Cervical HPV Infection in Indian Women: Screening and Immunization as Preventive Strategies

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ABSTRACT

Invasive cervical cancer (ICC) is the second leading cause of cancer related mortality among women in India. Human papillomavirus (HPV), the etiological agent of cervical cancer is widely prevalent worldwide. Persistent HPV infection, particularly with HPV 16, is essential for progression to cervical cancer. Human papillomavirus 16 and 18 are the most common genotypes detected among Indian HIV-infected and uninfected women, although their relative contributions vary. HIV-infected Indian women experience a higher risk for HPV infection compared to the general population. Although cervical screening and vaccination to protect against HPV infection are the two main strategies for prevention, there are significant challenges to their implementation in India. Scaling up of cervical screening using simple, rapid tests followed by colposcopy and treatment within a minimal number of visits is essential to prevent loss to follow-up. Increasing the uptake of the HPV vaccine combined with cervical screening can greatly reduce the burden of ICC in India.

Keywords: Cervical cancer, Human papillomavirus, Cervical screening, Human papillomavirus vaccination.

INTRODUCTION

Invasive cervical cancer (ICC) is the fourth leading cause of cancer among women worldwide and the second leading cause of cancer related mortality among women in India (Fig. 1). Nearly nine out of 10 ICC deaths (87%) occur in the developing world; at 67,000 deaths annually, India accounts for 29% of these ICC deaths. The etiology of cervical cancer has been clearly linked to infection with the human papillomavirus (HPV); and nearly 100% of cervical cancer cases are attributed to HPV infection. Additionally, HPV causes 88% of anal cancers, 43% of vulvar cancers, 70% of vaginal cancers, 50% of penile cancers, and 70% of oropharyngeal cancers, representing nearly 4.8% of all cancers worldwide. Globally, an estimated 50 to 80% of men and women will acquire an HPV infection in their lifetime, making it the most widely prevalent sexually transmitted infection (STI). Among HIV-infected individuals, studies worldwide demonstrate that HIV-infected women have a 2-25-fold risk for ICC compared to the general population and ICC is classified as an AIDS-defining illness. This paper describes the epidemiology of cervical HPV infection and ICC including risk factors among women in India with a special focus on HIV-infected women. We also examine strategies for ICC prevention, specifically screening and vaccination.

HUMAN PAPILLOMAVIRUSES (HPVs)

Of the more than 100 HPV genomes that are fully sequenced, nearly 50% have been isolated from the anogenital tract. Human Papillomavirus is a non-enveloped DNA virus that has a predilection for the skin and mucosal epithelial tissue. Human papillomaviruses are further classified into low-risk and high-risk based on their ability to integrate into the host genome and produce malignant lesions. There are 13 HPV genotypes HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 that are designated high-risk because of strong evidence of their carcinogenic potential. All of these have been isolated in varying proportions from ICC cases across the world. Human papillomavirus 16 and 18 are the most potent carcinogenic types and account for 70% of all cervical cancers globally.

EPIDEMIOLOGY OF HPV INFECTION

In 2012, an estimated 528,000 women had cervical cancer and 266,000 women died from the disease. Globally, the annual age standardized incidence of ICC is 14/100,000 women; 22/100,000 women in India; and incidence rates greater than 30/100,000 among women in Africa (Fig. 2). Two recent meta-analyses of studies worldwide provide information on HPV prevalence among women with normal cytology and those with abnormal cytology. Among >1 million cytologically normal women from 194 studies worldwide,
Fig. 1: Incidence, mortality and 5-year prevalence of various cancers among Indian women (Globocan 2012 with permission)\textsuperscript{5}

Fig. 2: Age standardized incidence of cervical cancer worldwide in 2012 (Globocan 2012 with permission)\textsuperscript{1}
HPV prevalence was 11.7% and ranged from 1.6 to 41.9%. Human papillomavirus 16 (3.2%) and 18 (1.4%) were the most prevalent genotypes, and about 3.2% of women tested harbored multiple HPV infections. An estimated 7.9% of Indian women had an HPV infection (4.8%-36.8%). In the second meta-analysis, among 115,789 high-risk HPV women with normal and abnormal cervical cytology, HPV prevalence rose with severity of cervical lesions from 73% in women with CIN1 to 93% in women with CIN3. This rise is reflected in Indian women as well; women with cervical disease in one study had a higher proportion of any HPV (normal cytology: 7.6%; CIN1: 42.3%; >CIN2: 87.5%), and HPV 16 infection (normal cytology: 28.6%; CIN1: 36.4%; >CIN2: 74.3%), and this proportion increased with severity of disease. Human papillomavirus infection also differs over the life span. Although younger women tend to have a higher prevalence of HPV infection in most populations, prospective data clearly indicate that 90% of women clear these asymptomatic infections within 2 years. Approximately, 4 to 10% of women with prevalent infections experience persistent carcinogenic infections that result in malignant cervical disease.

