

The Costs, Clinical Benefits, and Cost-Effectiveness of Screening for Cervical Cancer in HIV-Infected Women

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Background: Women with HIV infection have a higher risk for cervical squamous intraepithelial lesions than do women without HIV infection, and the optimal regimen for cervical cancer screening in these women is uncertain.

Objective: To assess the net health consequences, costs, and cost-effectiveness of various screening strategies for cervical neoplasia and cancer in HIV-infected women.

Design: A cost-effectiveness analysis from a societal perspective done by using a state-transition Markov model. Values for incidence, progression, and regression of cervical neoplasia; efficacy of screening and treatment; progression of HIV disease; mortality from HIV infection and cancer; quality of life; and costs were obtained from the literature.

Setting: Simulated clinical practice in the United States.

Patients: HIV-infected women representative of the U.S. population.

Intervention: Six main screening strategies—no screening, annual Papanicolaou smears, annual Papanicolaou smears after two negative smears obtained 6 months apart (recommended by the Centers for Disease Control and Prevention), semiannual Papanicolaou smears, annual colposcopy, and semiannual colposcopy—were considered.

Measurements: Quality-adjusted life-years (QALYs), lifetime costs, and incremental cost-effectiveness.

Results: Annual Papanicolaou smear screening resulted in a 2.1-month gain in quality-adjusted life expectancy for an incremental cost of \$12 800 per QALY saved. Annual Papanicolaou smear screening after two negative smears obtained 6 months apart provided an additional 0.04 QALYs at a cost of \$14 800 per QALY saved. Semiannual Papanicolaou smear screening provided a further 0.17 QALYs at a cost of \$27 600 per QALY saved. Annual colposcopy cost more but provided no additional benefit compared with that given by semiannual Papanicolaou smear screening, and semiannual colposcopy exceeded \$375 000 per QALY saved. Results were most sensitive to the rate of progression of neoplasia to invasive cancer.

Conclusions: In HIV-infected women, cervical cancer screening with annual Papanicolaou smears after two negative smears obtained 6 months apart offers quality-adjusted life expectancy benefits at a cost comparable to that of other clinical preventive interventions.

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More than 100 000 women are estimated to be living with HIV infection in the United States (1, 2). These women have an increased risk for anogenital human papillomavirus (HPV) infection and HPV-induced cervical squamous intraepithelial lesions (3–5). The prevalence of cervical dysplasia in HIV-infected women ranges from 11% to 60%, varying with the severity of immunosuppression (6–13). In a large, ongoing, prospective cohort study (14), abnormal results on cytologic examination were reported in 38% of 1680 HIV-infected women. The recurrence rate of cervical neoplasia may exceed 50% in HIV-infected women, whereas it is only 10% in non-HIV-infected women (15–19).

In 1993, the U.S. Centers for Disease Control and Prevention (CDC) included cervical cancer among AIDS-defining conditions (20). The CDC recommends initial screening with two Papanicolaou smears obtained 6 months apart, followed by annual screening if the results of both initial tests are normal (21). Others (22, 23) have recommended semiannual Papanicolaou smears, annual colposcopy, and even semiannual colposcopy. We estimated the clinical benefits (in life expectancy and quality-adjusted life expectancy), costs (in U.S. dollars), and cost-effectiveness of several strategies for cervical cancer screening in HIV-infected women.

Methods

The Model

We developed a state-transition Markov model to simulate cervical cancer screening, diagnosis, and treatment in hypothetical cohorts of HIV-infected women in order to calculate the lifetime costs, life expectancy, and quality-adjusted life expectancy associated with various strategies for cervical cancer screening. The main strategies considered were no screening, annual Papanicolaou smears, annual Papanicolaou smears after two initial smears obtained 6 months apart (the CDC screening strategy), semiannual Papanicolaou smears, annual colposcopy, and semiannual colposcopy. We evaluated lifetime screening strategies for three groups of women according to CD4 cell count at presentation: women with a CD4 cell count greater than 500 cells/mm³, women with CD4 cell counts of 200 to 500 cells/mm³, and women with CD4 cell counts less than

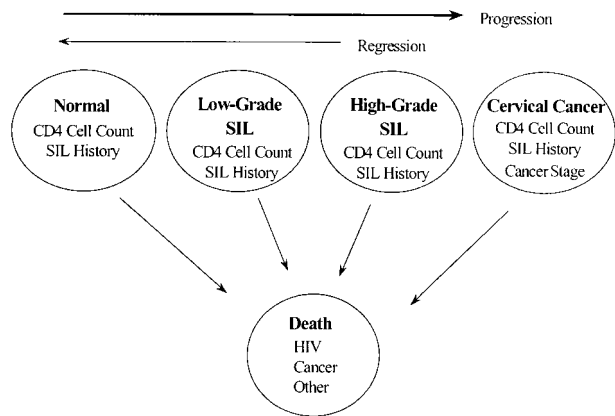


Figure 1. Overview of the Markov model. The model has five broad categories of states: normal, low-grade squamous intraepithelial lesions (SIL), high-grade SIL, cervical cancer, and death. Each cervical health state is stratified by CD4 cell count and history of cervical neoplasia. Cancer states are further stratified by stage of cervical cancer. Death may result from an acute or chronic AIDS-related condition, cervical cancer, or other causes.

