Potential Cost-effectiveness Of Cervical Cancer Screening of HIV-positive Kenyan Women

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OBJECTIVE

As antiretroviral therapy is scaled up in Africa, HIV-positive women are living longer and increasingly likely to die from cervical cancer. Cervical cancer screening methods used in this setting include Papanicolaou smear (Pap), visual inspection with acetic acid (VIA), and human papillomavirus testing (HPV). Our objective was to assess the cost-effectiveness of these methods among HIV-positive women.

Table 1: Base case parameters and sensitivity analysis parameters used in modeling cervical cancer in HIV positive women

	Base case	Range for Sensitivity Analysis	Source
Start age	**38**	30 - 46	Trial
Prevalence of cancer (per person)	**0.221**	0.177 - 0.266	Trial
Initial prevalence (per person)			
Among cancer			
Lesions LSIL	**0.0000**		
Lesions HSIL	**0.9524**	0.7619 - 1	
Local cancer	**0.0202**	0.0162 - 0.0243	1,2
Regional cancer	**0.0238**	0.0190 - 0.0286	
Distant cancer	**0.0036**	0.0029 - 0.0043	
Among normal			
Lesions LSIL	**0.0981**	0.0784 - 0.1177	
Normal	**0.9019**	0.7216 - 1	2
Loss-to-follow-up probability for 2-visits	**0.32**	0.256 - 0.384	3
Standardized mortality ratio for treated HIV patients compared to HIV negative	**1.77**	1.416 - 2.124	4
Untreated cancer parameters			
Cancer mortality probability (monthly)			
Local	**0.0035**	0.0028 - 0.0042	
Regional	**0.0207**	0.0166 - 0.0249	5
Distant	**0.0633**	0.0506 - 0.0759	
Progression probability (monthly)			
Normal to LSIL	**0.0006**	0.0004 - 0.0007	
LSIL to HSIL	**0.0025**	0.0020 - 0.0030	
HSIL to local invasive cancer	**0.0020**	0.0016 - 0.0024	1,5
Local to regional invasive cancer	**0.0034**	0.0027 - 0.0041	
Regional to distant invasive cancer	**0.0034**	0.0027 - 0.0041	
Regression probability (monthly)			
LSIL to normal	**0.0025**	0.0020 - 0.0030	
HSIL to LSIL	**0.0003**	0.0002 - 0.0003	5
HSIL to normal	**0.0003**	0.0002 - 0.0003	
Treated cancer parameters			
Treatment effectiveness probability (mortality, progression, lesion regression)	**0.9**	0.720 - 1	6
Treated cancer cure probability (monthly)	**0.1462**	0.117 - 0.175	7
Side effect probability (monthly)	**0.0051**	0.004 - 0.006	8
Probability side effect is major	**0.0009**	0.0007 - 0.0011	
Sensitivity			
Pap (HSIL+)	**0.718**	0.619 - 0.929	
VIA	**0.627**	0.619 - 0.929	Trial
HPV	**0.836**	0.671 - 1	
Specificity			
Pap (HSIL+)	**0.971**	0.785 - 1	
VIA	**0.659**	0.470 - 0.705	Trial
HPV	**0.557**	0.382 - 0.572	
Costs (US$)			
Screening			
PAP	**$30**	24 - 35	
VIA	**$16**	13 - 19	
HPV	**$40**	32 - 48	
Treatment			
Cryotherapy	**$43**	35 - 52	Cost Finding Study
Side effects			
Major	**$1,035**	828 - 1242	
Minor	**$198**	159 - 238	
Cancer			
Local	**$6,111**	4889 - 7333	
Regional	**$6,808**	5446 - 8169	
Distant	**$8,206**	6565 - 9848	
Hospice (monthly)	**$150**	120 - 180	

METHODS

The cost-effectiveness analysis was based on a trial of 500 HIV-positive women who underwent VIA, Pap smear, HPV, and gold-standard colonoscopy-directed biopsy at the Coptic Hope Center in Nairobi, Kenya (hereafter referred to as 'trial'). HPV DNA testing was performed on exfoliated cells at Vrije Universiteit (VU) Medical Center in Amsterdam. Sensitivity and specificity of positive Pap smear (HSIL+), VIA, and HPV were compared to CIN2/3+ results from the gold-standard biopsy (Table 1). Differences in sensitivity and specificity were statistically significant ($p<0.05$). Multivariate analyses of the trial data showed that CD4 count ≤350 cells/mm^3 was associated with decreased HPV specificity ($p=0.002$) and age <40 years was associated with increased VIA sensitivity ($p<0.001$) and decreased HPV specificity ($p=0.005$). We found that relevant, current, and applicable costs data was not available for this population and therefore undertook a cost finding study to determine direct and indirect costs on cervical cancer screening and related care (manuscript under development).