HUMAN PAPILLOMAVIRUS GENOTYPE DISTRIBUTION

Indian women from the general population harbor a wide range of genotypes. Human papillomavirus 16 and 18 are the predominant genotypes that are detected in women with normal and abnormal cytology. Human papillomavirus 16 and 18 combined prevalence ranges from 2.0 to 10.1% among women with normal cytology. Other high-risk genotypes that were commonly detected in women from some of these studies included HPV31, 33, 35, 39, 45, 51, 52, 56 and 59. Among women with high-grade cervical disease, HPV 16 and 18 combined prevalence ranged from 74 to 97% with >70% of the fraction attributed to HPV 16 in most studies. Other high-risk genotypes that were frequently detected in women with ≥ CIN2 were 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. Multiple HPV infections were also common in women with cervical abnormalities. The only 24 months prospective study of HPV infection in young women from a low-income community in Delhi found an any genotype cervical HPV incidence rate of 5.0 per 1000 women months with HPV 16 having the highest incidence rate of 3.0 per 1000 person months.

CERVICAL HPV INFECTION AMONG HIV-POSITIVE WOMEN

Worldwide studies have documented that compared to HIV-negative women, HIV-infected women experience a 2-5-fold risk of acquiring a cervical HPV infection, have higher HPV incidence and persistence rates, show a shorter time interval for development of cervical lesions, experience recurrent cervical disease and faster progression to invasive cervical cancer. Information regarding HPV infection among Indian women is limited in comparison to the developed world and there is a lack of prospective data. A large cross-sectional study of 1,109 HIV-infected women in Maharashtra reported an HPV prevalence of 44.8%. In other smaller cross-sectional studies of HIV-positive women from Pune, North India, West Bengal and Tamil Nadu and one 12-months prospective report from Mumbai, HPV (any type) prevalence ranged from 20 to 56% (Table 1). These reports are 3 to 8 times higher than the HPV prevalence in the general population of Indian women. Similar to studies worldwide, cytologically normal HIV-infected Indian women have a higher HPV prevalence than cytologically normal HIV-negative women.

Human papillomavirus genotypic distribution in HIV-positive Indian women is similar to studies in other parts of the world although the relative contributions may vary. Human papillomavirus 16 is the most prevalent type; other common high-risk genotypes include 18, 31, 33, 35, 51, 56, and 68. HIV-positive Indian women also had multiple high-risk HPV infections and a higher prevalence of non-HPV16/18 infections. Among HIV-infected women with cervical intraepithelial neoplasia (CIN), HPV 16 was the most commonly detected genotype—31.9% in CIN1 and 69.8% in CIN2/3. There was some variation in the detection of cervical lesions across studies. Prevalence of CIN1 ranged from 3.96 to 36.7% and CIN 2+ ranged from 4.71 to 11.2% (see Table 1).

RISK FACTORS FOR HPV INFECTION

Age, Sexual Behavior and STIs

As anogenital HPV infection is transmitted by sexual intercourse, sexual behavior patterns among women and their partners often dictate women’s risk for HPV exposure and acquisition. Data from many studies indicate that younger women are at greater risk for HPV infection and early age at first sexual intercourse is a risk factor for HPV acquisition. However, studies have also shown that this risk is potentially influenced by other sexual behaviors. Kahn et al. found that risk of HPV infection at early sexual debut was mediated by other risky behaviors including higher number of sexual partners, history of STIs, alcohol/drug use related to sexual behaviors, and higher number of a partner’s sexual partners. It has also been suggested that the increased risk may be due to biological factors such as an immature cervix with metaplastic epithelium, which is vulnerable
Table 1: Prevalence of HPV and cervical abnormalities among HIV-positive women in India