200 cells/mm³. The comparative performance of alternative strategies was measured by using the incremental cost-effectiveness ratio (defined as the additional cost of a specific screening strategy divided by its additional clinical benefit, compared with the next least expensive strategy). The base-case estimates were varied in univariate and multivariate sensitivity analyses to determine how changes in estimated values affected the results. We adopted a societal perspective and followed the reference-case recommendations of the Panel on Cost-Effectiveness in Health and Medicine (24).

Women representative of the HIV-infected population in the United States start in the Markov model in health states defined by HIV and cervical status (**Figure 1**). The five broad categories of cervical health are no neoplasia or cancer, low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions, local invasive cancer (stage 1), and regional or distant invasive cancer (stages 2, 3, and 4). Each of these categories is further stratified by CD4 cell count and history of cervical neoplasia. The three CD4 count strata are greater than 500 cells/mm³, 200 to 500 cells/mm³, and less than 200 cells/mm³.

The model uses transition probabilities established from the literature to move women through different health states over time. The time horizon of the analysis is divided into equal increments, referred to as Markov cycles, during which women may “transition” from one state to another. For example, in any given month, a woman may have progression or regression of cervical disease, HIV disease, or both. Although the probability of progression of HIV disease is independent of cervical disease, the progression of cervical neoplasia is modeled as dependent on the stage of HIV disease. Women in the earliest stages of HIV disease have

the lowest risk for cervical disease, and those with advanced immunosuppression are at the highest risk for cervical disease (7–10, 12, 14). Each month, women face competing mortality risks from HIV disease, cervical cancer, or other causes.

To estimate the effect of screening on the natural history of cervical neoplasia, the model distinguishes between detected and undetected cervical disease. In a designated screening month, a woman who has a positive test result moves temporarily to a detected state and undergoes a diagnostic work-up (25, 26). A woman with a true-positive result is treated and returns to a cervical disease-free state but retains her history of treated neoplasia. Her subsequent probability of cervical disease depends on both her stage of HIV disease and her history of neoplasia. A woman with a false-positive result accrues the costs and possible morbidity of a diagnostic work-up but returns to a cervical disease-free state, where her subsequent probability of cervical disease depends only on her stage of HIV disease. Screening may also detect invasive cervical cancer at an earlier stage, permitting the benefit of a more favorable prognosis (27).

Clinical Data

A range of clinical data was required to establish the natural history of cervical and HIV disease; the operating characteristics of screening tests; the effectiveness of early intervention; mortality from invasive cancer, AIDS, and other causes; and direct health care costs associated with cervical screening, cervical disease, and HIV disease. **Table 1** summarizes the variable estimates and plausible ranges used for the base-case analysis.

Natural History of Cervical Neoplasia

We estimated the incidence, progression, and regression of low-grade and high-grade squamous intraepithelial lesions on the basis of the published literature (8, 29–43). When multiple estimates were available for a particular variable, preference was given to estimates from studies with larger samples, well-defined control groups, and longer follow-up periods (86). Although the health states in the model were not stratified by HPV type, the transition probabilities for incidence and progression were based on data that reflect the combined effect of HPV and HIV-induced immunosuppression on risk for neoplasia. Women with CD4 cell counts greater than 500 cells/mm³ were conservatively assumed to have the same risk for progression and regression of cervical disease as non-HIV-infected women with similar risk factors (44–49, 77–81). We evaluated the implications of higher recurrence rates of cervical neoplasia in a sensitivity analysis (15–17).

