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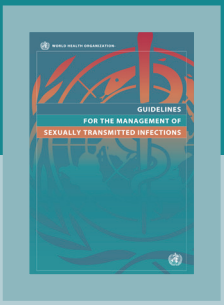
Meeting report



Report of the expert consultation and review of the latest evidence to update guidelines for the management of sexually transmitted infections

Contents

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Preface

Although sexually transmitted infections (STIs) are among the commonest causes of illness in the world, with serious long-term complications that affect reproduction and productivity, efforts to control them are usually relegated to lower priority by policy-makers. In the last 10 years, research on STIs and data collection for STIs at national level have been minimal, resulting in a paucity of good-quality data on the burden of STIs.

Nevertheless, there were sufficient new data from the limited research conducted and STI surveillance undertaken in some geographical settings to merit a review and update of the 2003 World Health Organization (WHO) Guidelines for the management of sexually transmitted infections (1). The areas that it was felt important to review, because there were either sufficient new data or availability of new technologies, were: (1) controlling genital herpes infection for the reduction of human immunodeficiency virus (HIV); (2) Neisseria gonorrhoeae antimicrobial resistance; and (3) rapid diagnostic tests for some STIs.

Although data were scanty on prevalence, detection, and diagnostic tests for rectal infections, WHO had received requests to address STIs in this anatomical site, not only among men who have sex with men, but also among any couples who practise anal sex. For this reason, the consultation also discussed the epidemiology and management of anorectal infections.

WHO convened an expert consultation in April 2008, in Montreux, Switzerland, to review any recent data in the thematic areas referred to above and make recommendations for a new, revised version of the Guidelines for the management of sexually transmitted infections. It became evident during the meeting that a number of trials were still in progress and most of the results would be available during the course of 2008 and 2009. A decision was made to select a small core group of individuals to analyse subsequent new data and use the information to feed into the updating of the guidelines. Relevant studies were analysed over the course of 2008 and 2009 and the information used to guide the revision of the guidelines. The references for these studies are shown in the document.

Additionally, in April 2009 WHO was invited to participate in the STD Treatment Guidelines meeting of the Division of Sexually Transmitted Diseases Prevention at the Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States of America, during which recent data on the management of various sexually transmitted pathogens were discussed, primarily to update the CDC Sexually Transmitted Diseases Treatment Guidelines due to be published in 2010.. This enabled a further sharing of recent data to feed into the revision of the WHO STI management guidelines.

Acknowledgments

The team on controlling sexually transmitted and reproductive tract infections (STI team) in the WHO Department of Reproductive Health and Research is grateful to a number of experts who helped as reviewers and/or presenters of the evidence and contributed to the development of a set of recommendations for updating the guidelines (Annex 1). The STI team is equally grateful to the core group of experts who helped tease out the salient features of note from the data of trials published since the meeting in Montreux in 2008, including Yaw Adu-Sarkodie (Department of Clinical Microbiology, Ghana), Ron Ballard (CDC, USA), Stuart Berman (CDC, USA), Connie Celum (University of Washington, USA), King Holmes (University of Washington, USA), Edward Hook (The University of Alabama at Birmingham, Birmingham, USA), David Lewis (National Institute of Communicable Diseases, Johannesburg, South Africa), David Mabey (London School of Hygiene and Tropical Medicine, United Kingdom), Philippe Mayaud (London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom), Lori Newman (CDC, USA), Rosanna Peeling (WHO, Geneva, Switzerland), Sam Phiri (Kamuzu Central Hospital, Lilongwe, Malawi), John Richens (University College London, United Kingdom), Richard Steen (WHO, South-East Asia), John Tapsall (University of New South Wales, Australia), Ye Tun (CDC, USA), Magnus Unemo (National Reference Laboratory for Pathogenic Neisseria, Örebro University Hospital, Sweden) and Helen Weiss (London School of Hygiene and Tropical Medicine, United Kingdom).

Introduction

Sexually transmitted infections (STIs) are among the most common causes of illness in the world and have far-reaching health, social, and economic consequences for many countries.

The emergence and spread of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) have had a major impact on the management and control of STIs. At the same time, resistance of several sexually transmitted pathogens to antimicrobial agents has increased, adding to therapeutic challenges.

In 1991, the World Health Organization (WHO) published recommendations for the comprehensive management of patients with STIs within the broader context of control, prevention, and care programmes for STI and HIV infection.

The WHO *Guidelines for the management of sexually transmitted infections* were last reviewed in November 2001, and were published in 2003 (*1*). This revision focused on the syndromes of genital ulcer disease (GUD) and vaginal discharge – the former because of the observed increase of herpes simplex virus type 2 (HSV-2) as the main cause of GUD in developing countries, and the latter for its continued complexity and controversy as an entry point for managing cervical gonococcal and chlamydial infections.

Since then, sufficient new data from surveillance and research have become available to merit a review and update of the current guidelines, particularly in the areas of: (1) controlling HSV-2 infection for the reduction of HIV; (2) *Neisseria gonorrhoeae* antimicrobial resistance; (3) rapid STI diagnostics; and (4) anorectal infections. WHO convened an expert consultation in April 2008, in Montreux, Switzerland, to review recent data and make recommendations for a new, revised version of the *Guidelines for the management of sexually transmitted infections*.

The report on this expert consultation focuses on the above-mentioned topics, and is organized as follows: for each of the four areas, a rationale is given for reviewing the evidence; a summary of findings from the consultation is presented, followed by conclusions and recommendations by the expert group. Data on the use of azithromycin for the treatment of syphilis were presented as well, and are included under the discussion of rapid diagnostic tests for syphilis. These recommendations in turn will inform a revision of the *Guidelines for the management of sexually transmitted infections.*

Controlling HSV-2 infection for the reduction of HIV

Rationale

Earlier research has suggested a potential role for HSV-2 infection in the spread of HIV. HSV-2 infection is associated with an increased risk of HIV acquisition and with increased shedding of HIV (*2–5*). HSV-2 is an increasingly important cause of GUD, which in itself is associated with increased acquisition and transmission of HIV infection. Lastly, HIV infection itself has been found to change the natural history of HSV-2 infection, resulting in more frequent recurrences, many of which are subclinical (*6*).

The following potential mechanisms of interaction between HSV-2 and HIV have been postulated:

1. symptomatic HSV-2 infection increases HIV transmission;
2. symptomatic HSV-2 infection increases HIV acquisition;
3. HSV-2 infection increases HIV transmission (and disease progression);
4. HSV-2 infection increases HIV acquisition.

Since HSV-2 has become, in many countries, the most important causative agent in GUD, recommendations for optional HSV-2 treatment were included in the 2001 revision of WHO's guidelines for the management of GUD (*1*). However, more information is needed about the effect of episodic therapy on ulcer healing and HIV shedding, and on the effect of suppressive therapy on the frequency of recurrences of clinical HSV-2 infection and associated shedding of both HSV-2 and HIV.

A series of randomized controlled treatment trials among HIV-infected and HIV-negative individuals have been conducted, which sought to provide evidence for one or more of the issues above, and, thus, for the role of HSV-2 treatment in the prevention of spread of HIV. HSV-2 treatment trials among HIV-1/HSV-2-coinfected individuals offer an opportunity to assess the role of HSV-2 infection in HIV transmission, while such trials among HIV-negative/HSV-2-infected individuals focus on acquisition of HIV infection. Some of these studies also assessed the prevalence of HSV-2 among genital ulcer patients, and evaluated the impact of HSV-2 treatment on ulcer healing.

The majority of the results presented relate to trials of suppressive treatment for HSV-2, while three trials evaluated the impact of episodic therapy. Most trials were among HIV-infected individuals, focusing on *transmission* of HIV infection, while three trials included were among HIV-negative individuals, with HIV incidence as the primary outcome measure (HIV *acquisition*).

Randomized controlled trials of suppressive therapy for HSV-2 among individuals coinfected with HIV-1 and HSV-2 were conducted in Burkina Faso, Peru, South Africa, Thailand, the United Republic of Tanzania, and Zimbabwe. Trials of suppressive therapy for HSV-2 among HIV-negative, HSV-2-infected individuals were conducted in the United Republic of Tanzania and Zimbabwe (enrolling women), and Peru and the United States of America (enrolling men who have sex with men [MSM]). Episodic treatment trials among unselected coinfected (HIV-1 and HSV-2) individuals were conducted in the Central African Republic, Ghana, Malawi, and South Africa, while the Malawi trial also considered treatment outcomes in HIV-negative study participants.

Current knowledge and discussion

Suppressive treatment of HSV-2, among HIV-1/HSV-2-coinfected individuals

Two trials with parallel design and procedures were conducted in Burkina Faso. These were double-blind proof-of-concept randomized controlled trials of daily valaciclovir 1000 mg versus placebo among co-infected women, 60 of whom were taking highly active antiretroviral therapy (HAART) and 136 of whom were not eligible for HAART. Study endpoints were detection and pattern of HIV-1 shedding and the mean quantity of genital HIV-1 ribonucleic acid (RNA), mean quantity of plasma HIV-1 RNA, detection and pattern of HSV-2 shedding, mean quantity of genital HSV-2 deoxyribonucleic acid (DNA), and, finally, occurrence of genital ulceration or vesicles. Among women not on HAART, there was a significant reduction in the number of study participants shedding HIV-1 and, for each woman, in the frequency and quantity of genital shedding of HIV-1, and in the quantity of plasma HIV-1 RNA. Furthermore, HSV-2-

suppressive therapy was associated with a significant reduction in the prevalence of detectable genital HSV-2 DNA, and in the occurrence of GUD. Overall, not surprisingly, no reduction in HIV-1 shedding was found among women on HAART who were well controlled by HIV treatment. However, in the subgroup of women who were still shedding HIV-1 during the baseline phase, a reduction in frequency and quantity of HIV-1 shedding was detected. In addition, a borderline significant reduction in the prevalence of detectable genital HSV-2 DNA was noted among women on HAART (*7*).

