The epidemiology of HPV and HIV among high-risk women and steady couples in Kigali, Rwanda

Veldhuijzen, N.J.

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General discussion
Sexually transmitted infections (STIs) continue to cause a large burden of disease. The World Health Organization (WHO) estimated that in 1999 approximately 340 million individuals worldwide acquired a curable sexually transmitted infection (Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae and Treponema pallidum), with developing countries accounting for 80-90% of the global burden. Although the burden of disease related to HIV/AIDS has understandably caught most attention, it is important to note the extensive morbidity and mortality associated with other STIs. The direct consequences of infection include cervicitis, vaginitis, urethritis, and pelvic inflammatory disease while long-term sequelae include infertility, preterm labour, anogenital cancers and congenital abnormalities in neonates. In this thesis, data were presented on the prevalence and incidence of STIs in two population groups in Kigali, Rwanda, with a focus on HIV and high-risk HPV (HR-HPV). The two population groups were women at high risk for HIV and STIs, mostly self-identifying as female sex workers (FSW), and heterosexual couples from the general population. The HIV prevalence was 24% among high-risk women, 13% among women in from the general population and 8% among their male partners. HR-HPV prevalence was 33% among HIV-negative high-risk women and 55% among HIV-positive high-risk women. Among the heterosexual couples from the general population, HR-HPV prevalence was 17% among HIV-negative women and 22% among HIV-negative men (Chapters 3, 4, 8).

Epidemiological synergy between different STIs, defined as the increased infectivity of and/or susceptibility to STI pathogens in the presence of other STIs, has been most thoroughly shown for HIV. The presence of an untreated inflammatory or ulcerative STI increases the risk of HIV acquisition, and onward HIV transmission by those who are already HIV-positive, independent of sexual behavior. This co-factor effect is strongest for herpes simplex virus type 2 (HSV-2), but has also been shown for T. pallidum, other genital ulcer diseases, N. gonorrhoeae, C. trachomatis, T. vaginalis, and imbalances of the vaginal flora in women (bacterial vaginosis and candidiasis). More recent studies also suggest an association between HPV infection and HIV acquisition in women. We confirmed this in our own study among high-risk women in Kigali. Women who seroconverted for HIV between the first and second HPV measurement visit were 4.9 times (95% confidence interval (CI) 1.2–19.7) more likely to have HR-HPV detected at the first visit compared with women who remained HIV-negative (Chapter 5). In the heterosexual couples, HR-HPV concordance was significantly higher in HIV concordant positive couples compared to HIV concordant negative couples (OR 3.89; CI 1.5–10.1); prevalent HSV-2 infection also seemed to increase HR-HPV concordance somewhat although this was mediated by couple HIV status (Chapter 8).

As the term ‘sexually transmitted infections’ indicates, the different pathogens share their mode of transmission. Therefore, one cannot try to prevent one STI without taking the ongoing epidemics of other STIs into account. This last chapter provides a brief overview of the available primary and secondary STI prevention methods and aims to discuss the implications of the results of the preceding chapters with respect to these prevention methods.
APPROACHES TO PRIMARY PREVENTION

Primary STI prevention interventions can be divided into behavioral, biomedical and structural interventions. Behavioral interventions mostly consist of promotion of the ABC approach (abstinence, be faithful to one partner (or partner reduction more generally), and condom use). Available biomedical interventions include male circumcision and vaccination; oral and topical pre-exposure prophylaxis for HIV with antiretroviral drugs may also become available in the near future. Structural interventions focus on factors in the social, economic or political environment and include for example mass media campaigns, social marketing of condoms and decriminalization of prostitution. These latter interventions are beyond the scope of this thesis.