Table 1. Natural History Variables*

Variable	Base Case (Range) [†]			Reference
	CD4 Cell Count >500 cells/mm ³	CD4 Cell Count 200–500 cells/mm ³	CD4 Cell Count <200 cells/mm ³	
Baseline prevalence, %				7–9, 11, 12, 14, 28–35
ASCUS [‡]	12.3	13.4	19.5	
LGSIL [§]	2.4	9.6	16.5	
HGSIL [§]	1.3	2.0	4.0	
Invasive cancer	0	0.1	0.2	
Progression rate (per 100)				
Normal to LGSIL	0.016 (0.08–0.24)	0.67 (0.16–2.60)	0.67 (0.16–2.60)	8, 30, 36–38
LGSIL to HGSIL	0.73 (0.36–1.10)	2.93 (2.00–3.80)	2.93 (2.00–3.80)	8, 38–43
HGSIL to early invasive cancer	2.0 (1.0–3.0)	2.42	2.42	–¶
Early invasive cancer to late invasive cancer	4.03 (2.00–6.00)	4.03 (2.00–6.00)	4.03 (2.00–6.00)	–¶
Regression rate (per 100)**				
LGSIL to normal	2.99 (1.49–4.5)	2.99 (1.49–4.5)	2.99 (1.49–4.5)	8, 38, 44–48
HGSIL to normal	0.30 (0.15–0.45)	0.30 (0.15–0.45)	0.30 (0.15–0.45)	8, 49
Symptoms (annual rate) ^{††}				
Late invasive cancer	0.80 (0.64–0.96)	0.80 (0.64–0.96)	0.80 (0.64–0.96)	
Five-year cancer survival rate ^{‡‡}				27
Invasive cancer, early (local)	0.86	0.86	0.86	
Invasive cancer, late (regional)	0.43	0.43	0.43	
Invasive cancer, late (distant)	0.11	0.11	0.11	
Natural history of HIV disease ^{§§}				
Mean duration of HIV stage, y	5.52	3.63	3.26	50–52
Mortality rate (per 100)	0.0023	0.2787	2.2373	53
HIV monthly care, \$	345 (173–518)	525 (263–788)	2658 (1329–3987) ^{¶¶}	54–57
Papanicolaou smear				12, 58–63
Sensitivity, %	70 (60–90)	70 (60–90)	70 (60–90)	
Specificity, %	90 (85–95)	90 (85–95)	90 (85–95)	
Colposcopy (biopsy/cytologic examination) ^{***}				62, 64–68
Sensitivity, %	95 (85–99)	95 (85–99)	95 (85–99)	
Specificity, %	91 (85–100)	91 (85–100)	91 (85–100)	
Screening costs, \$				69
Papanicolaou smear	24 (18–100)	24 (18–100)	24 (18–100)	
Colposcopy and biopsy	180 (100–320)	180 (100–320)	180 (100–320)	
Work-up and treatment costs, \$				69–73
LGSIL	1118 (559–1677)	1118 (559–1677)	1118 (559–1677)	
HGSIL	4597 (2299–6896)	4597 (2299–6896)	4597 (2299–6896)	
Invasive cervical cancer	15 759–22 843 (7880–34 260)	15 759–22 843 (7880–34 260)	15 759–22 843 (7880–34 260)	
Patient time costs, h ^{†††}	11.75 (6–18)	11.75 (6–18)	11.75 (6–18)	74, 75

* ASCUS = atypical squamous cells of uncertain significance; HGSIL = high-grade squamous intraepithelial lesions; LGSIL = low-grade squamous intraepithelial lesions; SEER = Surveillance, Epidemiology, and End Results. Rates are reported as monthly rates, unless otherwise noted, and are converted into monthly probabilities.

† If no plausible range is specified, the variable was varied \pm 50% in sensitivity analysis.

‡ We assumed that 15% of women with CD4 cell counts > 500 cells/mm³ and 38% of women with CD4 cell counts < 500 cells/mm³ who have ASCUS on cervical cytologic examination have underlying cervical neoplasia (25).

§ The term LGSIL replaces the term *cervical intraepithelial neoplasia I*; the term HGSIL replaces the terms *cervical intraepithelial neoplasia II and III* and *carcinoma in situ*.

¶ Assumes 40% early invasive cancer (stage I) and 60% late invasive cancer (stages II, III, or IV) (27, 76).

¶¶ Estimated by a separate Markov model developed to simulate the natural history of cervical neoplasia in HIV-negative women. Using published rates of incidence, progression, and regression of neoplasia (47, 71, 77–81), we derived the progression rate of HGSIL to early invasive cancer that would be required to match the U.S. incidence of cervical cancer (27).

** Corresponds to an annual regression rate of LGSIL of 15% to 60% and of HGSIL of 0% to 10%, depending on HIV stage (8, 44–48).

†† On the basis of a previous published analysis (70), we assumed that 80% of women with late cancer would develop symptoms within 1 year, and we derived the estimate of 10% for early invasive cancer by using our Markov model created for HIV-negative women calibrated to match SEER registry data, adjusting for 60% screened population (82).

‡‡ Stage-specific survival rates reported in SEER registry data were modified to reflect the racial distribution of HIV-infected women in the United States (27, 76).

§§ The impact of newer treatment on decreased HIV-related morbidity and mortality was evaluated in sensitivity analysis by using data from two clinical trials of highly active antiretroviral therapy (83–85).

||| A cost-to-charge ratio of 0.5995 was applied to convert charges to costs to approximate the true cost of resource use, based on Medicare data on hospital-specific ratios (54, 57).

¶¶ Weighted average of the cost of AIDS, with CD4 cell count < 200 cells/mm³, and asymptomatic HIV infection with CD4 cell count < 200 cells/mm³.

*** Includes cytologic examination if no abnormality is found on colposcopic examination. In contrast to screening colposcopy, a diagnostic colposcopy was assumed to be a perfect test.