This study was the first to confirm a causal link between HSV-2 and HIV-1 replication, and it suggested a possible role for HSV-2-suppressive therapy in reducing HIV transmission, by reducing genital shedding of HIV-1 RNA in HSV-2/HIV-1-coinfected women and by reducing the recurrence of genital ulceration, as well as in reducing HSV-2 transmission, by reducing genital shedding of HSV-2. This effect was significant among women not taking HAART or among those women on HAART who were shedding HIV-1 at baseline. It was noted that among women on HAART, two-thirds were shedding HIV-1 and thus capable of HIV transmission.

Two randomized, double-blind, placebo-controlled, crossover trials of HSV-2-suppressive therapy among HSV-2/HIV-1-coinfected women and MSM were conducted in *Lima, Peru*. Treatment consisted of 500 mg valaciclovir orally twice daily. Twenty men and 20 women participated in this study, half of whom were randomly assigned to either the intervention or the placebo group for a period of eight weeks, followed by a two-week washout period, after which participants crossed over to the other group for another eight weeks. Study endpoints were plasma and genital levels of HIV-1 RNA. Suppressive treatment with valaciclovir significantly decreased genital shedding of HSV-2, in both frequency and quantity, and it significantly decreased plasma HIV-1 viral load, cervical HIV-1 shedding in women, and rectal and seminal HIV-1 shedding, in men. The effect on HIV-1 plasma viral load was greater among men with a higher CD4 count. It should be noted that the treatment regimen used (500 mg valaciclovir twice daily) did not eliminate HSV-2 shedding from all participants and that it did not reduce plasma and genital HIV-1 viral load in all participants (*8, 9*).

The *South Africa* trial was a randomized, placebo-controlled, double-blind trial of HSV-2-suppressive therapy among 300 HIV-1/HSV-2-coinfected women not on HAART. Treatment consisted of 400 mg aciclovir twice daily. The primary study endpoint was the detection and quantity of genital HIV-1 RNA after 3 months of treatment, and secondary endpoints were quantity of plasma HIV-1 RNA, CD4 count, detection of genital HSV-2 DNA, frequency of GUD, and treatment adherence. A total of 152 women were randomly assigned to the intervention arm and 148 women to the control arm. While there was no significant reduction in genital HIV-1 in the treatment group compared to the control group, among the subgroup of persistent HIV shedders there was a greater reduction than among all women. Plasma HIV-1 RNA levels were significantly lower in the treatment group than the control group after 3 months of follow-up, resulting in a 46% decrease in plasma HIV-1 viral load. Aciclovir treatment also resulted in a reduction in genital shedding of HSV-2 DNA and in the frequency of clinical episodes of GUD. Among those with detectable HSV-2, there was no difference in the quantity of HSV-2 DNA between the treatment and the control groups (*10*).

In *the United Republic of Tanzania*, a randomized, double-blind, placebo-controlled HSV-2-suppressive treatment trial among HSV-2/HIV-1-coinfected women was conducted. Treatment consisted of aciclovir 400 mg twice daily, and study endpoints were prevalence and quantity of cervico-vaginal HIV-1 RNA and HSV-2 DNA. The trial followed both HIV-infected and HIV-negative women in the same cohort; results for the first 12 months of follow-up among HIV-infected women (n=383, 169 in intervention arm and 157 control arm) are presented here. Adherence, measured by pill count, was 90% or more for only 50% of participants in the placebo arm and 58% in the intervention arm, and less than 20% of participants in both arms had adherence between 75% and 89% in the 3 months preceding the 12-month visit. Median adherence was estimated to be 90%. There was no significant reduction in the prevalence of genital HIV-1 RNA between treatment arms, although there was a trend toward a slight reduction in the aciclovir arm. The odds ratio (OR) at month 12 was 0.83, with a 95% confidence interval (CI) of 0.56–1.24. There was no difference in the quantity of genital HIV-1 RNA between the two arms at month 12, or indeed between baseline and the observation at 12 months. Analysis of a subgroup of women without visible blood or presence of sperm (measured by Y-chromosome polymerase chain reaction [PCR]) suggested a modest

effect of suppressive therapy on genital HIV-1 RNA (OR=0.64, 95% CI 0.39–1.05). There was no effect of treatment on the prevalence of genital HSV DNA at month 12 (OR=0.97, 95% CI 0.48–1.93), and a small, but statistically non-significant effect on the prevalence of GUD (OR=0.33, 95% CI 0.08–1.35). It was postulated that adherence to treatment may well have been insufficient to achieve long-term HSV suppression in HIV-infected individuals.

The trial in *Thailand* was a randomized, placebo-controlled, crossover HSV-2-suppressive treatment trial with 800 mg aciclovir twice daily. The study was conducted among HIV-1/HSV-2-coinfected women in Chiang Rai, Thailand. The primary outcomes were the quantity of HIV-1 RNA in vagina and plasma, and secondary outcomes included symptoms, daily HIV/HSV shedding (self-collected genital swabs), and compliance. The latter was measured by a Medication Event Monitoring System (MEMS) cap, aciclovir levels, and weekly pill counts. Sixty-seven women were enrolled and randomized to receive either treatment or placebo for 1 month, followed by a washout period of 1 month, after which participants switched over to placebo or treatment for another month. Shedding of HSV-2 was significantly reduced in the treatment arm versus the placebo arm, as was the quantity of HIV-1 in both plasma and the vagina. The mean difference between the aciclovir and the placebo arm was –0.43 for plasma HIV-1 RNA (95% CI –0.56 to –0.29) and –0.33 for vaginal HIV-1 RNA (95% CI –0.19 to 0.48). This study, with a relatively short follow-up period, and among immunocompetent women, demonstrates a significant reduction in genital and plasma HIV among women taking relatively high doses of suppressive therapy for HSV-2.

In *Zimbabwe*, a randomized, double-blind, placebo-controlled trial of suppressive HSV-2 therapy was nested within an ongoing STI periodic presumptive treatment (PPT) feasibility study among high-risk women. One hundred and eight women were allocated to receive aciclovir and 106 women received placebo. The results of 69 and 56 women in each arm, respectively, who were coinfected with HIV-1 and HSV-2, are presented here. Treatment consisted of 400 mg aciclovir twice daily for 12 weeks. HSV shedding was significantly reduced in the aciclovir arm, compared to the placebo arm (10% versus 23% of visits, crude OR=0.24, 95% CI 0.12–0.50). Overall, there was no significant difference in HIV shedding between the two arms (67% of visits in the aciclovir arm versus 63% in the placebo arm, crude OR=1.1, 95% CI 0.47–2.6). Both self-reported adherence and pill counts suggest suboptimal adherence, with adherence declining over time, and even though suppressive therapy had an effect on HSV-2 shedding, adherence may have been insufficient to affect HIV shedding.

Suppressive HSV-2 treatment trials, HIV-uninfected participants

The second component of the randomized, double-blind, placebo-controlled trial in Mwanza, the United Republic of Tanzania evaluated the effect of HSV-2-suppressive therapy with 400 mg aciclovir twice daily on HIV incidence in HSV-2-infected women. Follow-up lasted between 12 and 30 months, depending upon enrolment date. Adherence was measured through monthly tablet counts and random and 3-monthly urine testing for aciclovir in a random sample of women. Of the 821 women enrolled in the study, 421 were allocated to receive placebo and 400 received aciclovir.

The incidence of HIV was 4.29 per 100 person-years (95% CI 3.0–6.1) in the intervention group and 4.25 per 100 person-years (95% CI 3.0 to 6.0) in the control group. Thus, there was no impact of HSV-2-suppressive therapy on HIV incidence (rate ratio=1.01, 95% CI 0.61–1.66). Analysis by level of adherence showed some evidence of an effect of HSV-2 therapy on HIV incidence, although this was not statistically significant. For person-years of follow-up with adherence at or greater than 90% (only approximately 50% of follow-up), HIV incidence in the intervention group was 2.52 per 100 person-years (95% CI 1.3–5.0) versus 4.31 per 100 person-years (95% CI 2.6–7.2) in the control group, giving a rate ratio of 0.58 (95% CI 0.25–1.38). A very small number of episodes of GUD were reported, and no statistically significant conclusions can be drawn with regard to the effect of aciclovir on GUD. HSV-2 shedding was reduced among those in the aciclovir arm with equal to or more than 90% adherence, though this difference was not statistically significant. The aciclovir tablets given during the trial were found to be of good quality, but there was evidence of suboptimal adherence to treatment: no aciclovir could be detected in the urine in more than 40% of women randomized to the aciclovir group (*11*).

The HIV Prevention Trials Network (HPTN) study 039 was a phase III, randomized, double-blind, placebo-controlled trial of suppressive HSV-2 treatment for the reduction of HIV acquisition. Heterosexual, HIV-

negative/HSV-2-infected women were enrolled in Zimbabwe (Harare), Zambia (Lusaka), and South Africa (Johannesburg). HIV-negative/HSV-2-infected MSM were enrolled in Peru *(*Lima) and the USA (Seattle and San Francisco). Treatment was with aciclovir 400 mg twice daily, and the primary endpoint of the study was HIV infection. Adherence was measured by monthly pill counts, and by self-reports when pill bottles were not available. The study was initially planned for 1 year, but follow-up was extended to 18 months, when accrual proved to be less than expected. A total of 1355 MSM were enrolled in Peru, 459 MSM in the USA, and 1358 women in the African sites. Retention was 85% in both arms. There was no difference in HIV incidence rate between the intervention and the control arm for women (4.9/100 person-years versus 3.1/100 person-years, respectively) or for men (3.0 and 3.4/100 person-years). The overall incidence was slightly higher in the intervention arm, though not significantly so: hazard ratio 1.16 (95% CI 0.83–1.62). Study participants in the intervention arm had significantly fewer episodes of GUD, with a 47% reduction in GUD overall, and a 64% reduction in HSV-2-related ulcers. Adherence to treatment was very good. While aciclovir 400 mg twice daily was well tolerated and led to a significant reduction in GUD, it did not reduce the acquisition of HIV among high-risk HSV-2 seropositive MSM and women (*12)*.

