

Ethical Issues Surrounding a Study on Cervical Cancer Screening of Women Living with HIV in Laos

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Cervical cancer, associated with human papillomavirus (HPV), is the second most common cancer among women in low- and middle-income countries. Worldwide incidence in 2012 was 528,000 new cases and 266,000 deaths;¹ approximately 175,000 new cases are diagnosed every year in the countries of Southeast Asia.²

Laos has a population of 1.79 million women aged 15 years and older. The annual estimated incidence of cervical cancer is 314 new cases per year, with 168 deaths,³ making it the third leading cause of female cancer among Laotian women. No other data on the incidence and types of papillomavirus in circulation are available in this country. Like most low-income countries, Laos has no national policy on cervical cancer prevention through mass HPV vaccination. An estimated 3000 women are living with HIV in Laos, of whom 1100 are aware of their status, with half of them receiving free antiretroviral therapy through a national HIV control program. However, there is no routine screening of precancerous lesions and cervical cancer, Pap smears, or HPV DNA testing for HIV-positive women.

HIV infection and the resulting immunodepression are associated with an increased risk of persistent HPV infection and invasive cervical cancer, an AIDS-defining illness. Various studies show links between HIV infection, HPV

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infection, and cervical cancer. In a cohort of HIV-positive and HIV-negative women in the United States, HPV infection was found 10 times more often in cases of HIV infection with a CD4 count of less than 200/mm³ (95% CI, OR = 7.32–14.04). It was seven times more frequent when the CD4 count was greater than 200/mm³ and HIV DNA was greater than 20,000 copies/mL (95% CI, OR = 4.17–8.08) and three times more frequent when the CD4 count was greater than 200 mm³ and the HIV DNA was less than 20,000 copies/mL (95% CI, OR = 2.36–4.12).⁴ A Thai study that provided a routine Pap smear and HPV screening for HIV-positive women showed a high-risk oncogenic HPV prevalence of 38.6%, an abnormal cervical cytology of 20.4%, and cervical cancer prevalence of 1.9%.⁵

Women living with HIV are therefore particularly affected by HPV screening. Routine screening by Pap smear has reduced the incidence rate of cervical cancer by 60% to 90% in high-income countries.⁶ In recent years, tests to detect DNA in oncogenic HPV have shown higher sensitivity, but lower specificity, than Pap smears for screening intraepithelial neoplasia.⁷

A new, easy-to-use test that detects oncogenic HPV DNA, called careHPV™, which can be performed without electricity or running water and provides results in two to five hours, was developed by QIAGEN, a company that sells molecular biology kits specifically for low-income countries. It has performed well, but further evaluation is needed at the local level to assess its conditions for use and its cost-effectiveness.

The LaoCol-VP research project

The primary objective of the LaoCol-VP study⁸ was to compare the efficacy of cervical cancer screening strategies using careHPV™ with a Pap smear and to determine its cost-effectiveness and the average cost per

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4. Palefsky, J. M., Minkoff, H., Kalish, L. A., Levine, A., Sacks, H. S., Garcia, P., ... Burk, R. (1999). Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. *Journal of the National Cancer Institute*, 91 (3), 226–36.
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 7. Mayrand, M.-H., Duarte-Franco, E., Rodrigues, I., Walter, S. D., Hanley, J., Ferenczy, A., ... Franco, E. L. (2007). Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med*, 357, 1579–88.
 8. "LaoCol-VP: Efficacy and cost-effectiveness of careHPV™ human papillomavirus screening versus Pap smear for the detection of precancerous and cancerous cervical lesions among HIV-infected women in Lao PDR".

diagnosis. Secondary objectives were to study the performance of the two screening tests (sensitivity, specificity, and positive and negative predictive values), their concordance, prevalence results of the various types of oncogenic HPV, and cervical cancer prevalence among HIV-positive women in Laos.

LaoCol-VP also aimed to inform the country's health officials of the magnitude of the problem for women living with HIV and the effectiveness of available screening options. In addition, the study sought to strengthen the capacities of Laotian health providers, who received additional training through the study on the screening, diagnosis, and treatment of cervical cancer.