††† Average total time was estimated, incorporating travel, waiting time, and direct care: 55 minutes for Papanicolaou screening, 2 hours for colposcopy screening, 4 hours for diagnosis and treatment of LGSIL, 8 hours for diagnosis and treatment of HGSIL, and 40 to 112 hours for invasive cervical cancer depending on stage. Time costs were based on average wage rates derived from U.S. mean annual earnings tables (74). Travel and waiting times were estimated from the 1987 National Medical Expenditure Survey (75).

Natural History of HIV Disease

Estimates of the natural progression of HIV disease and the mortality attributable to it were based on data from the San Francisco City Clinic Cohort and the Multicenter AIDS cohort study (50–53). Although these studies included mainly men, the mean duration of each stage of HIV disease predicted by the model was consistent with that in studies of the natural history of HIV infec-

tion in women (87–91). Because these studies relied on less intensive use of antiretroviral therapy than is now standard, we used more recent data to project the impact of highly active antiretroviral therapy on the results, incorporating decreased HIV-related morbidity and mortality and a slower rate of HIV progression (83–85, 92). Because the impact of highly active antiretroviral therapy on both HPV-mediated cervical disease and long-term survival is

uncertain (93), we present this analysis as a sensitivity analysis.

Test Characteristics

Estimates of the diagnostic performance of Papanicolaou smears in HIV-infected women vary (64, 94–97). Because the discriminatory ability of the Papanicolaou smear has recently been reported to be comparable in HIV-infected women and non-HIV-infected women, we used a sensitivity of 70% and a specificity of 90% (12, 59, 60, 96).

We distinguished between screening and diagnostic colposcopy in terms of both efficacy and cost. We assumed that screening colposcopy would include gross examination of the cervix, biopsy of visible lesions, and cervical cytologic examination if no lesions were seen. Although such screening colposcopy has greater sensitivity than the Papanicolaou smear alone, it has been documented to produce false-negative results (26). In addition, false-positive results may occur because a woman without disease may have a cervix with an abnormal appearance (64–66, 98). Diagnostic colposcopy, performed on a woman with an abnormal screening test result, includes colposcopy, endocervical curettage (if there is a discrepancy between the Papanicolaou smear and the colposcopic appearance or if the transformation zone is not well visualized), and cervical biopsies.

Health-Related Quality of Life

The incorporation of morbidity and mortality consequences into a single measure was accomplished by using quality-adjusted life-years (QALYs). No published studies have used preference-weighted scales to assess quality of life in women with both cervical cancer and HIV disease. The quality weights used for the base case were based on those used by Freedberg and coworkers (54) for health states characterized by CD4 cell counts greater than 200 cells/mm³ (0.94) and less than 200 cells/mm³ (0.84). We used a quality weight of 0.56 for women with HIV infection and regional or distant cervical cancer; this was derived from the same study (54) for a health state that included AIDS and AIDS-related cancer. We assumed that health-related quality of life would be greater with HIV infection and local cancer (0.65).

Costs

The costs of cervical cancer screening, diagnosis, and treatment protocols were estimated by applying Medicare average allowed charges (69, 99) to treatment algorithms outlined by Muller and colleagues (71). We modified these algorithms, replacing cryotherapy with laser therapy and loop electrosurgical excision, as others have done (72). Although we

incorporated time costs associated with the screening, diagnosis, and treatment of neoplasia and cancer (74, 75), the productivity costs of early morbidity and mortality were assumed to be captured in the quality adjustment of the life expectancy gains (24).

Costs of monthly HIV care were based on estimates from the AIDS Cost and Services Utilization Survey (55, 56), which did not include the costs of current antiretroviral regimens. In our sensitivity analysis of highly active antiretroviral therapy, we incorporated the costs of zidovudine, indinavir, lamivudine, and quarterly viral load testing and the savings associated with decreased progression to AIDS and AIDS-related morbidity (83, 100). All costs were updated to 1996 dollars by using the medical care component of the consumer price index from the Bureau of Labor Statistics (101).

Role of the Funding Source

The agencies funding our study had no role in the collection, analysis, or interpretation of data or in the decision to publish the study results.

Results

Base-Case Analysis

Because most HIV-infected women in the United States present to the medical system with CD4 cell counts of 200 to 500 cells/mm³ (1), we present this analysis as the base-case analysis (**Table 2**). With no screening, discounted lifetime costs were \$71 060 and quality-adjusted life expectancy was 62.40 months. The least aggressive nondominated option, annual Papanicolaou smear screening, increased quality-adjusted life expectancy by 2.51 months and increased total costs by \$2680, resulting in an incremental cost-effectiveness ratio of \$12 800 per QALY saved. Annual Papanicolaou smear screening after two smears obtained 6 months apart (the CDC screening strategy) offered an incremental benefit of 0.04 QALYs with an incremental cost-effectiveness ratio of \$14 800 per QALY saved compared with annual Papanicolaou smear screening. Semiannual Papanicolaou smear screening had an incremental cost-effectiveness ratio of \$27 600 per QALY saved compared with the CDC strategy. Annual colposcopy cost more but was no more effective than semiannual Papanicolaou smear screening and was therefore dominated. The most effective strategy, semiannual colposcopy, provided an additional 0.07 quality-adjusted months (2.1 quality-adjusted days) compared with semiannual Papanicolaou smear screening and cost more than \$375 000 per QALY saved. Results of the analysis unadjusted for health-