Behavioral interventions

Although the effectiveness of behavioral interventions on the prevention of STIs has been difficult to ascertain in (randomized controlled) clinical trials, the usefulness of reduction of sexual risk behavior in the prevention of STIs is widely accepted.9,11 The effectiveness of condom use – one important component of behavioral interventions - has been shown in clinical studies for HIV prevention, but much less consistent data are available for other STIs.11,12 An article reviewing the effectiveness of condom use and risk of gonorrhea and chlamydia concluded that condom use was associated with reduced risk of gonorrhea and chlamydia in men and women in most (though not all) studies.12 Self-reports on condom use are typically unreliable and overestimate actual use, leading to underestimation of condom effectiveness.12 The effectiveness of condom use in reduction of HPV acquisition is not proven, but an increasing number of studies show a trend towards a protective effect.13-15

Indirect evidence also exists, illustrated by the reduction of HIV incidence over time among study populations of several observational HIV incidence studies and biomedical HIV intervention trials. Researchers have attributed this to the HIV prevention interventions that all trial participants receive (usually HIV prevention counseling, condom distribution and prompt STI diagnosis and treatment). This is referred to as the Hawthorne effect.16 In our cohort study among high-risk women in Kigali, a non-significant downward trend in HIV incidence was observed during the first year of follow-up, from 4.6/100 (95% CI 1.6-7.7) persons-years (PY) in the first six months to 2.2/100 PY (0.4-3.7) in the second six months (Chapter 3). In the same period, 48 women (13%) had left sex work, and others had reduced their exposure risk by reducing the number of partners, reducing the frequency of sex, and/or increasing condom use. These self-reported data should of course be interpreted with caution because social desirability bias is often present.

A thus far neglected sexual risk behavior among heterosexuals, especially in sub-Saharan Africa, is anal intercourse. Anal intercourse is associated with a much higher HIV transmission probability compared to vaginal intercourse.17-18 We reported that anal intercourse among high-risk women in Kigali, and in Mombasa, Kenya, was associated with other indicators of vulnerability to STIs, such as lower frequency of condom use, higher number of sexual partners and a history of genital symptoms (Chapter 7). A better understanding of the prevalence and conditions under which anal
intercourse is practiced is crucial for behavioral STI prevention programs. However, negative connotations and stigma associated with anal intercourse – as documented in Chapter 7 – poses challenges to obtaining valid data.

Biomedical interventions

**Male circumcision**

The first documented evidence of male circumcision (MC) comes from an ancient Egyptian relief and dates back to the third century before Christ. Despite being heavily debated, MC has been practiced by many different cultures for religious, cultural or social reasons, including perceived health and sexual benefits. When MC was shown to protect men from acquiring HIV, Swazi men were queuing up to get circumcised.25

In 2007, the WHO/UNAIDS recommended to integrate MC in existing HIV prevention programs.21 This was 18 years after the first publication of a prospective (observational) study showing an increased risk of HIV-1 infection in uncircumcised men.22 The main reason for this long delay was concern about the quality of the evidence from observational studies, which are inherently more prone to bias and confounding than randomized controlled trials (RCTs). Three RCTs subsequently showed that MC reduced female to male HIV-transmission by approximately 50 - 60%, which led to the above-mentioned recommendation by WHO/UNAIDS.23-25 MC did not protect female partners of circumcised men from HIV, and may have increased transmission risk when men resumed sex prior to wound healing.26 These same RCTs also reported reduced rates of HR-HPV, genital ulcer disease and HSV-2 infection in the circumcised men and their female partners, and trichomoniasis and bacterial vaginosis in the female partners.26-28 As was detailed in Chapter 2, some studies provided evidence for a reduction of HPV prevalence among circumcised men through reduced incidence, others through increased clearance of prevalent infections, and yet others through both mechanisms; studies suggest that the reduced HR-HPV incidence and increased clearance in female partners is caused by reduced penile HPV carriage.29-31 More studies are needed to disentangle these biological pathways. Among the heterosexual couples in Kigali, (clinician-ascertained) MC was negatively associated with HR-HPV prevalence in men, but no association was found with HPV prevalence in women (Chapter 8). HIV prevalence was lower in circumcised men than in uncircumcised men, but this did not reach statistical significance (OR 0.29; 95% CI 0.03-2.11), perhaps due to limited statistical power as the study was not designed to determine predictors of HIV.