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Sample Size</th>
<th>Population</th>
<th>HPV(%)</th>
<th>LSIL(%)</th>
<th>HSIL(%)</th>
<th>CIN1(%)</th>
<th>CIN2(%)</th>
<th>CIN3+(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggarwal et al 2012</td>
<td>North India</td>
<td>130</td>
<td>Women attending ART clinic</td>
<td>20†</td>
<td>0.77</td>
<td>2.30</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Isaakidis et al 2013</td>
<td>Mumbai</td>
<td>95</td>
<td>Women attending ART clinic</td>
<td>32</td>
<td>14</td>
<td>5</td>
<td>8.40</td>
<td>5.30</td>
<td>2.10</td>
</tr>
<tr>
<td>Joshi et al 2005</td>
<td>Pune</td>
<td>287</td>
<td>Women attending voluntary counseling testing clinic</td>
<td>33*</td>
<td>4.18º</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Joshi et al 2012 and Joshi et al 2014</td>
<td>Pune</td>
<td>1109</td>
<td>Women in Pune, Maharashtra</td>
<td>45</td>
<td>4.44</td>
<td>1.76</td>
<td>3.96</td>
<td>1.71</td>
<td>3.10</td>
</tr>
<tr>
<td>Mane et al 2012</td>
<td>Pune</td>
<td>278</td>
<td>Women attending ART center &amp; through community outreach</td>
<td>53</td>
<td>32</td>
<td>2.52</td>
<td>36.70</td>
<td>6.50</td>
<td>4.70</td>
</tr>
<tr>
<td>Peedicayil et al 2009</td>
<td>Tamil Nadu</td>
<td>75</td>
<td>Women attending a multidisciplinary HIV clinic</td>
<td>39</td>
<td>1</td>
<td>13</td>
<td>—</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>Sarkar et al 2011</td>
<td>West Bengal</td>
<td>93</td>
<td>Women attending pre-ART clinic and reproductive and child healthcare clinic</td>
<td>56</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Testing for HPV16/18 only; †Testing for high-risk HPV only; ºIncludes LSIL and ASCUS

Several recent studies in India that looked at the association of age and HPV infection found that HPV prevalence was constant across all ages. In these studies, age at first sexual intercourse and young age at marriage (surrogate marker for first sexual intercourse) were not associated with HPV infection. Indian women mostly report low number of sexual partners and no history of other sexually transmitted infections, which might explain this difference from other reports worldwide. In one study, consistent with studies in other nations, husband’s sexual activity including extramarital sex and reported history of sexually transmitted infections, which might explain this difference from other reports worldwide. In one study, consistent with studies in other nations, husband’s sexual activity including extramarital sex and reported history of sexually transmitted infections was significantly associated with HPV infection and risk for ICC among Indian women. Coinfection with HIV (See previous section) and/or other STIs is also a strong risk factor for ICC. Data indicate that certain STIs, such as Chlamydia trachomatis and herpes simplex virus type 2 (HSV-2) increase HPV persistence as well as influence the development of high-grade cervical lesions and invasive cancer. Some researchers suggest that this high-risk is in part, due to cervical inflammation produced by these STIs, possibly resulting in genotoxic damage by reactive oxidative metabolites. As in HIV and other STIs, circumcision is a cofactor in reducing HPV infection. Castellsague et al found that monogamous women had a reduced risk for cervical cancer if their male partners were circumcised. In addition, a recent trial in Rakai, Uganda demonstrated that female partners of circumcised males had a lower HPV prevalence and a lower rate of newly detected high-risk infections.

High Parity, Smoking, Oral Contraceptives and Socioeconomic Status

Other contributing cofactors in cervical carcinogenesis are high parity, smoking, and long-term use of oral contraceptives (OC). HPV infection in women with higher number of pregnancies is more likely to progress to ICC. Likewise, multiparous Indian women had a higher risk for cervical cancer compared with nulliparous women. Data from many studies indicate that smoking not only influences HPV persistence and increases the risk for CIN3 and ICC but also there is a clear dose-response relationship. It is unclear whether the increased risk is due to carcinogens
in cigarettes that cause DNA damage or because smoking has a negative impact on the host immune response to viral infection.59-61 In studies, assessing smoking and ICC risk, Indian women do not report smoking but one study found a two-fold risk for ICC with reported pan chewing.47 An analysis of 35 studies among women with and without cervical cancer showed an enhanced ICC risk with recent and current use of OCs.62 In addition, a more recent study by Luhn et al found that high parity, smoking and long-term OC use resulted in an elevated risk for CIN3 vs <CIN2 suggesting that smoking and hormone-related factors play a role in the progression of HPV infection to precancerous lesions.54