Table 2. Costs, Quality-Adjusted Life Expectancy, and Cost-Effectiveness Associated with Cervical Cancer Screening Strategies*

Screening Strategy in HIV-Infected Women	Costs	Life Expectancy	Incremental Cost-Effectiveness Ratio†	QALYs	Incremental Cost-Effectiveness Ratio†
	\$	mo	\$/YLS	mo	\$/QALY
Lifetime screening, CD4 cell count of 200 to 500 cells/mm ³ ‡					
No screening	71 060	69.28	–	62.40	–
Annual Papanicolaou smear	73 740	72.15	11 200	64.91	12 800
CDC strategy§	73 790	72.19	13 100	64.95	14 800
Semiannual Papanicolaou smear	74 180	72.39	24 200	65.12	27 600
Annual colposcopy	74 910	72.37	Dominated	65.11	Dominated
Semiannual colposcopy	76 350	72.47	329 900	65.19	375 200
Lifetime screening, CD4 cell count > 500 cells/mm ³ ¶					
No screening	70 210	110.70	–	102.92	–
Biennial Papanicolaou smear	72 430	113.56	9300	105.48	10 400
Annual Papanicolaou smear	73 080	114.25	11 400	106.09	12 800
CDC strategy§	73 130	114.29	14 400	106.13	15 800
Semiannual Papanicolaou smear	73 780	114.50	35 900	106.32	40 300
Annual colposcopy	74 790	114.49	Dominated	106.30	Dominated
Semiannual colposcopy	77 070	114.59	484 600	106.39	540 000
Lifetime screening, CD4 cell count < 200 cells/mm ³ ‡					
No screening	75 410	37.94	–	31.87	–
Annual Papanicolaou smear	76 700	38.93	18 900	32.70	22 500
CDC strategy§	76 750	38.96	24 100	32.72	28 700
Semiannual Papanicolaou smear	76 990	39.03	36 700	32.79	43 700
Annual colposcopy	77 360	39.02	Dominated	32.78	Dominated
Semiannual colposcopy	78 160	39.07	376 500	32.82	448 200

* CDC = Centers for Disease Control and Prevention; QALY = quality-adjusted life-year; YLS = year of life saved. Values in the second through fourth columns are not adjusted for quality of life; those in the last two columns (reference-case analysis) are.

† The difference in cost divided by the difference in life expectancy or quality-adjusted life expectancy for each strategy compared with the next-best strategy.

‡ Biennial Papanicolaou smear screening dominated by annual Papanicolaou smear screening (not shown).

§ Annual Papanicolaou smear screening after two initial smears obtained 6 months apart.

|| Annual colposcopy screening is dominated because it costs more but is less effective than semiannual Papanicolaou smear screening.

¶ Assumes that a woman is identified as HIV-infected within 1 year of seroconversion.

related quality of life showed only minor differences in the cost-effectiveness ratios.

Sensitivity Analyses

The sensitivity analyses are outlined in **Table 3**. Estimates of cost-effectiveness were most influenced by the prevalence of squamous intraepithelial lesions and their rate of progression to cancer. The results were less sensitive to the incidence, regression, and recurrence of neoplasia; the mortality rate from invasive cancer; quality of life in all stages of cancer and HIV disease; the discount rate; and the costs of screening tests, patient time, and direct medical care for cancer.

Natural History of Cervical Neoplasia

As rates of progression of precancerous to cancerous lesions were increased relative to the base case, annual and semiannual Papanicolaou smear screening strategies became more cost-effective. When progression rates exceeded 1.3 times the base case, the CDC strategy dominated annual Papanicolaou smear screening. When progression rates exceeded 2.0 times the base case, semiannual Papanicolaou smear screening dominated the CDC strategy. Semiannual colposcopy cost more than \$150 000 per

QALY saved even if progression rates were 3.0 times those of the base case.

The relation between changes in progression and incidence and the cost-effectiveness of semiannual Papanicolaou smear screening is shown in **Figure 2**. Regardless of the cost-effectiveness threshold used (\$20 000, \$50 000, or \$100 000 per QALY), changes in incidence had far less effect on the choice of screening strategy than did changes in progression rate.

If the prevalence of baseline cervical neoplasia was increased, all screening strategies were more cost-effective. For example, if the prevalence of neoplasia was twice that of the base case, the incremental cost-effectiveness ratios of the CDC strategy and semiannual Papanicolaou smear screening decreased to \$12 100 and \$20 800 per QALY saved, respectively. The CDC strategy dominated annual Papanicolaou smear screening if the prevalence of low-grade lesions exceeded 50% or the prevalence of high-grade lesions exceeded 6%.