**HPV vaccination**

Effective prophylactic vaccines for STIs have been developed for HPV and Hepatitis B, and vaccines for HIV and HSV-2 are under development; only HPV vaccines will be discussed here.

HPV prevalence among HIV-negative women with normal cervical cytology worldwide is 12% and in sub-Saharan Africa 24%.32 HPV prevalence is highest among sexually active women below 25-35
years, and usually declines thereafter.\textsuperscript{32,33} Prevalence is higher among HIV-infected women and women at high-risk for other STIs.\textsuperscript{34,35} In Kigali, the prevalence of HR-HPV was 33\% among HIV-negative high-risk women (Chapter 3), 55\% among HIV-positive high-risk women (Chapter 3), 17\% among HIV-negative women from the general population and 41\% among HIV-positive women from the general population (Chapter 8). The literature suggests that the distribution of HPV types among women with normal cervical cytology is somewhat different from the one found in women with cervical cancer: the most prevalent types in women with normal cytology are HPV 16, 18, 52, 31 and 58 whereas the most prevalent types among women with invasive cervical cancer are HPV 16, 18, 45, 31 and 33.\textsuperscript{32,36} The great majority of high-risk women and of women from the general population in Kigali had normal cervical cytology. HPV 16, 45, 52 and 58 were among the top 5 HR-HPV types found in both female study populations, irrespective of HIV status. However, the exact order of importance differed slightly with HPV 52 being especially important in HIV positive women (Chapter 4, 8). A recent meta-analysis reported that up to 70\% of cervical cancer cases worldwide are caused by HPV types 16 and 18.\textsuperscript{38} HPV 45 was reported to be the third most common type detected invasive cervical cancer cases, although it is rare among women with normal cytology.\textsuperscript{32} It should be noted though that of the 10,575 cervical cancer cases included in this meta-analysis, only 691 (6.5\%) were from Africa (91 from Algeria, 232 from Mozambique, 187 from Nigeria and 181 from Uganda). In addition, the HIV status of patients was not known or reported. In general, there is a paucity of data on HPV type-specific distribution among HIV-infected women with cervical cancer from developing countries.

The acquisition of HPV and the subsequent development of cervical lesions can be prevented by one of two currently available prophylactic HPV vaccines. One of these is a quadrivalent vaccine (Gardasil, Merck), which protects against infection with HPV types 6, 11, 16 and 18. The other is a bivalent vaccine (Cervarix, GlaxoSmithKline), which protects against infection with HPV types 16 and 18. Vaccine efficacy is not influenced by positive HPV serology, an indicator of previous exposure to vaccine-type HPV. Prevalent HPV infection of vaccine-types, however, drastically reduces vaccine efficacy while clearance remains unchanged. Furthermore, cross-protection by vaccine-induced antibodies has been shown for types 31, 33 and 35, and to a lesser extent for HPV 45 and 52, in the case of the bivalent vaccine.\textsuperscript{37} Whether cross-protection is induced by the quadrivalent vaccine is much less clear.\textsuperscript{38,39} Clinical trials evaluating vaccine efficacy (of both vaccines) among HIV-positive women are currently ongoing.

