New evidence on the impact of cervical cancer screening and treatment using HPV DNA tests, visual inspection, or cytology

July 2009

A study published by Sankaranarayanan et al. in the April 2, 2009 edition of the *New England Journal of Medicine* added to the growing evidence that a significant impact on cancer mortality can be achieved by offering women even a single opportunity for cervical cancer screening using an HPV DNA test followed by treatment as indicated.1 In contrast to previous findings, the new study from India found no significant reductions in cancer cases among women offered screening/treatment using cytology (Pap screening) or visual inspection with acetic acid (VIA). It is not unusual for studies to show differing results, and it is important to consider the entire body of evidence before significantly revising policy. This Alliance for Cervical Cancer Prevention (ACCP) fact sheet seeks to put the new findings into context and respond to questions arising in light of this new information, especially questions related to continuing investment in VIA-based programs.

**ACCP recommends that countries, areas, or institutions...consider introducing or expanding VIA plus cryotherapy programs...until appropriate and affordable HPV DNA tests become available.**

ACCP history with HPV testing and VIA

Cervical cancer kills approximately 270,000 women each year, with nearly 85 percent of those deaths in resource-poor settings. Routine cytological screening of women has resulted in a dramatic decline in cervical cancer deaths over the past four decades in wealthier countries. A key reason for continuing high mortality in the developing world is the shortage of efficient, high-quality precancer screening and treatment programs in those regions. Most developing countries lack the infrastructure and trained personnel needed to replicate the cytology-based, multi-visit approach used in wealthier countries to detect precancer (Pap smears followed by colposcopy and biopsy).

In an effort to investigate sustainable alternatives to cytological screening, the ACCP—EngenderHealth, International Agency for Research on Cancer (IARC), Jhpiego, Pan American Health Organization (PAHO), and PATH—implemented a coordinated research agenda aimed at assessing a variety of approaches to cervical cancer screening and treatment (especially approaches that may be better suited to low-resource settings). The ACCP also focused on improving service-delivery systems—ensuring that community perspectives and needs are incorporated into program design—and raising awareness of cervical cancer and effective prevention strategies. In the nine years since the inauguration of the ACCP, the partners have conducted studies comparing a number of screening techniques including cytology, visual inspection methods using acetic acid or Lugol’s iodine, and an HPV DNA test. The tests were evaluated in over 20 low-resource settings around the world.

HPV DNA testing and VIA have proven to be of special interest. HPV testing has been shown to have better performance than either cytology or VIA for primary screening due to much higher test sensitivity.1,2,3,4,5 Furthermore, HPV testing has been coupled effectively with VIA for treatment triage. Both VIA and HPV testing have been successfully paired with cryotherapy—a relatively simple, inexpensive, and safe method of freezing affected cervical tissue. Studies of VIA have reported sensitivity values comparable to or greater than Pap and

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*In 2008 the ACCP expanded its membership to include the International Atomic Energy Association Programme of Action for Cancer Therapy (PACT), International Union Against Cancer (UICC), and Partners in Health.*
have described advantages related to the need for fewer specialized personnel and less infrastructure, training, and equipment.\textsuperscript{5,6,7,8,9,10} Also, VIA provides immediate results, making it possible to screen and treat women during the same visit. This is important since inability to follow up with women for necessary treatment is a major cause of low program impact worldwide.\textsuperscript{11} At the same time, studies have noted some challenges with VIA, including assuring consistent quality control and the fact that differing results have been obtained in differing settings.\textsuperscript{12}

**New study raises questions**

The new study, which followed more than 130,000 women for eight years in the Osmanabad district of India, found that a program strategy based on a single round of HPV testing was associated with approximately 50 percent reduced risk of cervical cancer incidence and mortality, whereas strategies based on a single round of VIA or Pap screening had little, if any, effect on cervical cancer rates and mortality. While the results related to HPV testing are not surprising, the results related to VIA and Pap vary significantly from other studies and from experience with Pap screening programs over the years. It is generally accepted that Pap programs have had significant impact on cervical cancer rates in high-resource settings over the past several decades (with, presumably, the relatively low sensitivity of Pap smears being balanced by repetition of the tests many times during a woman’s life). A number of studies have suggested equivalent or greater sensitivity of VIA compared with Pap tests. Further, a 2007 study that followed over 49,000 women in southern India for seven years reported an overall VIA-associated reduction in cervical cancer incidence and mortality of 25 percent and 35 percent respectively for women ages 30 to 59, with reductions of 38 percent and 66 percent in the 30 to 39 age group (compared with a control group where women received standard care focusing on health education and provision of screening services on request).\textsuperscript{11} Sankaranarayanan has noted the challenges of interpreting the varying results from the two Indian studies and observed that the treatment rate among VIA-positive women was much higher in the southern Indian trial than in the Osmanabad trial, which may be a factor in the different study results.\textsuperscript{1}

**Should we promote VIA-based programs?**

Taking into account the overall body of evidence related to using HPV DNA testing or VIA, the ACCP recommends that, once HPV testing becomes feasible and affordable,\textsuperscript{**} programs should consider introducing and scaling up HPV testing as soon as possible as the primary screening method, and utilizing Pap or VIA testing as a triage to evaluate those with HPV-positive test results. In the meantime, recognizing that HPV testing is currently not feasible or affordable for many low-resource settings and that Pap screening is difficult to implement, the ACCP recommends that countries, areas, or institutions seeking to initiate or strengthen cervical cancer screening programs consider introducing or expanding VIA plus cryotherapy programs.

The ACCP continues to support expansion of VIA plus cryotherapy because:

- As noted above, many studies have shown VIA to be effective in accurately identifying cervical precancers, and two key studies have shown VIA-based programs to be associated with a measurable reduction in cervical cancer precursors, cervical cancer, and/or cervical cancer mortality.\textsuperscript{2,11}
- VIA plus cryotherapy offers the potential for reaching many women, using local doctors, nurses, midwives, and paramedical personnel in primary care settings. Even though the sensitivity of VIA is lower than HPV testing, high VIA plus treatment coverage could result in significant program impact compared to doing nothing or to limited Pap or HPV testing (currently the most common situations in the developing world).
- VIA-based programs can be key to establishing the necessary programmatic structures for cervical cancer prevention, including community education and sensitization, provider training and supervision, referral methods for higher-level care, methods to invite women to screening, and monitoring systems to track screening coverage and follow-up rates. All of these structures are essential to success of an eventual HPV test-based program.

\textsuperscript{**}A lower-cost, easier-to-use HPV test, designed for low-resource settings, likely will become commercially available by 2011 or 2012.
• VIA will be an important component of an HPV DNA test-based program, as it is used to triage women who should not receive cryotherapy due to large lesions or suspected cancer. Trained providers who can visualize the cervix and identify acetowhite areas accurately will be a core component of any future cervical cancer prevention program, including those using HPV testing or future molecular assays.

Finally, it is important to note that screening programs are complex, and all screening study results are impacted by a variety of factors including underlying incidence of disease, overall capacity of the health system, and access to trained providers, among others. Further, screening tests are only one component of a secondary-prevention program—neither VIA, Pap, nor HPV testing can prevent disease unless followed by effective and timely treatment of precancerous lesions or invasive cervical cancer as indicated. Such programs require strong and consistent program leadership and management.

ACCP will regularly review new findings related to cervical cancer prevention and provide guidance on strategies and technologies that are most feasible and effective in low-resource settings. This will include how to design efficient screening programs for the future when large cohorts of women will have been vaccinated against HPV.

References