Episodic HSV-2 treatment trials, including among HIV-1/HSV-2-coinfected individuals

A multicentre, randomized, double-blind, placebo-controlled trial of episodic HSV-2 treatment, in combination with syndromic management of GUD, was conducted among 441 women in *the Central African Republic* and *Ghana*. Study participants were unselected women presenting to STI clinics with proven GUD, and the overall treatment outcome was GUD-healing rates. A subgroup of 118 women were coinfected with HIV-1 and HSV-2. In these women, primary outcomes were detection, frequency, and quantity of HIV-1 RNA in cervico-vaginal specimens. Secondary endpoints were detection of HIV-1 RNA in ulcers; quantity of plasma HIV-1 RNA; detection, frequency, and quantity of HSV-2 DNA in cervicovaginal specimens; and ulcer aetiologies and healing rates. In the placebo arm, 220 women were enrolled (syndromic management plus placebo), and in the intervention arm (syndromic management plus aciclovir), 221. Overall, 50% of the women had HSV-2 ulcers (45% in Ghana and 58% in the Central African Republic). Of enrolled women, 64 and 54 in the placebo and aciclovir arms, respectively, were found to be coinfected with HIV-1 and HSV-2, with HSV-2 ulcers, and 59 and 47, respectively, were analysed at day 7 after having received 5 days of treatment. There was a slight, but non-significant, reduction in cervico-vaginal HIV-1 RNA between both arms, and a larger, but still statistically non-significant reduction in lesional HIV-1 RNA (risk ratio [RR]=0.70, 95% CI 0.4–1.2), and no difference in mean plasma HIV-1 viral load at day 28 post-enrolment. There was a more pronounced reduction in HSV-2 shedding in the intervention arm (reduction from 80% at day 0 to 24% on day 7) compared to the placebo arm (81% on day 0 to 35% on day 7). The mean quantity of HSV-2 DNA was significantly lower (by nearly one $\log_{10}$) in the aciclovir arm. Aciclovir use was also associated with a larger reduction in the size of ulcers compared to the placebo arm, and there was a tendency towards faster healing of ulcers in the treatment arm.

In conclusion, the effect of aciclovir on HSV-2 and ulcer healing was modest, and there was no effect on HIV-1 shedding. Treatment may not have been potent enough and may have been started too late. The median duration between onset of ulcers and initiation of treatment was 7 days for women in this study. Many women had advanced HIV disease, with relatively low CD4 counts, and this may have reduced the treatment effect as well.

In *Malawi*, a randomized, double-blind, placebo-controlled trial of episodic treatment of HSV-2 was conducted among 422 men and women presenting with GUD in Lilongwe. The primary objective of the study was to evaluate the impact of aciclovir episodic treatment on genital ulcer healing. Secondary objectives were to measure the impact of aciclovir 800 mg twice daily for 5 days on the detection and quantity of lesional, genital, and plasma HIV-1 RNA in the subgroup of HIV-1/HSV-2-coinfected men and women, and to evaluate the impact of aciclovir on the detection and quantity of HSV-2 DNA. Lastly, the trial provided insight into the aetiologies of GUD, which were as follows: HSV-2 67% (63% in males, 80% in females), *H. ducreyi* 14%, *T. pallidum* 5.5%, lymphogranuloma venereum (LGV) 6%, mixed aetiologies 14%, and unknown aetiology 20%. Seventeen per cent of GUD patients had first-episode genital HSV-2, which is the largest proportion ever seen in Africa. Overall, there was no difference in the proportion of

patients with a healed ulcer at day 7 or day 14 between the intervention and placebo arms. At day 14, nearly 85% of ulcers were healed in both treatment arms (RR=1.02, 95% CI 0.93–1.11). In the subgroup of 244 HIV-1/HSV-2-coinfected individuals, there was a reduction in the proportion of participants with lesional and seminal HIV shedding at day 14 in the aciclovir arm. The adjusted rate ratio for lesional shedding was 0.6 (95% CI 0.4–0.9), and for seminal shedding also 0.6 (95% CI 0.4–0.9). There was no statistically significant difference for cervical HIV-1 shedding or the frequency of detection of plasma HIV-1 RNA between the two arms. The data suggest strongly that antibacterial treatment for chancroid, syphilis, and LGV should be maintained in the management of GUD, but the study showed little clinical benefit from adding aciclovir to GUD management. It is possible that, in general, treatment was initiated too late, since the median period between onset of symptoms and initiation of therapy was one week. Also, treatment was given for 5 days only, and this may well have been too short. The reduction in frequency of lesional and seminal HIV-1 shedding at day 14 suggests a possible role for HSV-2 treatment in limiting HIV transmission.

A randomized, double-blind, placebo-controlled episodic HSV-2 treatment trial was conducted in *South Africa*. Treatment consisted of 400 mg aciclovir three times a day for 5 days. All patients enrolled in the trial also received syndromic management for syphilis and chancroid. The primary objective of the study was to evaluate the efficacy of aciclovir episodic treatment in reducing the duration of clinical HSV-2 infections. A secondary objective focused on the efficacy of aciclovir on reducing lesional and plasma HIV-1 RNA in HIV-infected men.

The aetiologies of GUD were as follows: HSV-2 70%, HSV-1 0.3%, HSV-2 plus other 3%, LGV 1%, *H. ducreyi* 2%, *T. pallidum* 3%, and unknown 21%. By day 7, a significantly larger proportion of patients in the aciclovir group had a healed ulcer compared to the placebo group (49.6% versus 64.4%, adjusted rate ratio=1.3, 95% CI 1.1–1.5). On subgroup analysis, this difference remained statistically significant for HIV-infected men, for men with primary genital herpes, and for men with a CD4 count of more than 200 cells/µl. The study was insufficiently powered to assign significance to differences among HIV-negative men. The aciclovir effect on ulcer healing was significant for patients with a short interval between onset of symptoms and initiation of therapy, 0–3 days RR=1.4 (95% CI 1.0–2.2), 4–5 days RR=1.8 (95% CI 1.1–3.0), but not for ulcer with a longer interval. Time to healing of ulcer was also reduced in the aciclovir group compared to the placebo group, among all participants, HIV-infected participants, and those with primary genital herpes. Significant reductions were also found at day 7 for lesional HIV-1 RNA, plasma HIV-1 viral load, and lesional HSV-2 in the aciclovir group compared to the placebo group. Thus, in this study among men in South Africa, aciclovir episodic treatment, with a higher dose than was used in other trials, improved ulcer healing among all participants, among HIV-infected men with HSV-2 ulcers, and among men with first-episode genital HSV-2. Treatment with aciclovir also reduced HIV-1 and HSV-2 shedding from ulcers. In conclusion, treatment with aciclovir was found to be beneficial in this group of men in Johannesburg.

Subsequent to the meeting, results from the outstanding trial were published. The trial was a multicentre, randomized, placebo-controlled and double-blinded trial in which standard oral doses of aciclovir, 400 mg twice daily, were given as suppressive treatment to people dually infected with HSV-2 and HIV, with the aim of reducing transmission of HIV to their HIV-negative sexual partners. Although aciclovir suppressive therapy was associated with a significant reduction in plasma HIV-1 levels and the incidence of HSV-2-positive genital ulcers, there was no reduction in the transmission of HIV-1 infection (*13*).

Conclusions and recommendations

While there is ample evidence that HSV-2 is an increasingly important (and in many parts of the world, the most important) cause of GUD, both *H. ducreyi* and *T. pallidum* are still frequently found, and treatment for these conditions remains indicated. Shedding of HSV-2 was much more frequent than was thought on the basis of the recurrence of visible lesions, and especially short, subclinical reactivations seem to be responsible for the frequency of shedding. First episodes of genital herpes simplex (with HSV-2) were frequent (10–15%) in GUD patients. The effects of the body's immune response to HSV-2 are not completely understood, but epidemiological evidence suggests susceptibility to HIV beyond episodes with GUD.

With regard to episodic therapy for HSV-2, one out of three studies reported on during the meeting showed impact on HSV-2 infection (see Table 1): ulcer healing was reduced, by up to 3 days (in South Africa), and shedding of HSV-2 was reduced. This effect was strongest in HIV-1-infected individuals (although this was not uniformly found) and in cases of first-episode genital HSV-2. The impact of episodic HSV-2 therapy on HIV-1 shedding was limited, and is likely to have limited public health consequences. Aciclovir may be the right drug, but the dosage generally used may be too low, and the duration of treatment may well be too short. One economic and modelling analysis found a potential positive cost–benefit profile of adding aciclovir to current syndromic management guidelines, as this would increase the number of ulcers correctly treated thereby reducing the cost per ulcer treated (*15*). However, there are indications that the longer the delay between onset of symptoms and initiation of therapy, the less the impact of treatment. Consequently, self-initiated therapy could facilitate early treatment of recurrent episodes, and the efficacy and feasibility of self-initiated therapy is an urgent topic for research. Episodic therapy does provide an important entry point for HIV-1 counselling and testing, and the provision of care.