Adolescent girls in sub-Saharan Africa would benefit from HPV vaccination and a pilot program was initiated in Uganda in 2008.\textsuperscript{40} Rwanda has developed a combined nationwide cervical cancer screening and HPV vaccination program and is preparing for implementation.\textsuperscript{41} The HPV vaccination program, using the quadrivalent vaccine, targets girls in the sixth year of primary school and a catch-up program for girls in the third year of secondary school. Out-of-school girls will be approached by community outreach workers. Data on type-specific HPV infection among women with cervical cancer are currently not available from Rwanda. A baseline case-series of HPV-type distribution among women with cervical cancer would be important for vaccination impact assessment and future monitoring.
Apart from adolescent girls, adult high-risk women may also benefit from vaccination, even if they have been previously exposed to HPV. We found that HR-HPV prevalence among HIV-negative high-risk women in Kigali was 33%, but only 9% had HPV 16 and/or 18. That means that 91% of these high-risk women would benefit from HPV vaccination. Assuming a vaccine efficacy close to 100% (as was demonstrated in clinical trials)\textsuperscript{32}, 70% of cervical cancer cases (those caused by HPV 16 and 18) in this group could be prevented. Furthermore, when the prevalence of HPV is reduced among vaccinated high-risk women, their clients would be at lower risk of acquiring HPV infection from them. Therefore, we argue in Chapter 4 that high-risk women in settings with a high prevalence of high-risk HPV would benefit from screen-and-vaccinate (and screen-and-treat) programs. Polyvalent vaccines that include additional oncogenic HPV types over and above HPV 16 and 18 would prevent even more cervical cancer cases; for example, including HPV 45 would prevent 10% more cases in Africa (10% of cervical cancer cases in Africa are caused by HPV 45).\textsuperscript{36} In addition – although a causal association has not yet been firmly established – the impact on HIV acquisition may also be larger with polyvalent vaccines. Some recent studies have shown that prior HR-HPV infection is associated with an increased risk of HIV acquisition, especially for other types than HPV 16 and 18.\textsuperscript{5} In Chapter 5, we demonstrated this among high-risk women in Kigali, Rwanda, where HPV 52 was the most prevalent subtype among women who subsequently seroconverted for HIV. HPV vaccination, particularly with polyvalent vaccines, may therefore also contribute to a reduction in HIV acquisition.

**Pre-exposure prophylaxis**

Pre-exposure prophylaxis (PrEP) for HIV using antiretroviral drugs can be divided into oral and topical prophylaxis. Both methods are not yet on the market but proof of concept trials have recently shown promising results. Topical PrEP products, such as vaginal and rectal microbicides containing antiretroviral drugs, are applied to mucosal surfaces. In oral PrEP, antiretroviral drug regimens are taken orally. An RCT comparing pre- and post-coital use of vaginal tenofovir gel with a placebo gel (CAPRISA 004) found a reduced HIV incidence of 54% among high-adherent women (gel adherence of at least 80%), 38% in intermediate adherers (gel adherence 50-80%) and 28% in low-adherers (gel adherence less than 50%).\textsuperscript{55} In addition, a protective effect of 51% against HSV-2 acquisition was found.\textsuperscript{\textsuperscript{54}} An RCT using a combination of two oral antiretroviral drugs, and tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) once a day compared to placebo, demonstrated a reduction in HIV incidence by 44% in the TDF-FTC arm.\textsuperscript{\textsuperscript{51}} These promising results for both topical and oral PrEP need to be confirmed in additional studies in a variety of settings, several of which are ongoing.

**APPROACHES TO SECONDARY PREVENTION**

**Syndromic management**

Among high-risk women in Kigali, baseline prevalences of 17% for trichomoniasis, 12% for gonorrhea, 5% for chlamydia and 7% for syphilis were found (Chapter 3). The incidence per 100 person-years of follow-up was 17 for trichomoniasis, 12 for gonorrhea, 8 for chlamydia and 6 for syphilis (Chapter 3). Among women from the general population in Kigali, the prevalence rates
were much lower: 6% for trichomoniasis and gonorrhea and 3% for chlamydia and syphilis (Chapter 8). Both higher and lower prevalence rates are reported from female sex worker (FSW) populations in other sub-Saharan African populations and these are strongly dependent upon the HIV prevalence in the population. For example, gonorrhea prevalence among FSW in Tanzania (HIV prevalence 68%) was 22% compared to 8% among FSW from Congo (HIV prevalence 12%).46-48 The epidemiological synergy described earlier not only explains the higher incidence of HIV among persons with other STIs but also the higher prevalence of STIs among HIV infected persons, independent of exposure level (sexual risk behavior).