LaoCol-VP was a transversal multicenter study⁹ conducted among 600 Laotian women living with HIV, aged 25 to 65 years, who provided written consent, and who were receiving follow-up care in the country's four main HIV treatment centers. The study was not open to pregnant women or any woman who had given birth in the last three months, or to women who had precancerous or cancerous cervical lesions, or women who were unable or unwilling to give their consent.

In practice, after presenting the study to a participant and obtaining her consent, we collected certain medical and demographic information and offered her a gynecological consultation appointment. The consultation was conducted by a gynecologist, who proposed a gynecological exam to the participant. During the exam, several samples were taken: (i) a cervical swab, (ii) a Pap smear,¹⁰ and (iii) and a cervical exam using a colposcope¹¹ plus a biopsy if the gynecologist detected an abnormality on the cervix. The various samples were analyzed in two laboratories in Laos and one in Thailand.

The women who were diagnosed with precancerous or cancerous lesions received surgical treatment in accordance with the current practices in Laos. This treatment was provided free of charge through the project.

This study was conducted between May 2013 and June 2015.

Ethical issues surrounding this study

A study of this type must consider the usual ethical aspects of any health research: informing participants, obtaining their consent, ensuring confidentiality, assessing benefits and risks for study participants, reimbursing travel costs, etc. For example, informing participants requires

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9. A transversal study collects all data needed for the study at a specific point in time, and a multicenter study is conducted simultaneously in several different places where the same data is collected.
 10. This involves using a small wooden spatula to scrape superficial cells from the cervix.
 11. A colposcopy is a direct visual examination of the cervix using a binocular microscope.

translating the information documents and consent forms into the country's various lingua francas to ensure they are easily understood.

Moreover, this type of research program highlights four key ethical aspects:

- ***The study's relevance relative to current global scientific knowledge and existing local medical infrastructure:***

Cervical cancer screening in low-income countries is a major public health issue. Until recently, one factor limiting screening was the complexity of screening techniques that required a level of medical infrastructure that was often unavailable in these countries. In 2012, a new screening technique was validated (HPV DNA test). Although the LaoCol-VP study was developed in 2013, the efficacy of this technique still needed to be validated in various epidemiological contexts. Therefore, this study was entirely appropriate given the scientific knowledge at the time. One of the study objectives was also to assess this technique's diagnostic efficacy and costs in order to guide the Government of Laos in defining its public health policy. Another goal was to strengthen health professionals' expertise by providing training on cervical cancer screening and therapeutic care for women diagnosed with lesions. Hence, this study improved cervical cancer screening and treatment in Laos.

- ***Enrolling and informing the women participating in the study:***

This study involved HIV-positive women, who were already diagnosed with HIV and who were being treated in suitable facilities. One major ethical issue is obtaining their consent to participate in the study. On the one hand, the women must have the right to refuse to participate in this study without being excluded from their treatment center. On the other hand, the information that they are given must explain that cervical cancer screening is recommended for all HIV-positive women, without implying that they already have cervical cancer. This distinction may prove difficult for the women to understand. Information that is imprecise or poorly adapted to the women's ability to comprehend it may cause them to think that in addition to being infected with HIV, they also have cancer. This lack of comprehension may have serious psychological consequences. Information for participants must also consider the women's concerns about modesty during a gynecological exam; they must know in advance whether a male or female gynecologist will conduct the consultation. Lastly, participants need a full explanation detailing exactly what happens during a gynecological examination, without minimizing the inconvenience or pain. For example, health professionals often present cervical biopsy as painless, even though many women describe actual pain.

- ***Confidentiality of medical information:***

The primary criterion for enrolling women in this study is that they are HIV positive and receiving care in specialized centers. As part of the LaoCol-

VP study, they underwent a gynecological consultation. Based on the research protocol, the gynecologist and any assisting staff would obviously know that the women were HIV positive. These health professionals must ensure that they fully respected doctor-patient confidentiality about the HIV disease so that participation in this research did not constitute a risk of revealing the diagnosis to a third party without the women's consent.