Table 1. Effect of HSV-2 episodic treatment on ulcer healing and HIV shedding (14; Weiss H, presentation at consultation)

	Placebo	Aciclovir	RR (95% CI)	Placebo	Aciclovir	RR (95% CI)
	Percentage healed at day 7			Percentage with lesional HIV		
All patients	57	63	1.10 (1.0–1.2), P=0.13	27	19	0.71 (0.5–0.9)
Ghana	81	80	0.99 (0.9–1.1)	3	3	
The Central African Republic	34	35	1.02 (0.6–1.6)	39	38	0.96 (0.6–1.6)
Malawi (female)	69	70	1.01 (0.8–1.3)	8	6	
Malawi (male)	53	54	1.02 (0.8–1.3)	26	23	0.90 (0.5–1.6)
South Africa	52	65	1.24 (1.1–1.4), P=0.14	31	18	0.58 (0.4–0.9)
HIV infected	49	57	1.17 (1.0–1.3)	—	—	—
HIV negative	68	70	1.02 (0.9–1.1)	—	—	—

CI, 95% confidence interval; RR, relative risk.

Regarding suppressive therapy for HSV-2, studies evaluated the effect of treatment on HIV acquisition and on HIV transmission. In terms of acquisition, no impact of suppressive HSV-2 therapy was seen in women and MSM with prevalent HSV-2 infection. As for the effect on HIV transmission, suppressive therapy has been demonstrated to result in reduced genital HSV-2 shedding, to reduce the frequency and quantity of genital HIV shedding, and to reduce HIV-1 plasma viral load. Adherence to treatment issues may well have played a major role in the inability of two of the trials presented to show an effect of suppressive HSV-2 treatment on HIV shedding.

Findings to date raise a number of questions, and allow for a number of programmatic recommendations. Although there was felt to be enough evidence to support the hypothesis that HSV-2 infection and reactivation play a role in HIV transmission, the current trials failed to demonstrate an effect of HSV-2 treatment on HIV incidence. It is possible that the intervention was insufficient to have an effect on HIV incidence. This could be due to suboptimal adherence to treatment, unfavourable pharmacokinetics (i.e. a short effective half-life of aciclovir), frequent subclinical reactivation of HSV-2 (a problem especially with episodic treatment), or even the susceptibility of HSV-2 to aciclovir. Questions remain on the relevance

of the immune response to HSV-2 for HIV acquisition, replication, and vaccine development. A number of research issues were identified:

- what is the effect of longer-duration episodic therapy for HSV-2 and what are the efficacy and feasibility of patient-initiated treatment, so as to reduce the interval between onset of symptoms and initiation of therapy?
- what is the impact of suppressive HSV-2 treatment on HIV-1 transmission, in terms of male-to-female and female-to-male transmission? What are the underlying biological mechanisms, and what are the reasons for non-response to suppressive therapy in some individuals?
- what is the impact of suppressive HSV-2 treatment on HIV disease progression, and can this delay the time to HAART?
- what are the population-level impact and cost-effectiveness of HSV-2 and HIV-1 interventions?

There are, however, implications of the current findings for programme managers. First, in the context of the various trials it became clear that generally there is low public and health-care worker awareness of HSV-2 in most developing countries. Aciclovir is generally not used in the management of GUD, which puts into question the understanding and appropriateness of the current GUD algorithm. Then, a number of recommendations can be made to programme managers.

1. Treatment guidelines for GUD should include treatment for HSV-2, and should thus consist of benzathine penicillin, ciprofloxacin, and aciclovir. The duration of aciclovir should be reviewed, and may have to be longer than currently recommended to achieve maximum effect.
2. Where possible, more data on GUD aetiologies should be collected. This will assist in informing decision-makers and will raise awareness of the prevalence of HSV-2.
3. Public education on HSV-2 is needed, both as a cause of (recurrent) genital ulceration and as a factor in HIV transmission.
4. Ministries of health and donors should collaborate to ensure a stable supply of acyclovir.
5. Suppressive therapy has been shown to reduce HSV-2 and HIV shedding, and should therefore be contemplated, especially in situations where HIV prevalence is high.
6. HIV and STI programmes should be better coordinated and make optimal use of opportunities for synergy. Patients attending GUD treatment offer an opportunity for HIV counselling, testing, and initiation of care, and HIV testing and counselling services should provide access to STI screening and treatment, including, possibly, suppressive therapy for HSV-2, where indicated.

Neisseria gonorrhoeae antimicrobial resistance

Rationale

Gonorrhoea remains a serious public health problem, especially in the developing world, and is responsible for considerable morbidity. The ability of *Neisseria gonorrhoeae* (*N. gonorrhoeae*) to develop resistance against antibiotics, and its antigenic variability, continue to be major impediments to successful control of the disease (*16*). Inexpensive treatment regimens are ineffective in most parts of the world, and resistance against the latest-generation antibiotics is being reported from many countries. These latest treatment regimens are often unaffordable, resulting in programmes continuing to use ineffective drugs. Treatment for gonorrhoea should ideally be single-dose treatment to ensure compliance, and should be highly effective – WHO recommends a cure rate below 95% as a trigger for switching to a different treatment regimen. However, despite recommendations to implement continuing, high-quality susceptibility surveillance of *N. gonorrhoeae*, data on antimicrobial resistance (AMR) are not available for many countries, especially in the developing world. Available data were presented and considered by the participants, and recommendations for appropriate treatment regimens and AMR monitoring were made.

Current knowledge and discussion

Surveillance for AMR in *N. gonorrhoeae* has been difficult to set up and maintain. In some instances, this is due to a lack of linkage between AMR monitoring in general, and STI/sexually transmitted disease (STD) control programmes, and it has been difficult to ensure sustained funding for regional susceptibility monitoring. Nevertheless, gonococcal antimicrobial surveillance programmes are operational in some WHO Regions, particularly the Western Pacific Region, as well as in a number of other countries.

There is consensus that the methods used to monitor such antimicrobial susceptibilities do not need to be standardized across the world or even a region, and that the percentage of resistant strains is the most critical information for decisions regarding treatment regimens – not the actual minimum inhibitory concentration (MIC). It is important to ensure both internal and external quality assurance, since these will ensure the availability of good-quality data that can be acted on, as well as identifying opportunities and needs for further training and capacity-building. Utilization of data generated by antimicrobial susceptibility monitoring to inform treatment protocols continues to be variable. In some countries, treatment regimens have been adapted on the basis of surveillance data, while in others a lack of resources has prevented changes to treatment regimens, with ineffective antibiotics continuing to be used. The experience to date emphasizes the importance of clear linkages between monitoring of AMR and disease-control programmes – and the need to establish and strengthen such linkages.

Data on antimicrobial-resistant *N. gonorrhoeae* were presented from the following regions and countries: WHO Western Pacific Region, South-East Asia Region, European Region, and Latin American Region, Australia, the USA, and South Africa.

Western Pacific and South-East Asia Regions

In the Western Pacific and South-East Asian Regions, AMR has long been a problem: penicillin-resistant *N. gonorrhoeae* were identified in the 1970s, spectinomycin resistance in the 1980s, resistance against quinolones in the 1990s, and there are reports from Japan of resistance against oral third-generation cephalosporins. While the Western Pacific and South-East Asia Regions are by no means the only ones to report emergence of antimicrobial-resistant strains of *N. gonorrhoeae*, the sheer volume of gonococcal infections in these regions suggests a reservoir for global spread of resistant strains. Over the years, AMR has led to changes in treatment options, from cheap oral agents to expensive, often injectable agents.

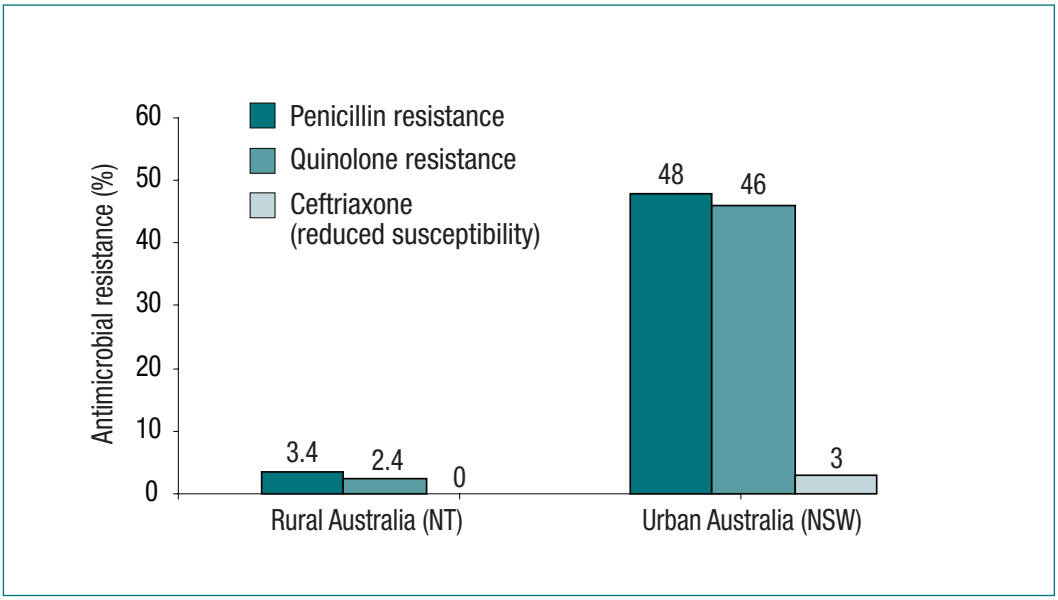
The Gonococcal Antimicrobial Surveillance Programme (GASP) has been measuring AMR in the Western Pacific and South-East Asia Regions since the early 1990s. By 2006, the prevalence of quinolone-resistant *N. gonorrhoeae* (QRNG) was well over 50% in Brunei Darussalam, the Philippines, Singapore, and Viet Nam, more than 70% in the Republic of Korea, and over 90% in China and Hong Kong. In Australia and New Zealand, respectively, the prevalence of QRNG was 38% and 17%. These data suggest that quinolones should no longer be used for the treatment of gonorrhoea in the Western Pacific Region.