Obstacles in the timely diagnosis and treatment of STIs in developing countries include the large proportion of asymptomatic infections in women, lack of diagnostics, poor availability and quality of treatment, and lack of partner notification and treatment. In 1991, the WHO published the first syndromic management guidelines for STIs.52 These guidelines were updated in 2003 with revisions in the management of genital ulcers and vaginal discharge.53 In the absence of cheap, reliable, and user-friendly diagnostics, the syndromic management approach offers a simple clinical tool for controlling and treating STIs, thereby reducing onward transmission and/or complications. Studies indicate that the approach works well for urethral discharge and genital ulcers in women and men, but that the low specificity of vaginal discharge syndrome results in overtreatment.52 Furthermore, by definition, all asymptomatic infections are missed. Adding a risk score assessment may reduce the overtreatment rate, but not convincingly.52 The interest in STI control gained momentum in the late 1990s with the advent of HIV prevention programs. There is however, a broader relevance to STI control programs than ‘just’ HIV prevention, which is not always taken into consideration. As mentioned earlier, bacterial and other viral STIs are a cause of significant morbidity and mortality in their own right, independent of their effect on HIV acquisition and transmission. Timely diagnosis and treatment would reduce the overall STI-related morbidity and mortality. In our study among steady couples in Kigali, for example, secondary infertility was associated with higher prevalence of STIs in women (HIV aOR 4.03 (95% CI 2.44-6.65); HSV-2 aOR 2.59 (95% CI 1.68-4.05) genital symptoms aOR 3.98 (95% CI 1.71-9.29)) and in men (HIV aOR 3.28 (1.78-6.41); HSV-2 aOR 2.57 (1.58-4.16)).53 The syndromic treatment guidelines are often reported to be widely implemented, but few formal assessments are published for the African region.

Of note, STI control involves more than syndromic management guidelines alone: health education, condom promotion and partner notification and treatment are other important aspects. Importantly, these services are only of benefit to symptomatic patients who present themselves to appropriate health clinics. However, many women (and to a lesser extent men) are asymptomatic and not all symptomatic patients will seek care. Some may not recognize the symptoms, be unaware of the risks involved, delay seeking care or consult unqualified sources. Among the high risk women in Kigali, 20% self-reported genital symptoms in the past month but only 24% of women with symptoms sought treatment (unpublished). In a qualitative study among the same study population, shame and stigma were identified as obstacles for seeking medical care for genital symptoms (manuscript in preparation). Such local barriers for access to and acceptability of care should be identified and taken into account in program design and evaluation. Furthermore, to reach asymptomatic patients screening programs (targeting high-risk groups) should be implemented. Asymptomatic patients constitute an important source of ongoing STI transmission and remain at risk of developing long-term complications. The development of rapid STI tests would facilitate screening of asymptomatic persons and would reduce overtreatment of women with
vaginal discharge syndrome. The Sexually Transmitted Diseases Diagnostics Initiative was initiated by the WHO in 1990 to facilitate the development and evaluation of rapid diagnostic STI tests but such tests are still not widely available for chlamydia and gonorrhea. Finally, targeted STI screening programs could also identify HIV-positive persons who may otherwise not have presented themselves to the health care system. For example, 50% of HIV-positive women participating in a post-diagnosis visit of our HIV incidence study in Kigali had never received an HIV test before the baseline survey (Chapter 6).

**Cervical cancer screening**

Several screening methods are available to detect precancerous cervical lesions. They include cytology and visual inspection of the cervix with either acetic acid (VIA) or lugol’s iodine (VILI) to detect the lesions themselves, and HPV DNA testing to find women who are at increased risk for having or developing lesions. The personnel and health care infrastructure requirements for a cytology-based screening program are prohibitively difficult for many developing countries. A screen-and-treat approach using visual inspection or HPV DNA testing combined with cryotherapy - in which diagnosis and treatment all occur during the same visit – is more feasible and pilot programs are underway in several countries.