Screening HIV-Infected Women Who Present in Earlier or Later Stages of HIV

Projected QALYs gained by screening women who were identified as HIV-infected with CD4 cell

Table 3. Sensitivity Analyses*

Variable	Incremental Cost-Effectiveness Ratio†		
	Annual Papanicolaou Smear	CDC Strategy‡	Semiannual Papanicolaou Smear
Base case	12 800	14 800	27 600
Incidence rate of SIL			
0.5 times baseline	12 500	14 400	37 500
2 times baseline	13 700	16 200	23 000
Regression rate of SIL§			
0.5 times baseline	12 200	13 200	25 300
2 times baseline	13 700	17 500	31 800
Recurrence rate of SIL			
0.5 times baseline	12 200	13 800	31 600
2 times baseline	14 000	16 800	26 100
Mortality rate with cancer			
0.5 times baseline	11 700	15 700	34 300
2 times baseline	13 800	14 600	23 900
False-negative rate Papanicolaou test¶			
0.5 times baseline	12 600	20 500	40 100
1.5 times baseline	13 200	13 300	21 100
Compliance with screening**			
0.4 times baseline	Dominated††	13 000	13 200
0.8 times baseline	Dominated††	12 800	18 700
Compliance with diagnostic work-up**			
0.4 times baseline	Dominated††	13 700	15 000
0.8 times baseline	Dominated††	13 000	19 900
Cost of Papanicolaou smear‡‡			
0.5 times baseline	12 500	13 200	23 000
2 times baseline	13 500	18 200	36 800
Cost of diagnostic work-up			
0.5 times baseline	Dominated††	10 500	18 600
2 times baseline	17 600	23 700	45 600
Cost of cervical cancer§§			
0.5 times baseline	15 800	19 500	33 900
1.5 times baseline	9 900	10 200	21 300
Discount rate			
0%	13 500	14 800	25 300
5%	12 500	15 100	29 500
10%	12 200	16 600	35 300

* Values given are the cost in dollars divided by the number of quality-adjusted life-years saved. CDC = Centers for Disease Control and Prevention; SIL = squamous intraepithelial lesions.

† Annual Papanicolaou smear screening was compared with no screening, the CDC strategy was compared with annual Papanicolaou smear screening, and semiannual Papanicolaou smear screening was compared with the CDC strategy.

‡ Annual Papanicolaou smear screening after two initial smears obtained 6 months apart.

§ Included regression of both low-grade and high-grade SIL without treatment.

|| Included recurrence of both low-grade and high-grade SIL after initial successful treatment relative to base-case assumption of 10%.

¶ Provided that the false-negative rate was less than 45%, semiannual Papanicolaou smear screening dominated annual colposcopy.

** Base case assumes perfect compliance.

†† Eliminated because of extended dominance: strategies with a higher incremental cost-effectiveness ratio than a more effective alternative strategy.

‡‡ Provided that the cost of a Papanicolaou smear was less than \$100 and the cost of colposcopy was more than \$50, semiannual Papanicolaou smear screening dominated annual colposcopy.

§§ Included cost of early and late invasive cervical cancer.

counts greater than 500 cells/mm³ ranged from 2.56 to 3.47 months. Although biennial screening cost only \$10 800 per QALY saved, annual Papanicolaou smear screening and the CDC strategy offered additional quality-adjusted life expectancy for only \$12 800 and \$15 800 per QALY saved, respectively. In comparison, the QALY gains associated with screening women with CD4 cell counts less than 200 cells/mm³ ranged from 0.83 to 0.95 months. The cost-effectiveness of screening in women with late-stage HIV disease was most sensitive to the competing mortality of HIV disease and the valuation of health-related quality of life in the years of life to be saved. When quality-adjusted life expectancy was less than 1 year, the benefit of screening women with late-stage HIV disease provided less than 3 additional quality-adjusted days and cost more than \$75 000 per QALY.

Effect of Highly Active Antiretroviral Therapy

Because the data from AIDS Clinical Trial Group protocol 320 (83) reported a follow-up period of 40 weeks, we explored the implications of viral suppression lasting 1 year or longer. In women with CD4 cell counts less than 200 cells/mm³ who began receiving highly active antiretroviral therapy, annual Papanicolaou smear screening had an incremental cost-effectiveness ratio of \$22 000, \$21 100, or \$20 300 per QALY saved, assuming a benefit of 1, 2, or 3 years, respectively. The incremental cost-effectiveness ratio for the CDC strategy was \$28 600, \$22 800, or \$21 400 per QALY saved, assuming a benefit of 1, 2, or 3 years, respectively.

To estimate the effect of highly active antiretroviral therapy started earlier in HIV disease (in women with a CD4 cell count of 200 to 500 cells/

mm³), we incorporated data from Gulick and associates (84, 85) reporting 2-year follow-up on intermediate outcomes with highly active antiretroviral therapy. Assuming a 2-year clinical benefit, the cost-effectiveness ratio of annual Papanicolaou smear screening was \$11 700 per QALY and that of the CDC strategy was \$12 100 per QALY. If viral load suppression was sustained for longer periods, screening became even more cost-effective.