Among Indian women, another factor associated with an increased risk for HPV infection in India and subsequent development of ICC is low socioeconomic status.63 One case control study by Franceschi et al found that surrogate markers of poverty or low socioeconomic status, such as poor hygienic conditions, low education, pan chewing and poor nutrition were associated with higher risk of HPV infection and higher ICC risk.47

Risk Factors for HIV-infected Women

Data from a few studies on HIV-infected women in India indicate an increased HPV risk associated with multiple sexual partners,37 parity,34 and young age at first sexual intercourse.36 Declining CD4 counts at study enrollment and nadir CD4 < 200 cells/µL were also significantly associated with HPV infection.34,37 Worldwide, published reports on the effect of antiretroviral therapy (ART) on HPV risk and cervical cancer are inconclusive.64 Likewise, in India, Isaakidis et al reported a higher odds of HPV infection among HIV-infected women receiving ART for <12 months compared to ≥12 months (OR = 3.57, p = 0.025), while Joshi et al did not find any effect of ART duration on HPV risk; and Mane et al reported a higher odds of HPV 16 infection (OR = 3.47, CI: 1.47-8.59) as well as more severe CIN among ART-experienced women. It has been postulated that the increased survival time due to ART may allow the development of cervical disease as well as other cancers in HIV-positive patients.64,65

PREVENTION OF INVASIVE CERVICAL CANCER

Pap Cytology, Visual Inspection with Acetic Acid (VIA) and HPV DNA Testing

Invasive cervical cancer is a preventable disease. Cervical cancer screening followed by treatment of abnormal lesions, and HPV vaccination, remain the two key modalities for ICC prevention. In the developed world, women can be screened by (1) cytology using the conventional Papanicolaou (Pap) test or the newer liquid-based, thin layer cytology,66 and (2) high-risk HPV DNA testing (for women older than 30) as cotesting. The employment of extensive cytology screening to detect abnormal lesions early has resulted in a remarkable decline in ICC incidence worldwide.67 However, developing countries, such as India have not been able to successfully implement Pap smear screening because of a weak health infrastructure for adequate collection and transport of specimens, lack of competent cytopathologists, inadequate laboratory infrastructure, inability to manage follow-up visits and other barriers.58,60 In addition, cytology-based screening is not especially sensitive and requires repeated screening or cotesting with HPV DNA to be efficacious for reducing ICC risk, thus making it a less cost-effective option in developing countries.32

An alternate screening technique, visual inspection of the cervix after application of acetic acid (VIA) or Lugol’s iodine (VILI) has gradually gained acceptance in resource-constrained settings such as India. VIA/VILI are simple to conduct and allow for same day ‘screen and treat’ approaches in non-urban or low-resource settings where loss to follow-up remains a critical issue in treating women early.69 Two large-scale randomized control trials of VIA screening among 80,000 women in Tamil Nadu and 150,000 women in Mumbai that included colposcopy and directed biopsy of positive cases followed by treatment, showed a 35% and 31% reduction in ICC mortality.70,71 Overtreatment of women without precancerous lesions using cold coagulation or cryotherapy is of concern in a VIA one visit ‘screen and treat approach’.69,72 A few recent studies have also evaluated a ‘see and treat’ approach, which combines VIA with colposcopy/directed biopsy and treatment with loop electrosurgical excision procedure (LEEP) in one visit with inconsistent results.72,73 This approach requires experienced colposcopists that could make accurate diagnoses to prevent overtreatment.