For the cost-effectiveness analysis, we used a decision tree to assess overall cost-effectiveness comparing Pap, VIA, and HPV. A decision tree was used to model outcomes of each screening strategy (Figure 1). We additionally examined a strategy of giving cryotherapy to all women without screening. Each woman either had neoplasia or was neoplasia free. Dependent on the sensitivity and specificity of the screening type, they tested positive or negative, received cryotherapy treatment, and could be lost-to-follow up (LTFU) or have side effects A Markov model consisting of 7 disease states[2] projected life expectancy and costs following each strategy (Figure 2). We addressed the impact of parameter uncertainty using univariate and probabilistic multivariate sensitivity analysis. We assumed that hysterectomies were not included, and progression, regression, and mortality rates were not dependent on a previous history or lesions or cancer. The base case analysis included those with CD4 count 200-500 cells/mm^3. Additionally we modeled patients with low and high CD4 counts. Costs included direct and indirect medical and non-medical costs from a semi-societal perspective.

Figure 1: Decision tree representing cancer, testing, treatment, and side effects

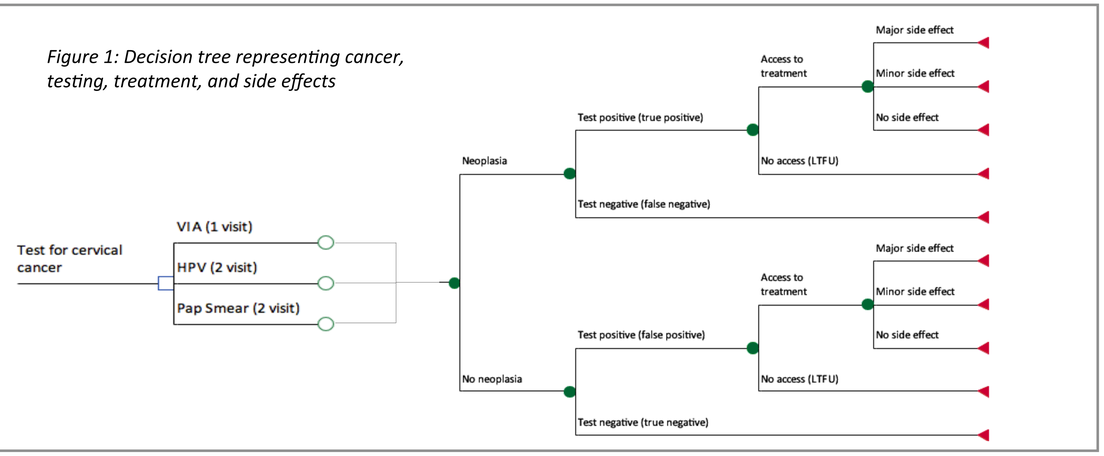
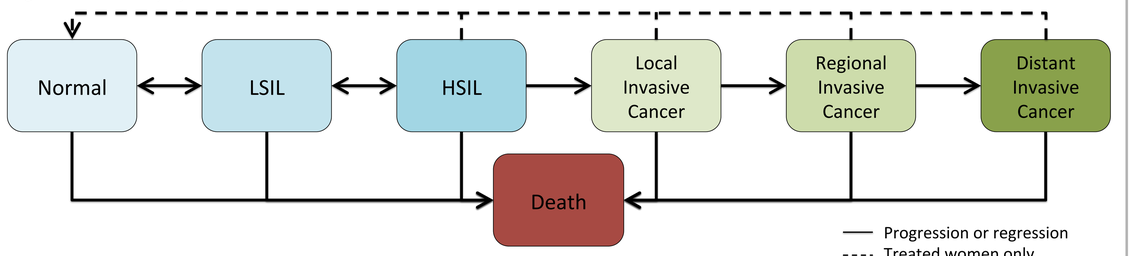


Figure 2: Summary of states in Markov model



RESULTS

VIA had lowest cost and highest life expectancy (due to reduced loss-to-follow-up) ($473, 17.2 LYs), followed by HPV ($754, 17.1 LYs), Pap ($790, 17.1 LYs), (Table 2). CD4 level did not affect this rank order, though VIA at low CD4 showed the lowest cost ($203, 15.3 LY), while VIA at high CD4 produced most health gains ($620, 19.9 LY) [ICER: $91/LY]. Costs were sensitive to prevalence of cancer, sensitivity, age, and cost of cancer (Figure 3). Life expectancy was sensitive to age at screening. Results were robust to probabilistic sensitivity analysis (Figure 3). The cost giving cryotherapy to every woman was $131 with 17.2 expected life-years gained.