We also explored the potential impact of highly active antiretroviral therapy on decreasing the risk for HPV-mediated cervical disease. Even if the progression rate of established neoplasia was reduced by 50%, the cost-effectiveness ratios for annual Papanicolaou smear screening (\$13 100 per QALY) and the CDC strategy (\$15 600 per QALY) remained favorable.

Discussion

Substantial evidence indicates that HIV-infected women are at increased risk for cervical disease (1, 5–7, 9). Our objective was to give clinicians explicit

information about the incremental benefits and costs of choosing one cervical screening strategy over another. Over a wide range of variable estimates, cervical cancer screening prolonged both life expectancy and quality-adjusted life expectancy. In strategies targeted to women with CD4 cell counts of 200 to 500 cells/mm³, the cost-effectiveness ratios for annual Papanicolaou smear screening (\$12 800 per QALY) and the CDC strategy (\$14 800 per QALY) were robust over a wide range of sensitivity analyses. The cost-effectiveness of more frequent screening was sensitive to assumptions about the natural history of neoplasia. The most aggressive strategy, semiannual colposcopy, never had a cost-effectiveness ratio less than \$100 000 per QALY even under the most favorable assumptions.

Our analysis showed that the rate of progression of cervical neoplasia was the critical factor in projecting the cost-effectiveness of alternate screening frequencies. In contrast, over a wide range of estimated incidence, regression, and recurrence rates, results were less variable. The sensitivity of the Papanicolaou smear had a minimal effect on the results, although the cost-effectiveness ratio for semiannual

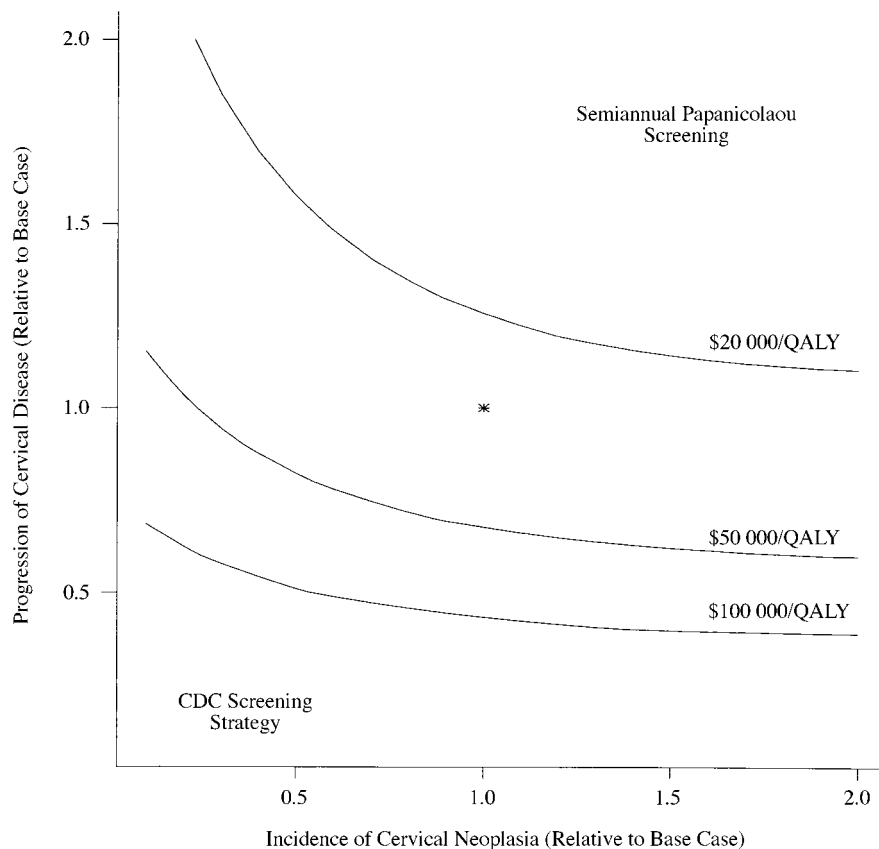


Figure 2. Three-way sensitivity analysis of the incidence of squamous intraepithelial lesions (SIL), progression of SIL to cancer, and the acceptable cost-effectiveness threshold for the choice of semiannual Papanicolaou smear screening or the Centers for Disease Control and Prevention (CDC) screening strategy (annual Papanicolaou smear screening after two initial smears obtained 6 months apart). The lines show the incremental cost per quality-adjusted life-year (QALY) gained necessary to use semiannual Papanicolaou smear screening (\$20 000, \$50 000, and \$100 000 per QALY). For a particular cost-effectiveness threshold, points to the upper right of the line indicate that semiannual Papanicolaou smear screening is preferred; points to the lower left of the line indicate that the CDC screening strategy is preferred. Asterisk represents the base case.

screening was much more attractive when the false-negative rate exceeded 45%. Decreases in the specificity of the Papanicolaou smear shifted the proportion of screening costs associated with false-positive diagnostic work-ups upward, decreasing the cost-effectiveness of strategies that included Papanicolaou smears. Finally, over a wide range of testing costs, the results were robust.