Human papillomavirus DNA testing has recently been found to be a valuable alternative tool to Pap cytology under specific conditions. Data from a large population-based trial in Osmanabad, India demonstrated that HPV DNA screening of women 30 years and older, at least once in their lifetime can result in a 36% reduced lifetime risk of cervical cancer at a cost of <$500 per life saved.74,75 Several other published reports also indicate that HPV DNA testing is superior to cervical cytology and VIA screening in reducing ICC risk among women older than 30 years.36,77 Human papillomavirus DNA testing is highly sensitive but has a low specificity, and is not recommended among younger populations and HIV-infected women, given the high HPV prevalence in these populations. In addition, HPV DNA tests are expensive, require trained technical staff, and results are not available quickly.69 The care HPV test, a less expensive
option, has shown favorable results with good sensitivity and specificity and is currently being marketed in some developing countries. The equipment is portable, provides results rapidly and can be performed with simple training and without expensive infrastructure.76

National cervical screening guidelines in India that were developed in 2005 with assistance from WHO and IARC have not been implemented widely.78 These guidelines recommend screening women between the ages of 30 and 59 at least once in their lifetime at a primary health center using VIA and if indicated, a follow-up single visit at the district hospital to include colposcopy and treatment when necessary.78 These guidelines are a minimum for those settings in India that have limited resources. Table 2 compares guidelines by the American Society for Colposcopy and Cervical Pathology (ASCCP)67 and WHO.79 Of note, ASCCP recommends that HIV-infected women should be screened more often with two Pap smears 6-months apart during the first year after diagnosis, and if normal, then annual screening thereafter.80 Implementing frequent screening for HIV-infected Indian women is feasible through creative utilization of the existing infrastructure during regular care visits.

**BARRIERS TO CERVICAL SCREENING**

Cervical screening rates in India are extremely low. In a large population study of 100,800 women in Maharashtra, only 8 women reported ever being screened prior to the study.81 A WHO household survey in 2001-2002 found an overall 2.6% rate of Pap smear screening among urban and rural women.10 In rural Kerala, 6.9% of women in one study reported being screened.82 Community participation was noted as the key barrier to screening women in Andhra Pradesh.68 Women did not perceive a need to seek medical attention in the absence of symptoms. Other common reasons cited by women were fear/anxiety of medical providers, fear of pelvic exam, pain, discomfort, embarrassment, fear of cancer diagnosis, fear of community perception and gossip, since ICC is associated with sexual activity, and not knowing where to go for the test.68,82 Lack of support from husband and other family members were also important reasons for low participation in screening.68,82 Self-collection of samples for HPV screening improved participation rates from 53.8% (clinician collected) to 71.5% in a rural setting.83 Currently, there is no national policy on cervical screening in India and therefore no significant investment has been made to implement nationwide screening. Developing countries, such as Mexico, Thailand and Brazil have implemented national cervical screening initiatives that have been designed to meet the needs of their unique populations.72 India can learn from these successful initiatives.

**HUMAN PAPILLOMAVIRUS VACCINATION**

Two HPV vaccines Gardasil®, a quadrivalent vaccine to protect against infection from HPV genotypes 6, 11, 16, and 18 and Cervarix®, a bivalent vaccine to protect against infection from HPV genotypes 16 and 18 are expected to

<table>
<thead>
<tr>
<th>Population</th>
<th>WHO*</th>
<th>ASCCP</th>
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<tbody>
<tr>
<td>Age &lt;21 years</td>
<td>No screening for women &lt;30 years unless HIV+ or living in high HIV prevalence area</td>
<td>No screening</td>
</tr>
<tr>
<td>Age 21-29 years</td>
<td>No screening for women &lt;30 years unless HIV+ or living in high HIV prevalence area</td>
<td>Cytology screening only every 3 years</td>
</tr>
<tr>
<td>Age 30-65 years</td>
<td>Prioritize women 30-49 years Screening interval with VIA/cytology should be 5 years (not less) Screening interval with HPV testing should be 10 years (not less)</td>
<td>Cytology and HPV co-testing every 5 years (preferred) Cytology screening alone every 3 years (acceptable)</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>No screening, if previous history of negative screening Women with prior history of ≥ CIN2 must continue routine screening for at least 20 years</td>
<td>No screening for women without cervix and previous negative screening for CIN2</td>
</tr>
<tr>
<td>After hysterectomy</td>
<td>Same as age-specific recommendations for unvaccinated women</td>
<td></td>
</tr>
<tr>
<td>HPV vaccinated</td>
<td>Same as age-specific recommendations for unvaccinated women</td>
<td></td>
</tr>
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</table>

VIA: Visual inspection with acetic acid; CIN2: Cervical intraepithelial neoplasia grade 2; ICC: Invasive cervical cancer; HPV: Human papillomavirus; “WHO guidelines are ‘minimum guidelines’ for countries that do not have national programs for cervical screening, specifically in resource-limited settings”76