Cervical cancer screening in Rwanda is only available in some private clinics and some research settings such as ours. The Women’s Health clinic at the Kigali University Teaching Hospital, which was established in the context of our study among heterosexual couples, has facilities for visual inspection, colposcopy-directed biopsies and cryotherapy. High-risk women participating in the HIV incidence study were referred to the Women’s Health Clinic in case of abnormal cytology results. All women participating in the heterosexual couple study underwent visual inspection with acetic acid in the Women’s Health Clinic. The median age of high-risk women was 25 years and of the women from the general population 28 years. The prevalence of precancerous lesions in both populations was low (4.4% among HIV-negative high-risk women, 9.4% among HIV-positive high-risk women and 4.0% among women from the general population), which is expected among women this age (Chapter 4, 8). Among women from the general population, 6% had positive VIA results; only 22% of them (2/9) had abnormal cytology results and 44% of them (4/9) were HR-HPV positive (not published).

The Rwandan national cervical cancer screening program, as developed by the Rwandan government, foresees mobile HPV-screening teams. HR-HPV DNA positive women will receive VIA. The program will target women aged 35 years during the first year, and women aged 35 and 45 years during subsequent years; women testing HR-HPV positive / VIA negative at the age of 35 will be re-screened at the age of 45 years. HPV DNA positive/ VIA positive women will be treated with cryotherapy. If more extensive lesions are diagnosed, women will be referred to provincial hospitals for more advanced treatment and colposcopy-directed biopsy.

Clinical specificity of HPV DNA testing is determined by the age-specific HR-HPV distribution in the population. It is expected to be low among women below the age of 30 years because the majority of these HPV infections will be transient. Current recommendations are therefore to use HPV testing for cervical cancer screening only in women older than 30-35 years. Clinical specificity of
HPV testing may also be improved by carefully selecting relevant HPV types included in the test and by choosing a (higher) threshold for a positive result. Novel biomarkers of HPV-associated transformation are being developed and may be used in the future for triage of HPV DNA positive results. These tests would ideally identify women who currently have precursor lesions but also women who are likely to develop such lesions in the future. Whether these tests will be appropriate and accessible for screen-and-treat programs in low-resource settings is not yet known.

**Antiretroviral treatment for HIV prevention**

Combination antiretroviral therapy (cART) has reduced HIV-related morbidity and has improved the life-expectancy of HIV patients. Although comprehensive HIV care and treatment programs aim to treat HIV-positive individuals, they may also serve as an important tool for reducing risk of onward HIV transmission to uninfected individuals, so-called ‘ART for prevention’. HIV infected individuals who are successfully treated (with undetectable viral load) are less infectious and therefore less likely to transmit the virus to their sexual partners. The expanding availability of treatment and care facilities offers other prevention possibilities as well. As indicated earlier, the infectivity of HIV is increased in the presence of other STIs. Comprehensive HIV care and treatment programs should therefore include STI control services. Other components of ‘prevention for positives’ include behavioral interventions (reduction in sex partners, condom use, disclosure of HIV status); access to prevention of mother-to-child transmission programs; prevention of unintended pregnancies in HIV-infected women and testing and counseling of sexual partners of HIV-infected individuals.

HIV care and treatment programs have proliferated in sub-Saharan Africa in recent years, with cART coverage now estimated at 44% (41-48%) of those in need. However, ART access remains variable across countries, and challenges in linking and retaining newly HIV-diagnosed individuals in care in resource-limited settings are well known. In Rwanda, the number of health facilities offering cART increased rapidly from only 4 in 2002 to 269 in 2009. The number of people receiving cART has increased impressively from 870 in 2002 to 76,726 in 2009, with 77% of adults in need of CART receiving treatment. It is relevant to note that CD4 eligibility criteria for CART changed over time from lower or equal to 250 cells/ml to lower or equal to 350 cells/ml since 2007. In our study, 85% of high-risk women who tested HIV-positive during screening had enrolled in care after a median of 30 days after diagnosis (Chapter 6). (Self-reported) CART initiation among eligible individuals was 77% approximately two years after diagnosis. During the post-diagnosis visit, nearly all women reported having disclosed their HIV status to one or more close relatives or friends and unfortunately, many of them had experienced HIV-related stigma. Many women had reduced their sexual risk behavior, most notably discontinuing transactional sex. However, two-thirds of women continued to engage in sex work, and a substantial number reported ongoing unprotected sexual contacts. Linkage-to-care rates were high in our population, but there was a clear need for strengthening of ‘prevention for positives’ initiatives.
RECOMMENDATIONS FOR FUTURE RESEARCH

