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Advancing STI care in low/middle-income countries: has STI syndromic management reached its use-by date?

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Syndromic management of sexually transmitted infections (STIs) using algorithms based on the patient's presenting symptoms has been the cornerstone of STI care in many low/middle-income nations for over three decades; usually because of limited resources and lack of adequate laboratory services and also to deliver care as quickly as possible. The shortcomings of this approach have been well documented and include the inability to detect asymptomatic STIs,[1] the lack of antibiotic susceptibility testing, the poor positive predictive value (PPV) of syndromic treatment resulting in the overuse of antibiotics (of particular concern in relation to antibiotic resistance to gonorrhoea)[2] and limited opportunities for surveillance and partner notification. Of the three main STI syndromes (vaginal discharge, urethral discharge in men and genital ulceration), vaginal discharge has the lowest PPV for a laboratory diagnosable STI. Without adequate partner notification and treatment, the source partner is often rapidly reinfected. At a population level, asymptomatic STIs constitute the majority of those infected[3] and the inability to test and treat these individuals means that most infected individuals remain untreated, resulting in long-term clinical complications and ongoing transmission.

As an example, South Africa introduced STI syndromic management in 1995 and has followed WHO guidance including the recommendation that national guidelines should be regularly evaluated with periodic aetiological and antimicrobial resistance surveys and antibiotic treatment adjusted accordingly.[4] However, training and implementation are often poor.[5] A study in rural KwaZulu-Natal (KZN), in the epicentre of the HIV epidemic, estimated that the overall effectiveness of syndromic STI services to successfully treat

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curable symptomatic episodes was only 13.1% (95% CI 8.9% to 17.8%), and that the prevalence of gonorrhoea and chlamydia has not fallen since the introduction of syndromic management.[6]

Perhaps the most concerning aspect of ongoing STI syndromic management, is that this approach continues to be used in many HIV high-prevalence countries, despite the recognition of the strong epidemiological and biological links between STIs and HIV.[7] Furthermore, the overwhelming economic and service burden of HIV in some sub-Saharan countries has further exacerbated poor and inadequate STI care. Moreover, virtually all sub-Saharan countries have systems in place to collect detailed HIV epidemiological data, whereas STI data is usually limited to numbers of patients presenting with STI symptoms to the small number of available public STI services, leaving healthcare providers with limited information about the incidence and prevalence of STIs.

Studies at the Centre for the AIDS Programme of Research in South Africa (CAPRISA) have shown a high prevalence of laboratory-diagnosed STIs in women at the time of acute HIV infection (over 25% had at least one STI) and that clinical assessment alone missed 88% of laboratory-diagnosed STIs. In addition, elevation in inflammatory genital tract cytokines, a possible marker of HIV acquisition, was shown to be just as likely in women with or without STI-related symptoms,[8] further strengthening the argument that without diagnostic testing the impact of STIs on HIV transmission will continue unabated. In addition, bacterial vaginosis, which is very common in many young women in KZN is also associated with elevated inflammatory cytokines and increased HIV acquisition.

Improving economic conditions in some low/middle-income nations, more trained healthcare workers, and the prospect of reliable, relatively cheap, simple, automated point-of-care STI testing and the possible use of expedited partner therapy (EPT), where the patient is provided with treatment or a prescription for their sexual partner(s), have prompted a rethink of this model.[9] In response, in January 2016, a workshop was held at CAPRISA. The goal of this workshop was to assemble key stakeholders involved in STI care or policy development to evaluate the current STI epidemic and care provision in KZN and to discuss the latest evidence for and against the transition to a diagnostic care model. Among the matters considered were the latest local epidemiology and long-term complications of STIs; the association of genital tract inflammatory cytokines with STIs and HIV acquisition; point-of-care tests and other recent diagnostic advances; and partner notification including the possible implementation and problems with EPT.

Despite initial concerns about the legality of EPT, this approach is increasingly being used in the UK, the USA and Australia particularly for chlamydial infection. Studies have shown that it is well accepted by patients and healthcare providers and can reduce the risk of chlamydial reinfection in women by 20%–29%.[10] In contrast, in many communities in South Africa, women have low power within relationships and intimate partner violence (IPV) is common and these factors will need to be carefully considered before EPT can be appraised. Fundamentally transforming gender relationships, engaging male partners and providing women with additional skills to reduce the IPV are essential for EPT implementation.

Among a plethora of new point-of-care assays for chlamydia and gonorrhoea, the combined Xpert CT/NG (Cepheid, Sunnydale, California, USA) stands out due to its high sensitivity and specificity,[11] and the available GeneXpert infrastructure that already exists for the rapid diagnosis of tuberculosis in South Africa. In addition, a GeneXpert assay for *Trichomonas vaginalis* (TV) has recently been developed. CAPRISA has now introduced screening for STIs in its studies with the Xpert CT/NG and the Osom rapid TV antigen assays (Sekisui Diagnostics, Lexington, Massachusetts, USA) providing rapid results at an affordable cost.[11] In the future, these assays could be replaced by multiplex arrays, for example, the Randox STI Multiplex Array (Randox Laboratories, Crumlin, UK), to test for multiple organisms with a single sample close to patient care. Considering the large population of sexually active people potentially requiring access to diagnostic care, an alternative strategy would be to provide laboratory-based high-throughput Openarray testing (eg, Thermo Fisher Scientific, Waltham, Massachusetts, USA).[12] These technologies are still being optimised, but could potentially allow for the testing of thousands of self-collected samples at a fraction of the cost.

One of the hallmarks of STI diagnosis in the developed world has been the use of microscopy from genital secretions supplemented by culture and sensitivity testing. This technology also existed in the developing world including South Africa, but unfortunately few technicians retain these skills, with the introduction of syndromic management partially to blame. Perhaps it would be conceivable to resurrect cheap and trusted microscopy services and marry them with new point-of-care technology.

How do we bring all these elements together to develop a workable diagnostic care model? First, all stakeholders, including healthcare providers, laboratories, patient advocacy groups, local and central governments, the WHO, interested research and non-governmental organisations and technology companies need to engage. Next, the most promising point-of-care tests and technologies need to be carefully and systematically tested in a variety of urban and rural settings, to evaluate sensitivity and specificity, patient and healthcare worker acceptability, cost, ease or problems with implementation and the reliability and durability of equipment. In areas where HIV and tuberculosis are major public health problems the possible sharing of technology, such as the GeneXpert system should be considered. Similarly, EPT will need careful and systematic evaluation. Once this has been done, new algorithms will need to be developed and evaluated, if possible, with the help of the WHO.

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