $CD4^+$ cell counts could affect a large proportion of WLHIV [35,36]. It is unclear whether eART itself (independent of its effect on $CD4^+$ cell 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 $CD4^+$ cell 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 6–12-month 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-US 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, although we have identified some opportunities for tailoring screening by $CD4^+$ cell 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 $CD4^+$ cell count 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.

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Conflicts of interest

There are no conflicts of interest.

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