This thesis has identified several questions that remain to be answered. In addition, several public health interventions that need strengthening in the context of Rwanda were identified, but this most likely also applies to similar settings in sub-Saharan Africa.

Research questions:

What are determinants of susceptibility to and infectivity of HPV? How do the different other STIs interact with HPV? And what is the role of mucosal immunology and human microbiota on susceptibility to and infectivity of HPV? A better understanding of HPV transmission dynamics – but also of the mucosal immunology in general – is needed to identify new therapeutic and prophylactic products.

What is the effect of HIV co-infection on HPV genital shedding in men? Studies have shown that HIV co-infection in women increases their HPV genital viral load, thus infectivity. For men however, this remains to be established. The answer to this question would also increase our knowledge about HPV transmission dynamics.

What is the contribution of anal intercourse in the HIV epidemic among heterosexual couples in sub-Saharan Africa? This information is needed to inform prevention programs as well as the design and interpretation of HIV prevention intervention trials, including vaginal microbicide trials.

Does HPV indeed increase the susceptibility to HIV? Which particular HPV types are involved? This can be evaluated in randomized controlled clinical trials with HIV incidence as the trial outcome and HPV vaccination as the intervention. However, if non-HPV 16/18 types play an important role then the current vaccines will have limited impact. Polyvalent vaccines are not yet available but may have a larger impact.

Is a screen-and-treat program including vaccination for (vaccine type) HPV negative women (a so-called screen-treat-or-vaccinate program) cost-effective among high-risk women? In developed countries, where efficient cervical cancer screening programs are in place, vaccination of ‘older women’ is not considered cost-effective. In developing countries without cervical cancer screening programs, a well-targeted screen-treat-or-vaccinate program among high-risk women might be cost-effective if indirect benefits (such as a reduction in HIV acquisition) are taken into account.

Public health interventions that need strengthening

**Strengthening of STI control program.** The coverage and quality of implementation of the WHO STI syndromic management guidelines in Rwanda and other sub-Saharan African countries is currently not known. Periodic evaluation of the implementation of syndromic guidelines is needed. The indicators to be evaluated would include: the number of sites providing syndromic treatment for STIs; knowledge among the medical staff about the guidelines; number of patients presenting with symptoms; percentage correctly diagnosed cases; percentage correctly treated cases; implementation of partner notification and treatment; STI prevention counseling and identification.
of barriers for health care seeking. STI control programs could also be strengthened by including active case seeking among targeted most-at-risk-groups. The development of affordable, sensitive, specific and rapid tests for STIs would greatly improve patient-care (reducing overtreatment in women with vaginal discharge syndrome) and facilitate screening of asymptomatic patients.

Prevention for positives. Many female sex workers in Kigali who were diagnosed HIV-positive continued their sexual risk behavior despite having enrolled in HIV care and treatment programs. Strengthening of prevention of onward HIV transmission is needed in Rwanda and likely also in other sub-Saharan African countries. The focus is on access to treatment and treatment adherence but other components – risk-reduction counseling and STIs control – should be incorporated.

STI control, in the broadest sense, has continued relevance in the prevention of HIV/AIDS – but its broader benefits, in terms of reducing overall STI-related morbidity and mortality, needs greater attention. A renewed commitment at global and country level is needed joined with appropriate financial and technical support for the implementation, monitoring and evaluation of STI control programs.
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