There are reports from the Western Pacific Region of increasing numbers of clinical treatment failures with oral, third-generation cephalosporins, resulting in up to 2% treatment failures in Japan (*17*, *18*). There have been no documented treatment failures with injectable ceftriaxone. Still, an increasing number of centres are reporting ceftriaxone 'non-susceptibility', the percentage of gonococcal strains with such 'non-susceptibility' is increasing, and MICs for ceftriaxone are increasing, from 0.0001 to as high as 0.5 mg/l. Spread of gonococcal strains with reduced cephalosporin susceptibility within Japan (*19*) and to Hawaii (*20*) has been documented. Emergence of 'non-susceptibility' for cephalosporins has been associated with an altered penicillin-binding protein 2 (PBP2) – a mosaic-like PBP2 that may have been derived from commensal *Neisseria* by transformation. Gonococcal strains with such mosaic-like PBP2 were multiresistant to penicillins, quinolones, and other antibiotics, as well as having reduced susceptibility to cephalosporins, including cefixime. Multiple subtypes of *N. gonorrhoeae* with mosaic, multiple PBP2 changes are currently circulating widely in the Western Pacific Region (*21*). While it is not clear whether susceptibility of *N. gonorrhoeae* to cephalosporins will further decrease, it is expected that spread of current gonococcal strains with reduced susceptibility to cephalosporins will increasingly compromise the use of oral agents, even though higher doses of ceftriaxone may well still succeed in achieving cure.

Australia

The situation with regard to QRNG in Australia illustrates well how solutions to the spread and emergence of AMR require fundamental changes in how antibiotics are used, as opposed to relying on the development of new antibiotics. QRNG was first detected in Sydney in 1984, but quinolones were only discontinued in 1995, when rates of QRNG were rising rapidly. Since 1995, quinolones have no longer been used for STIs in Australia, quinolone use in humans for other conditions has not increased, and there has been no quinolone use in animal husbandry. Yet, QRNG rates are currently around 46% in urban Australia. This has been associated with continued importation of QRNG strains into sexual networks in Australia, especially in urban areas. Rates of penicillin- and quinolone-resistant and reduced-cephalosporin-susceptibility strains of *N. gonorrhoeae* remain very low in rural Australia (see Figure 1 (*22*).

Figure 1. Rural/urban differentials in antimicrobial resistance of N. gonorrhoeae (16; Tapsall J, presentation at the consultation).NT, Northern Territory ; NSW, New South Wales



Thus, while a reduction in the global burden of gonococcal disease would undoubtedly result in a reduction in antimicrobial-resistant *N. gonorrhoeae*, it is also clear that the rational use of drugs and monitoring of drug resistance and early changeover to still-effective antibiotics, are essential components of a comprehensive control effort against *N. gonorrhoeae*. Reducing the global burden of any STI, including gonorrhoea, however, requires more than appropriate use of antibiotics, and more attention should be paid to changing risky behaviour. Or, considering the adaptation of the equation for the reproductive rate (R_0) of an infectious disease:

$$R_0 = \beta \times c \times D$$

to gonococcal infections, where β is the transmissibility of the organism, c is the rate of partner exchange, and D the duration of infectiousness, for control of gonorrhoea, all three need to be simultaneously reduced. Thus, effective treatment (reduction of D) should go hand in hand with behaviour-change interventions, to reduce β and c.

Sub-Saharan Africa

Despite limited antimicrobial susceptibility surveillance and the lack of data for many countries, there is nevertheless evidence that antimicrobial resistance is a serious problem in the sub-Saharan African region. Gonococcal resistance against co-trimoxazole has reached 83% in Zambia (2006), while only

7.7% and 9% of strains were sensitive to co-trimoxazole in Ethiopia (2001) and Benin (2001) respectively. In 1997, resistance to co-trimoxazole ranged from 18% in the Gambia to more than 90% in Zimbabwe

Resistance against tetracyclines ranged from 16% (Zimbabwe, 1997) to 52% in South Africa (2000), 63% in Liberia (1998), and 84% in the Gambia (1997). More recent data from unpublished literature presented at the consultation confirm levels of tetracycline resistance ranging from 72% to 100%.

Resistance to penicillin has been reported to be over 80% in studies conducted in the late 1990s in Benin, Liberia, Nigeria and South Africa, and, with high rates of penicillinase-producing *N. gonorrhoeae* (PPNG), e.g. 45% in Zimbabwe (1997), 70% in Ethiopia (1997), 95% in Nigeria (1997), and 31% in South Africa (2000). Data from recently conducted studies presented at the consultation confirm very high levels of PPNG, ranging from 16% in South Africa (2007) to between 70% and 100% in Cameroon, the Central African Republic, Ethiopia, Guinea-Bissau, Madagascar and Malawi.

Studies conducted in the mid- to late 1990s showed high levels of resistance to kanamycin, gentamicin, and spectinomycin in a number of countries. However, recently conducted studies in the Central African Republic, Guinea-Bissau, Madagascar, and Malawi reveal very high levels of susceptibility to these drugs, and up to 100% sensitivity (presented at the meeting, publication forthcoming).

Resistance to erythromycin, in studies conducted in between 1997 and 2007, ranges from 3.4% in Guinea-Bissau to a high 80% in South Africa. On the other hand, no resistance to azithromycin was found in South Africa and Guinea-Bissau, with 1% and 6.4% of strains being resistant in Malawi and Nigeria, respectively.

Ciprofloxacin resistance was generally low to absent in the early part of this century, but recently conducted studies show resistance to ciprofloxacin to be widespread in southern Africa, with rates of resistant gonococcal strains as high as 46% in Namibia, 60% in South Africa, and 89% in Lesotho. No ciprofloxacin resistance was found in central Africa, and less than 3% resistance in Madagascar.

Lastly, resistance to ceftriaxone is still absent to low in most of the studies reported at the meeting, with the exception of Guinea-Bissau, where 10% of gonococcal isolates were found to be resistant to ceftriaxone (study to be published).

South Africa

A national microbiological surveillance programme for STIs is operational in South Africa. Serum (all patients), ulcer swabs (patients with GUD), urethral swabs and urine (male urethral discharge), and vaginal and endo-cervical swabs (women with vaginal discharge) are obtained and tested. The most common STI syndromes in South Africa are urethral discharge (64%) and GUD (15%) in men and vaginal discharge (59%) and lower abdominal pain (24%) in women. Among men with urethral discharge, gonorrhoea is the most common cause, ranging from 37% in Northern Cape to 85% in Western Cape, with *Chlamydia* infection ranging from 9% in Northern Cape to 24% in Gauteng.

Gonococcal resistance to ciprofloxacin was first identified in Durban, KwaZulu-Natal, in 2003. Subsequent research in 2004 confirmed 12.2% resistance to ciprofloxacin, but none to ceftriaxone and spectinomycin. Resistance to ciprofloxacin ranged from 7% in Cape Town to 24% in Durban, and national surveillance has confirmed an increase in ciprofloxacin resistance, from 12.2% in 2004 to 29.8% in 2007, during which period ceftriaxone resistance has remained at 0%. Despite these high levels of resistance, ciprofloxacin, in combination with doxycycline, continues to be recommended as a first-line drug for the treatment of urethral discharge, with the advice that patients, if not better, return after a week for second-line treatment. In KwaZulu-Natal, ceftriaxone is currently prescribed as first-line therapy, and the new essential drug list guidelines will recommend cefixime and ceftriaxone respectively for uncomplicated and complicated gonococcal infections.

Maintaining ciprofloxacin as a first-line treatment for gonococcal infection in the presence of quinolone resistance has implications for both gonorrhoea control and HIV transmission: non-responding gonorrhoea prolongs the duration of mucosal inflammation, which in turn increases the likelihood of transmission or acquisition of HIV; and the initial inappropriate treatment increases the period that patients with resistant strains of *N. gonorrhoeae* remain infectious, which, in turn, leads to further preferential transmission of resistant strains.

Americas – the United States of America

In the USA, a national sentinel surveillance system to monitor trends in antimicrobial susceptibility of *N. gonorrhoeae* has been in operation since 1986. The Gonococcal Isolate Surveillance Project (GISP) collects male urethral gonococcal isolates from sentinel clinics. Susceptibility testing is done for penicillin, tetracycline, spectinomycin, ceftriaxone, ciprofloxacin, azithromycin, and, until 2007, cefixime.

Resistance to ciprofloxacin increased from 0.2% in 1999 to 15.4% in 2007, but gonococcal strains remain susceptible to ceftriaxone, cefixime (one resistant isolate in 2006), and spectinomycin. QRNG is much more common among MSM than among heterosexual men. Azithromycin susceptibility testing reveals a small increase in the number of isolates with a MIC ≥2.0 µg/ml, from 0.2% in 2006 to 0.6% in 2007. Penicillin and/or tetracycline resistance is 20% or more.

Based on the above resistance patterns, the United States Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA treatment recommendations for uncomplicated gonorrhoea include ceftriaxone or cefixime, with treatment for *C. trachomatis*, if *Chlamydia* is not ruled out. Alternative treatments include spectinomycin, injectable cephalosporins, single-dose oral cephalosporins, azithromycin (2 g – widespread use is discouraged), and ceftriaxone for the treatment of pharyngeal gonococcal infections (*23*).