Table 2: Summary of cervical cancer screening guidelines by the World Health Organization (WHO)*79 and American Society for Colposcopy and Cervical Pathology (ASCCP)67

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prevent up to 70% of all cervical and anal cancer cases caused by HPV 16/18 infections and >95% of genital warts (quadrivalent vaccine) in both women and men globally. The two vaccines approved by the WHO are typically recommended for girls 9 to 26 years in a series of three doses over 6 months. Data from clinical trials and other follow-up studies have demonstrated the safety and tolerability of both vaccines showing high immunogenicity, low adverse events and sustained protection of up to 8.4 years. Recently, the quadrivalent vaccine was found to be safe and immunogenic for HIV-infected children and women, although women with CD4 counts <200 cells/µl and HIV viral load >10,000 copies/ml had slightly lower seroconversion rates. There is growing evidence from countries that have implemented HPV vaccination among girls and young women that the vaccines have had a significant impact on reducing genital warts and decreasing incidence of high grade cervical lesions. Clinical trial data of the much anticipated nonavalent vaccine which protects against nine high-risk HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 indicate that the vaccine has the same efficacy as the quadrivalent vaccine against HPV 16 and 18 and has a 97% efficacy in preventing cervical disease from the additional five HPV types. It is estimated that the nonavalent vaccine will prevent up to 90% of cervical cancers.

**BARRIERS TO HPV VACCINATION**

Although Gardasil and Cervarix have been licensed by the Drug Controller General of India and recommended by the Indian Academy of Pediatrics, Committee on Immunization and the WHO, the vaccine has not been introduced into India’s national immunization schedule. Human papillomavirus vaccine uptake in India has been slow, encountering significant challenges as in other countries, including the need for three doses, high vaccine costs, poor awareness about the vaccine and its benefits, safety concerns, strong cultural beliefs that adolescent females are not sexually active and therefore fear of encouraging promiscuity, and lack of physician recommendations. Currently, the vaccine is only available through private providers because, in April 2010, the Indian government halted two vaccine feasibility studies due to demands from advocacy groups about adverse events related to the vaccine as well as other alleged ethical violations. An extensive inquiry determined that the deaths of seven girls who were vaccinated were not linked to the vaccine. However, the resultant public distrust and concerns about the vaccine have not been addressed preventing any further evaluation of implementation strategies through the national public health system. The cost of the HPV vaccine is a significant barrier and although the cost has been reduced from $100 to 4.50 per dose for GA VI eligible countries, the vaccine is still expensive for low-resource countries.

Increasing vaccine uptake in India will require that the delivery of HPV vaccine becomes a priority on the government’s agenda, by developing a national policy for preventing ICC that is lacking. Australia and Scotland have implemented successful national HPV immunization campaigns for girls 9 to 12 years and catch up vaccinations for adolescents and young adults through schools, community clinics and general practitioners. The South African government has announced that starting in 2014, it will begin to provide around 500,000 HPV vaccines to 9 to 10 year old girls. India has been successful in their national immunization campaigns for other childhood diseases and can learn from other countries as well to implement such campaigns. It would be essential to first address public concerns about the vaccine, gain public trust, garner support from all stakeholders including women activists, media, schools, community leaders and particularly physicians that are a highly valued resource by the Indian population.

In summary, Indian women continue to share a significant burden of invasive cervical cancer. Human papillomavirus infection is widely prevalent among Indian women, with HIV-infected women at higher risk for cervical disease. Human papillomavirus 16 is the predominant genotype in both HIV-infected and uninfected women. Cervical screening rates are extremely low, and modest improvements to screening participation rates have the potential to significantly reduce ICC burden. Implementing Pap cytology nationwide as the main cervical screening modality is not feasible because of the substantial infrastructure investment and quality control needed to screen accurately. VIA might be a better option in the short-term, if VIA can be standardized with well-trained staff to increase specificity. The long-term goal must include the development of rapid, inexpensive screening tests requiring low-resources and able to detect HPV DNA or biomarkers that can predict precancerous lesions in women. New screening and treatment algorithms using such tests will allow the scale up of prevention programs in countries that share a large burden of ICC. Lastly, a national public policy regarding cervical screening of women and HPV vaccination for girls and young women in India is integral to the scale up of both primary and secondary prevention programs and must become a priority.

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