The CDC screening strategy modifies the strategy of annual Papanicolaou smear screening by adding an extra screening smear in the first year of testing (21). The incremental cost-effectiveness of the CDC strategy was affected most by the prevalence of cervical neoplasia and the sensitivity of the Papanicolaou smear. Only if the sensitivity of the smear improved to more than 90% or the baseline prevalence rate of neoplasia decreased to less than 5% did the incremental benefit of two initial smears obtained 6 months apart disappear.

We also evaluated optimal lifetime screening strategies for women who present for medical care earlier (with CD4 cell counts > 500 cells/mm³) or later (with CD4 cell counts < 200 cells/mm³) in the course of HIV disease. The analysis for early HIV disease was the only time when biennial Papanicolaou smear screening was not dominated by annual screening, reflecting the lower risk for neoplasia in women with early disease compared with those with more advanced immunosuppression. Although biennial Papanicolaou smear screening was the least costly approach, the CDC strategy provided greater benefit for a reasonable cost. In fact, this strategy provided almost 95% of the survival benefit of semi-annual Papanicolaou smear screening. In women with later HIV disease, screening was associated with smaller benefits in quality-adjusted life expectancy and was sensitive to competing HIV-related morbidity and mortality.

In the setting of highly active antiretroviral therapy, suppression of viral replication can be sustained for at least 2 years (84) and progression to AIDS and death can be reduced in patients with CD4 cell counts less than 200 cells/mm³ (83, 102–104). Incorporating these data, we projected that in women with CD4 cell counts less than 200 cells/mm³ (83), the cost-effectiveness of the CDC strategy varied between \$20 000 and \$30 000 per QALY saved, depending on the duration of viral suppression. In women with CD4 cell counts of 200 to 500 cells/mm³, the cost-effectiveness of the CDC strategy ranged from \$11 000 to \$14 000 per QALY saved, again depending on the duration of sustained viral load suppression. Although these cost-effectiveness ratios are favorable, we stress that they are preliminary estimates: The long-term impact of the newer antiretroviral drugs on the natural history of HIV infection is not yet known (93, 102). If we

further consider the real-world failure rates of these antiretroviral regimens due to resistance (93), non-adherence (102), and less effective second-line treatment options for patients receiving sequential therapy (84, 105), the lifelong effect of highly active antiretroviral therapy is even more uncertain.

The impact of highly active antiretroviral therapy on persistent HPV infection, the incidence of new cervical neoplasia, and the progression of established neoplasia is also not yet known (3, 5, 106, 107). Preliminary data from one study (108) showed that no significant change occurred in overall HPV infection, that most high-grade lesions did not regress, and that new high-grade lesions continued to develop. We found that unless the risk for progression of neoplasia was reduced to a fraction of the base case, annual screening remained both effective and cost-effective.

It is useful to compare these results with the cost-effectiveness ratios of other accepted medical interventions. Cervical cancer screening in the non-HIV-infected population costs \$10 100, \$184 000, or \$263 000 per year of life saved (in 1985 U.S. dollars) if screening is done every 4, 3, or 2 years, respectively (73). Prophylaxis against *Pneumocystis carinii* pneumonia with trimethoprim-sulfamethoxazole costs \$16 000 per QALY saved, and prophylaxis against *Mycobacterium avium* complex infection costs \$35 000 to \$74 000 per QALY saved (in 1995 U.S. dollars) (54).

Our analysis has several limitations. Our information on the natural history of cervical disease was drawn from many small studies (86). Some of the early data rely on older classification systems for neoplasia. We did not include some potential advantages of colposcopy, such as detection of non-cervical lesions (for example, vulvar neoplasia) (109, 110). Health-related quality-of-life measures in HIV-infected women are uncertain. We did not consider primary screening using HPV testing, although a priority for future research will be to better understand the natural history of HPV in HIV-infected women and the long-term impact of highly active antiretroviral therapy on both new and established HPV-induced cervical neoplasia. One key attribute of our model is that as better data become available from longitudinal cohort studies with longer follow-up, the impact of new information can be rapidly evaluated.

This analysis sends a clear message to those who might advocate a policy of no cancer screening, given the high competing mortality in HIV disease (111). Over the broadest range of variable estimates, encompassing nearly all reported values in the literature, the screening of HIV-infected women for cervical cancer was associated with projected life expectancy benefits equal to or greater than those

provided by other preventive measures in general medicine or in HIV disease. On the basis of these results, we recommend that all HIV-infected women, regardless of their CD4 cell count, have two Papanicolaou screening smears obtained 6 months apart and then annual Papanicolaou smears thereafter. Clinicians and their patients should be aware that the clinical benefits of screening are substantially decreased when quality-adjusted life expectancy decreases to less than 2 years.

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Personae

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We look forward to receiving your photographs.

Christine Laine, MD, MPH
Deputy Editor