Despite limitations of the GISP, such as limited coverage, lack of sampling from women, and lack of private-sector participation, it has nevertheless been possible to track trends in antimicrobial resistance of *N. gonorrhoeae* in the USA, which in turn inform national treatment guidelines. Thus, neither quinolones nor azithromycin are recommended for the treatment of gonorrhoea, the former because of widespread QRNG in the USA and the latter because of concerns about the development of resistance, evidenced by slowly increasing MICs in gonococcal isolates.

A serious concern for the capacity to perform gonococcal-susceptibility monitoring is the evident shift away from culture toward nucleic acid amplification tests (NAATs). This results in a situation where fewer organisms are available for susceptibility testing and fewer culture tests are done. For instance, of the 3.1 million gonorrhoea tests done in public health laboratories in the USA in 2000, 11% were NAATs and 18% were culture. In 2004, 3.5 million gonorrhoea tests were done in public health laboratories, but 61% were NAATs and only 8% were culture (*24*, *25*).

Americas – Latin America

Only limited data on antimicrobial resistance of *N. gonorrhoeae* are available, and virtually no recent data. Both chromosomal resistance to penicillin and PPNG are common in Latin America, as is tetracycline resistance, both chromosomal and plasmid mediated. There is little or no resistance against spectinomycin. Both resistance and reduced susceptibility to azithromycin are increasingly common: in the mid- to late 1990s, reduced susceptibility ranged from 22% to 72.5%, and resistance ranged from 3% to 38% of isolates in Brazil, Cuba, Guyana, Manaus and Saint Vincent. Virtually no information is available on susceptibility of *N. gonorrhoeae* to ciprofloxacin.

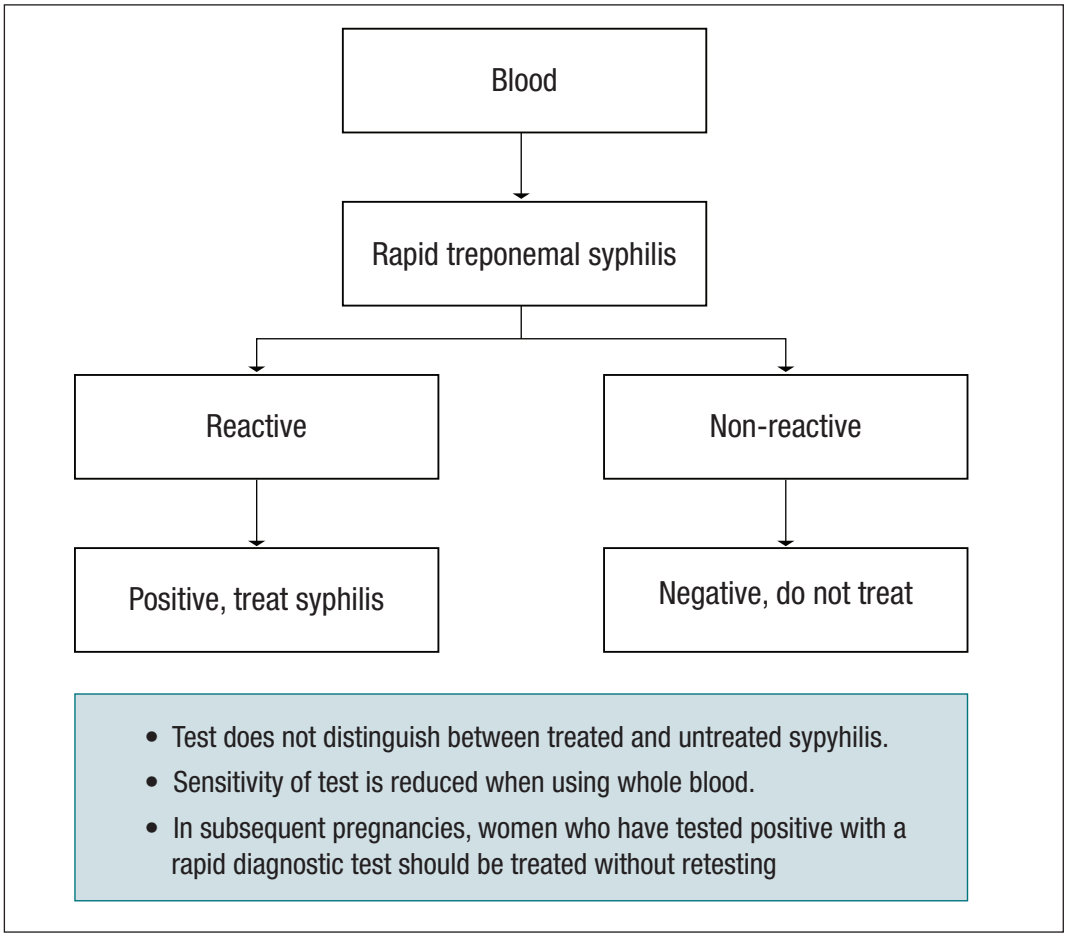
Europe

Surveillance of STIs in Europe is done by the European Surveillance of Sexually Transmitted Infections (ESSTI) network, in which 25 countries participate. Within ESSTI, a European gonococcal antimicrobial susceptibility programme (Euro-GASP) has been established. The number of participating countries has increased from 12 in 2004 to 17 in 2007. In the United Kingdom of Great Britain and Northern Ireland, which also participates in Euro-GASP, the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) was launched in 2000, and in Russia, a Russian gonococcal antimicrobial susceptibility programme (Ru-GASP) was initiated in 2004, with 36 participating centres throughout the Russian federation (*26*).

Antimicrobial resistance within the Euro-GASP network is summarized in Figure 2 (*27*). It should be noted that in 2004 ciprofloxacin resistance was already (well) over 5% in all participating countries, with rates of over 40% in Austria, Belgium, Denmark, and Sweden.

Azithromycin resistance ranged from 0% to 31.2% in participating countries, and in 6 of 12 countries more than 5% of isolates were resistant against azithromycin. While ceftriaxone resistance has not yet been found in the Euro-GASP network, the MIC_{50} has increased from 0.003 µg/ml in 2004 to 0.008 µg/ml in 2007, raising concern that ceftriaxone resistance will eventually develop as well (*28*).

Figure 2. Antimicrobial resistance in 2004 and 2007, Euopean Gonococcal Antimicrobial Surveillance Programme



Resistance monitoring in the United Kingdom reveals some resistance to azithromycin (5% in 2007), 20–21% QRNG, and continued high levels of resistance against penicillin and tetracycline, but there is no resistance against cephalosporin or cefixime, and since 2000 only six isolates with resistance to spectinomycin have been identified. Ciprofloxacin resistance, on the other hand, is substantial, and has increased since 2002, in heterosexual men but especially in MSM, where in 2006 44% of isolates were resistant to ciprofloxacin.

Data on gonococcal resistance in Eastern Europe prior to 2004 are rare, in part because most laboratory diagnoses are on the basis of direct microscopy, and in part because antimicrobial susceptibility testing is rarely done. Data from Ru-GASP show that *N. gonorrhoeae* is increasingly resistant to penicillin (18.6% in 2007), tetracycline (42.5% in 2007), and ciprofloxacin (49.6% in 2007), but that the organism is susceptible to ceftriaxone (no resistant strains), while very little resistance against spectinomycin has been found. Thus, the recommended first-line treatment of gonorrhoea in Russia is ceftriaxone or, if ceftriaxone is not available, spectinomycin.

Summarizing findings from the various European gonococcal antimicrobial surveillance networks, gonococcal antimicrobial susceptibility can be characterized as follows: very high levels of resistance against traditional antibiotics (penicillin, tetracycline, erythromycin) and against ciprofloxacin in most countries; azithromycin resistance has rapidly increased and is relatively high in many countries; resistance to spectinomycin is rare but exists; rare strains with reduced susceptibility to cefixime and ceftriaxone have been identified; and multidrug-resistant strains are widespread.

Conclusions and recommendations

While there are vast regions of the world where data on gonococcal antimicrobial resistance are lacking or out of date, evidence is available from the Western Pacific Region, South-East Asia Region, Europe, including the Russian Federation, South Africa, and some other sub-Saharan African countries, and from the USA.

A global pattern of gonococcal resistance emerges, with some local exceptions. Resistance against traditional antimicrobials, such as penicillin, tetracycline, and erythromycin, is generally high, and these antibiotics should no longer be used in the treatment of gonorrhoea.

Resistance against quinolones is high in almost all regions and countries, with the exception of West Africa, and, unless *N. gonorrhoeae* is known to be susceptible to quinolones, this class of drugs should probably no longer be used for the treatment of gonorrhoea. Where quinolones are still in use, close monitoring of antimicrobial susceptibility is clearly indicated.

Azithromycin resistance seems to be developing in Asia, the Western Pacific, Europe, and the Americas, and is already high in some countries in Europe and Latin America. Resistance to azithromycin is still low in some countries in sub-Saharan Africa. With continued use of azithromycin, it is likely that resistance will continue to develop.

Gonococcal strains tend to have become susceptible to antimicrobials that are not frequently used, such as kanamycin, gentamicin and spectinomycin. Spectinomycin, especially, would seem an appropriate second-line treatment for gonorrhoea, although it is expected that widespread use of these antibiotics will quickly result in development of resistant *N. gonorrhoeae.*

Gonococcal isolates are still susceptible to cephalosporins in all regions, although in both the Western Pacific and Europe, there is evidence of emerging reduced susceptibility of *N. gonorrhoeae* to ceftriaxone and even cefixime, and of spread of “reduced-susceptibility” strains. Multidrug-resistant gonorrhoea is not uncommon in Europe.