• ***Adapted medical care based on the diagnoses:***

This study enables early diagnosis and treatment of cervical lesions. The study also covers all medical costs: consultations and care—including treatment of the diagnosed cancers—are free of charge for study participants. This study therefore provided a genuine benefit for participants. The diagnostic and treatment methods were the same in the four treatment centers, thus ensuring the women had equal access to care, despite living in different areas of the country.

ETHICS AND REGULATORY REFERENCE DOCUMENTS

The ethical issues presented above are highlighted (but not exclusively) in the following documents:

1. The World Medical Association Declaration of Helsinki:

• **General principles:**

Article 9: It is the duty of physicians who are involved in medical research to protect the (...) privacy, and confidentiality of personal information of research subjects.

• **Informed consent:**

Article 26: (...) each potential subject must be adequately informed of the aims, methods, (...) the discomfort it may entail.

Article 31: The physician must fully inform the patient which aspects of their care are related to the research.

• **Privacy and confidentiality:**

Article 24: Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

2. International Ethical Guidelines for Biomedical Research Involving Human Subjects, CIOMS, 2002

• **Guideline 5: Obtaining informed consent:** Essential information for prospective research subjects: Before requesting an individual's consent to participate in research, the investigator must provide the following information [about] (...) any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research (...)."

- Guideline 10: Research in populations and communities with limited resources: the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out.
- Guideline 18: Safeguarding confidentiality: The investigator must establish secure safeguards of the confidentiality of subjects' research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality.

3. Universal Declaration on Bioethics and Human Rights, UNESCO, 2005

Article 9: Privacy and confidentiality: The privacy of the persons concerned and the confidentiality of their personal information should be respected.

Article 10: Equality, justice and equity: The fundamental equality of all human beings in dignity and rights is to be respected so that they are treated justly and equitably.

Article 11: Non-discrimination and non-stigmatization: No individual or group should be discriminated against or stigmatized on any grounds, in violation of human dignity, human rights and fundamental freedoms.

Article 21: Transnational practices: Transnational health research should be responsive to the needs of host countries.

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The Paths of Ethics in Research in Laos and the Mekong Countries

Health, Environment, Societies

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Cervical cancer is the fourth most common cancer in women. In 2018, an estimated 570 000 women were diagnosed with cervical cancer worldwide and about 311 000 women died from the disease. Effective primary (HPV vaccination) and secondary prevention approaches (screening for, and treating precancerous lesions) will prevent most cervical cancer cases. When diagnosed, cervical cancer is one of the most successfully treatable forms of cancer, as long as it is detected early and managed effectively. Cancers diagnosed in late stages can also be controlled with appropriate treatment and palliative care. Women infected with human immunodeficiency virus (HIV) have a higher risk of HPV infections and developing cervical cancer , thus screening them is imperative. This study was aimed to evaluate and compare the performance of 3 cervical cancer screening options among HIV -infected women in Uganda .

Materials and Methods. Data from 2,337 Ugandan women who reported their HIV status were obtained from a population-based cervical cancer screening study. Women infected with HIV had a higher prevalence of cervical intraepithelial neoplasia grade 2+ (CIN2+) than uninfected women (12.9% vs 1.7%; $p < .001$). The sensitivity for cervical care HPV among the HIV -infected women was 94.3% compared to 81.3% among the uninfected women.

Abstract The number of women living with HIV continues to increase. Thirty years into the AIDS epidemic, we now expect those with access to highly active antiretroviral to survive into their seventh decade of life or beyond. Here, we review cancer screening strategies for women living with HIV/AIDS with a focus on cancers of the lung, breast, cervix, anus, and liver. Although the NLST study include breast, lung, colon, anal, and cervical cancers. participants reflected well the demographics of high-risk US smokers, it is worth emphasizing that the decision to screen WLWHA for cancer should include an assessment of individualized risk for the particular cancer, life expectancy, the harms and benefits multidisciplinary teams.