Table 2: Lifetime costs and expected life-year results

	Strategy	Lifetime cost	Life expectancy
Base case (CD4 200-500 cells/mm^3)	PAP	$790	17.1
	HPV	$754	17.1
	VIA	**$473**	**17.2**
Low CD4 (CD4≤200 cells/mm^3)	PAP	$839	15.1
	HPV	$682	15.3
	VIA	**$203**	**15.3**
High CD4 (CD4>500 cells/mm^3)	PAP	$736	19.9
	HPV	$651	19.9
	VIA	**$620**	**19.9**

Figure 3: Lifetime costs and expected life-year results

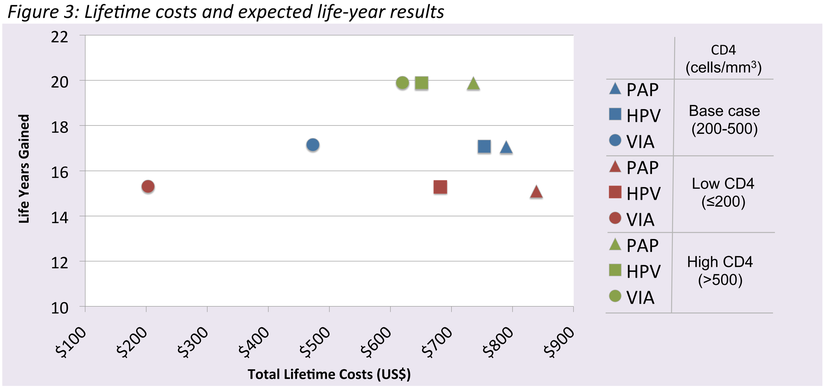
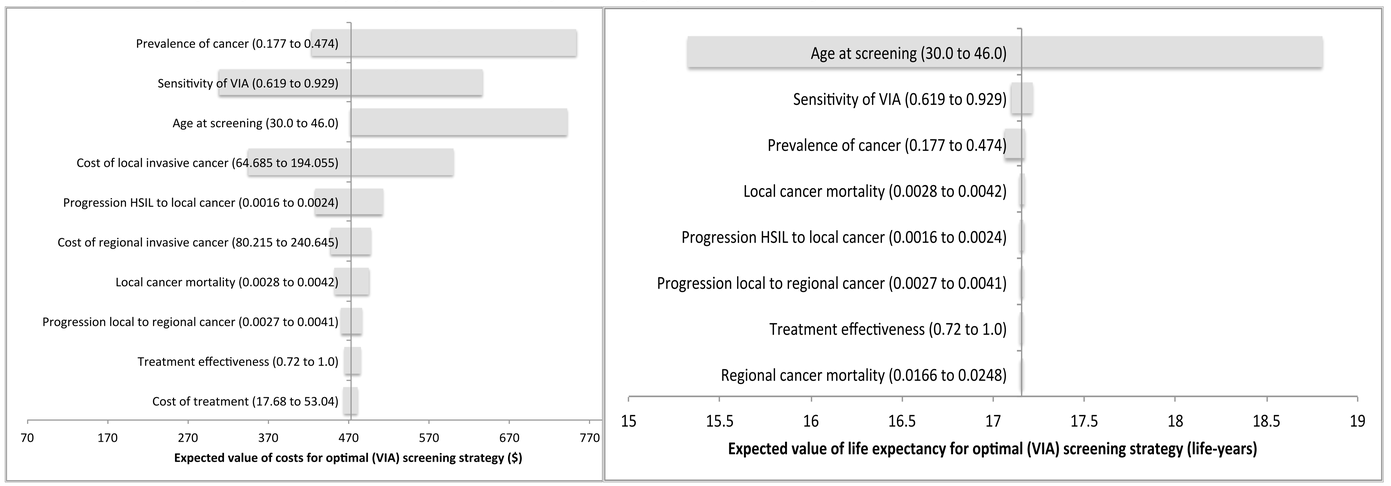


Figure 4: Tornado diagram for sensitivity analysis of mortality (left) costs (right) for VIA screening



DISCUSSION

While VIA had lower sensitivity (62.7%), its low cost ($16) projected it to have the lowest lifetime cost while producing the highest health gains. Although there are significant differences in sensitivity and specificity between cervical cancer screening methods among HIV-positive women, these are not great enough to justify choosing one over another based on a cost-effectiveness analysis. HPV testing was the most sensitive test (83.6%); however, its relatively high cost ($40) made VIA a better choice. Low risk treatment and high cervical cancer cost caused screening cost to drive the model. Life expectancy after screen was sensitive to age at screen. Expected costs were sensitive to prevalence of cancer, sensitivity of the screen, age at screening, and cost of local invasive cancer. It was cheapest to screen women at low CD4 count, though screening at high CD4 count allowed for improvements in survival at only $91/life-year, a highly cost-effective intervention. The cost of cryotherapy is much lower than the cost of cancer, and cryotherapy has a very low risk of side effects. Therefore treating more women is advantageous from both a cost and mortality perspective.

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