Thus, while global monitoring of antimicrobial resistance in *N. gonorrhoeae* is far from perfect, available data clearly point to a very limited choice of antimicrobial agents for the treatment of gonorrhoea, with indications that susceptibility against the last remaining class of effective antibiotics, the cephalosporins, might be decreasing.

It is thus of the utmost importance that comprehensive STI-control programmes combine behavioural-change interventions to reduce transmission and prevent acquisition and spread of gonococcal infections with appropriate antibiotic treatment, with effective drugs, under careful and continued monitoring of antimicrobial sensitivity. At the same time, research is urgently needed to develop new antibiotics.

Rapid sexually transmitted infection diagnostics

Rationale

Control of STIs is, in many parts of the world, constrained by a lack of easily available, easily performed, and inexpensive diagnostic tests. Especially in those regions where the burden of STIs is high, access to STI diagnostic tests is severely limited. Traditionally, the role of laboratory tests in STI control is:

- to provide a definitive diagnosis, allowing for aetiological treatment;
- to provide screening services for generally asymptomatic individuals at risk of infection;
- to provide statistical information on the prevalence of various infections;
- to determine antimicrobial susceptibility of causative organisms.

In the absence of rapid point-of-care diagnostic tests for STIs, the syndromic approach to the management of STIs is widely used for the clinical management of symptomatic infections. By treating for the most common causative agents for a particular syndrome, the syndromic approach is generally highly sensitive at the expense of specificity, thus resulting in overtreatment. The syndromic approach has been found to perform well in the management of male urethral discharge and of the bacterial

causes of GUD, but it performs poorly in the identification and management of cervical infections, such as gonococcal or chlamydial infections. The syndromic approach is of no use in screening for and the detection of asymptomatic infections. The identification of asymptomatic STIs, appropriate management of cervical infections, and, indeed, improvements in the specificity of the syndromic approach, all depend on the availability of diagnostic tests.

While high-quality diagnostic tests for STIs are available, these tests are often expensive, frequently labour intensive and, at this stage, not suitable for use as rapid point-of-care tests. This situation is further complicated by a lack of interest from pharmaceutical industries to develop low-cost, quality diagnostic tests for diseases that are prevalent in developing countries, by a lack of regulatory control on diagnostic tests, resulting in tests being marketed without evidence of effectiveness, and by a lack of standards for the assessment of quality of diagnostics.

Recently, however, considerable progress has been made in the development and validation of rapid diagnostic tests for a number of STIs, and while few tests are available at this time, it is expected that diagnosis, case-finding, and screening will eventually benefit greatly from rapid and inexpensive tests.

Current knowledge and discussion

While gold-standard tests, with high levels of sensitivity and specificity are generally used to develop management algorithms, and to subsequently evaluate and improve those algorithms, these tests are typically not available for the day-to-day management of STI patients.

Ideal diagnostic tests meet the following criteria: affordable, sensitive, specific, user friendly, rapid and robust, equipment-free, and deliverable. At the moment, though, there are often trade-offs. NAATs are very sensitive and specific, but they often take 3–4 hours to complete. More rapid immunochromatographic strip (ICS) tests may be less sensitive, but results may be available in 30 minutes or less. In day-to-day practice, if longer waiting times or having to return for test results leads to loss of follow-up of patients, the less sensitive test may well result in a larger number of infected individuals receiving treatment (*29*).

Traditional rapid tests include microscopy (Gram stain, wet mount, and dark field), pH strip tests, the Whiff test using potassium hydroxide solution, and the rapid plasma reagin (RPR) test for syphilis. More recently, a number of immunoassay-based tests have been developed. Examples of such tests are ICS tests for the detection of specific antibodies against *T. pallidum*, *C. trachomatis*, *N. gonorrhoeae,* and HSV-2. These tests are typically easy to perform, can often be done on whole blood instead of serum, and results are available in 10–30 minutes. Further developments include multiplex tests that test for the presence of multiple organisms in a single biological specimen, that are fully automated, and that come with a hand-held reader, which in turn increases the objectivity of the results.

Rapid tests for gonorrhoea and *Chlamydia*

As indicated above, currently available rapid tests often have low sensitivity. This is also the case with the current generation of rapid tests for *Chlamydia* and gonorrhoea. For example, the Clearview *Chlamydia* test, which is used extensively in STI clinics in China, was found to have a sensitivity of 50% on cervical swabs and only 33% on vaginal swabs. The specificity is high, at 98% and 99% for cervical and vaginal samples, respectively, and in the context of the clinics where the test is used (prevalence of *C. trachomatis* 13%), positive predictive value was 78% for cervical samples and 86% for vaginal samples (*30*). Compared to NAATs, with a sensitivity close to 100%, the sensitivity was deemed to be unacceptably low, but no other test is currently widely available for screening and diagnosis of *Chlamydia*.

Two rapid ICS tests for *N. gonorrhoeae* were evaluated in Brazil and Benin, and were found to have a sensitivity of 60% and 70% respectively, a specificity of 91% and 97%, and a positive predictive value of 56% in Brazil (prevalence of *N. gonorrhoeae* 15%) and 55% in Benin, where the prevalence of *N. gonorrhoeae* was 5% (*31, 32*). In all cases, however, it was suggested that the rapid tests, despite their lower sensitivity, may be as efficient as, or more efficient than, the more sensitive gold-standard test in treating gonococcal infections, given the proportion of women who do not return for the results of the more sensitive test.

Rapid tests for syphilis

The rapid ICS test for *T. pallidum* has been proven to greatly increase the number of pregnant women who are tested and receive treatment when infected with syphilis. This test, which gives results in 10–20 minutes (which allows for same-visit treatment), can be done in primary health-care settings on whole blood. Test kits can be transported and stored at room temperature, and there is no prozone effect, and thus no potentially false-negative results. Evaluation of the performance characteristics of these tests shows high levels of sensitivity and specificity. For instance, against a *Treponema pallidum* haemagglutination assay (TPHA), the Quorum/Abbott Determine test, a syphilis ICS test, was found to have a sensitivity and specificity of 92% and 98%, respectively. In the test panel, with a prevalence of TPHA reactivity of 30%, positive and negative predictive values were 94% and 96%, respectively (Ballard R, personal communication). A laboratory-based evaluation of a number of rapid syphilis tests showed that sensitivity was generally between 93% and 98%, with only two tests having sensitivities around 85%, and specificity between 93% and 98% (*33*). Four of these tests can be done on whole blood, and these tests were subsequently evaluated under field conditions. Sensitivity ranged from 64% to 100%, and was generally lower in whole blood than in serum, and specificity ranged from 96% to 100% (*34*).

It should be noted that the ICS test for syphilis is a specific test for treponemal antibodies, comparable with other treponemal tests. Even after successful treatment, treponemal antibodies tend to remain present for many years, if not lifelong. Treponemal tests, therefore, measure lifetime exposure to *T. pallidum* and are unable to distinguish between old and likely cured infections and new, untreated infections.

Non-specific tests, such as the RPR and venereal disease research laboratory (VDRL) tests, on the other hand, measure antibodies against cardiolipin, which is found in patients with acute syphilis and some other diseases, and, occasionally, in pregnancy. These antibodies typically disappear after successful treatment, generally within a period of 2 years. Titration (performing the test on increasingly diluted serum samples) is often done to exclude weak-reactive results and can be used to confirm successful treatment. Non-specific tests can thus be used to identify recent and untreated infections. Since non-specific tests can be false positive, ideally one should confirm a positive RPR or VDRL test with a treponemal test. Conversely, a positive treponemal test result with a negative RPR or VDRL suggests an old and very likely cured infection.

Both the RPR and the VDRL are relatively rapid, with the RPR test taking only eight minutes. However, these tests need to be performed on serum or plasma, instead of whole blood, require laboratory facilities and trained personnel, and require refrigeration of the reagent. In most situations where RPR or VDRL tests are routinely done, specimens for syphilis testing are batched, and tests are performed once a sufficient number of tests are ready to be done. This necessitates long waiting times for patients or, more commonly, patients are asked to return for their test results on another occasion. In either case, there tends to be significant loss to follow-up which, in turn, results in a number of diagnosed infections that remain untreated or that are treated late.

The following evaluation of antenatal on-site syphilis testing in Eastern Cape, South Africa illustrates the implications for patient management of different testing strategies. Among antenatal clinic attendees, 5.7% were RPR and TPHA positive, 7% were RPR negative and TPHA positive, and only 61% of women returned for their test results. For every 1000 patients, when using routine laboratory testing with RPR and TPHA, only 34 were treated of the 57 identified as infected, with the remainder failing to return. Using RPR on-site testing, 26 women were treated, due to poor performance of the RPR test on-site. Using an ICS test, 52 women were treated correctly (RPR and TPHA positive – five women went untreated since the ICS was 90% sensitive), but another 70 women who were TPHA positive, but RPR negative were treated incorrectly. In this situation, though, using the ICS test resulted in the largest number of actual infections being treated (*35*).

To assist in the differentiation between current and old infections with *T. pallidum*, it is desirable to test ICS-positive specimens with an RPR or VDRL test or equivalent. Two rapid tests currently under development combine assessment of antibodies against cardiolipin and against *T. pallidum* on a single

test platform. Both tests are immunochromatographic tests, with the second having the option of adding fluorescence latex technology, to allow for reading of test results with a simple ultraviolet light instead of a digital reader. Initial evaluation of the combined treponemal/non-treponemal test against conventional tests reveals sensitivities ranging from 83% to 91%, and specificities ranging from 93% to 100% (Ballard R, personal communication).

The next steps are to confirm the performance characteristics of both tests against a panel of known sera, followed by initial in-house clinical trials on whole-blood specimens by the CDC in Atlanta, GA, USA. Based on the results of these evaluations, the manufacturers will be asked to collaborate with WHO's STI Diagnostic Initiative to conduct further laboratory and field evaluations. It is anticipated that such field trials may be conducted within the next few years.

Rapid tests for *T. vaginalis*

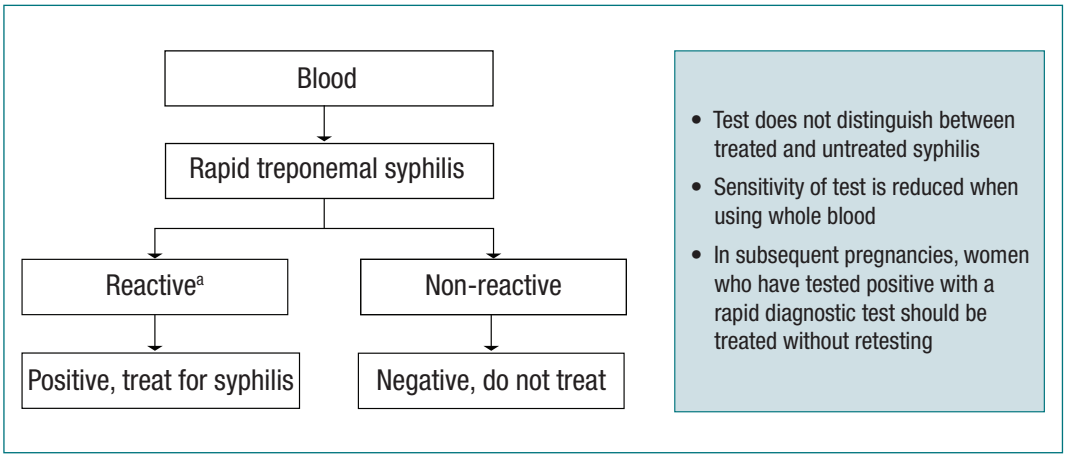
A rapid immunochromatographic test for *T. vaginalis* was evaluated against wet mount and PCR test. Sensitivity was found to be 66.7% and specificity 100%, with a positive predictive value of 100% in a population with 12.6% prevalence of trichomoniasis. The test had much higher sensitivity than wet mount (sensitivity 48.2%) and was both rapid and easy to perform. Its use is recommended, especially in situations where microscopy is impractical (*36*).

Use of rapid point-of-care tests

The high levels of sensitivity and specificity associated with amplified nucleic-acid-based testing, and the potential for automation and multiplex testing make such tests ideally suited for accurate diagnosis and for screening purposes. However, the cost of such tests and the equipment and the training and skills needed, limit their use to reference laboratories and in research situations. It is anticipated, however, that NAATs will become cheaper and their use more widespread.

Currently available rapid point-of-care tests can be used to increase the specificity of the syndromic approach, which in turn will result in reductions in the number of patients that receive treatment for conditions they do not have, and to screen for asymptomatic infections. For instance, adding Gram-stained smear microscopy to the urethral discharge algorithm could assist in excluding gonorrhoea as a cause of the discharge (no Gram-negative diplococci seen in five high-powered fields). However, given that microscopy requires special training, is time-consuming, and adds relatively little given the amount of time and resources it requires, it is generally not recommended at the primary health-care level. Similarly, adding a wet mount or an ICS test for *T. vaginalis* or point-of-care tests for gonorrhoea and for *Chlamydia* could assist in identifying specific causes for the vaginal discharge and in detecting cervical infections with *N. gonorrhoeae* and/or *C. trachomatis*, respectively. In both cases, adding point-of-care tests for syphilis and HIV could assist in detecting asymptomatic infections with *T. pallidum* and HIV, followed by treatment, counselling, and partner notification, as appropriate.

Figure 3. Proposed algorithm for antenatal syphilis screening, no RPR testing available

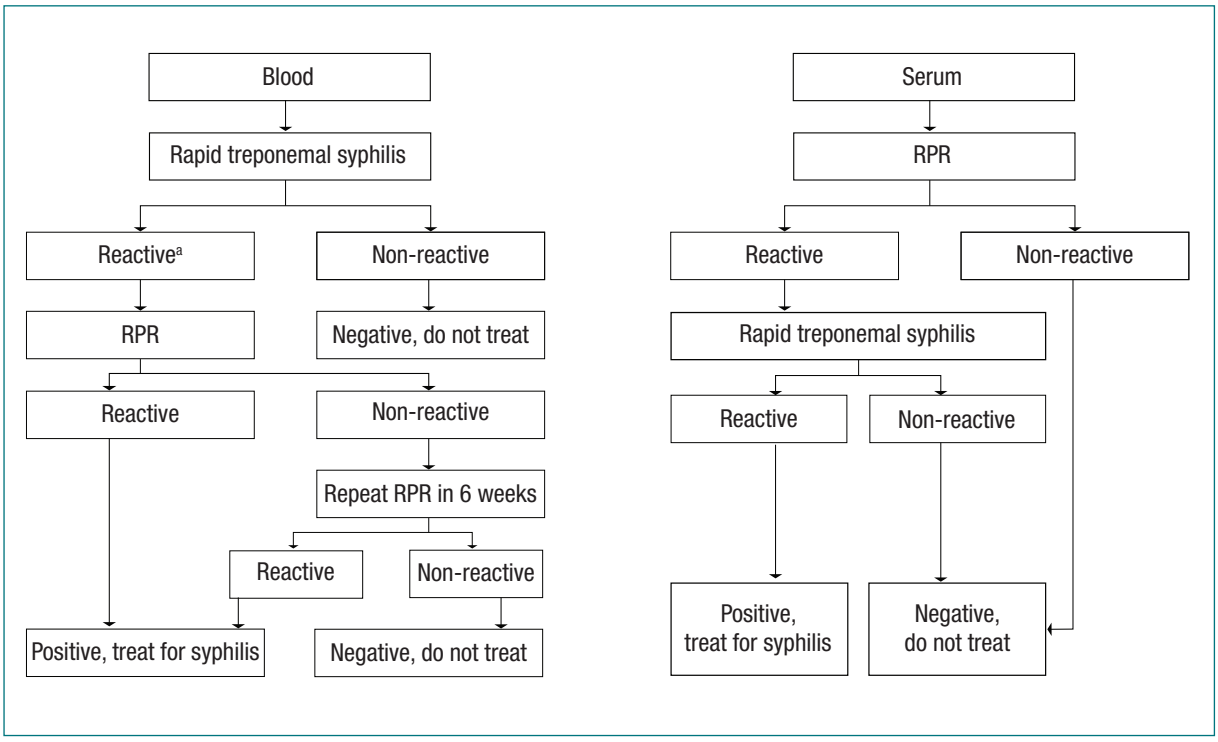


Particular attention has been paid to the use of rapid ICS tests for syphilis in antenatal clinics. Rapid ICS tests have been introduced in a number of countries for antenatal syphilis screening in situations where laboratory facilities are not available. Since the currently available rapid syphilis tests remain positive even after successful treatment and are unable to distinguish between treated and untreated syphilis, it is clear that these tests are not very helpful in subsequent pregnancies, once a woman has tested positive. Algorithms proposed for antenatal screening for syphilis, in situations with and without access to RPR or VDRL tests, are shown in Figures 3 and 4.

It was noted that antenatal syphilis screening offers an opportunity for integration with HIV testing for prevention of mother-to-child transmission (PMTCT) of HIV. Efforts should be made to treat the partner(s) of women testing positive during antenatal screening. The expected availability of a dual treponemal/non-treponemal test will greatly simplify antenatal syphilis screening, as follows:

- *women testing positive for both tests*: infected with syphilis and are to receive same-day treatment;
- *women testing negative for both tests*: uninfected;
- *women testing positive on the non-treponemal test only*: uninfected (false-positive test result);
- *women testing positive only on the treponemal test*: old, treated infection, or, especially if there is no history of prior syphilis testing and treatment, possibly early infection – treat with one dose of benzathine penicillin and repeat the test after 2–4 weeks.

Figure 4. Proposed algorithm for antenatal syphilis screening, RPR and rapid syphils testing available



Conclusions and recommendations

Much progress has been made in the development of rapid point-of-care tests for a number of STIs over the past 10 years. A number of tests are ready for deployment in the field, or almost so. The cost of these tests is still relatively high for a number of tests (e.g. ICS tests for gonorrhoea and *Chlamydia* are US$ 5–10 per test), and in some cases sensitivity is still unacceptably low.

Rapid point-of-care tests have the potential to contribute greatly to patient management, by increasing the specificity of the syndromic approach, and as instruments in screening and case detection. Whether such tests will be widely used depends on a number of factors, such as cost and cost–benefit ratio, the performance of the test, its stability under field conditions, the need for additional supplies, the format

of the test (dipstick versus cassette), the training required, the ease of interpretation of results, and in-country regulatory approval.

Given the performance characteristics of the current generation of rapid tests, the most appropriate use might be in screening in low-prevalence populations and to strengthen syndromic case management. Unresolved questions concern the required performance characteristics of rapid tests in different populations, and their cost–benefit ratio. An associated issue is the development and implementation of appropriate quality-assurance mechanisms for the tests and the testing procedures.

Anorectal infections

Rationale

Anorectal symptoms and sexually transmitted anorectal infections are prevalent in MSM and in female sex workers, yet no approach for case management is included in the WHO *Guidelines for the management of sexually transmitted infections* (*1*). In the absence of such guidelines, it is likely that a substantial number of anorectal infections go unrecognized and untreated, especially when low levels of clinical suspicion are combined with stigmatization of anal intercourse. Indeed, STIs are rarely discussed in the context of male-to-male sexual intercourse.

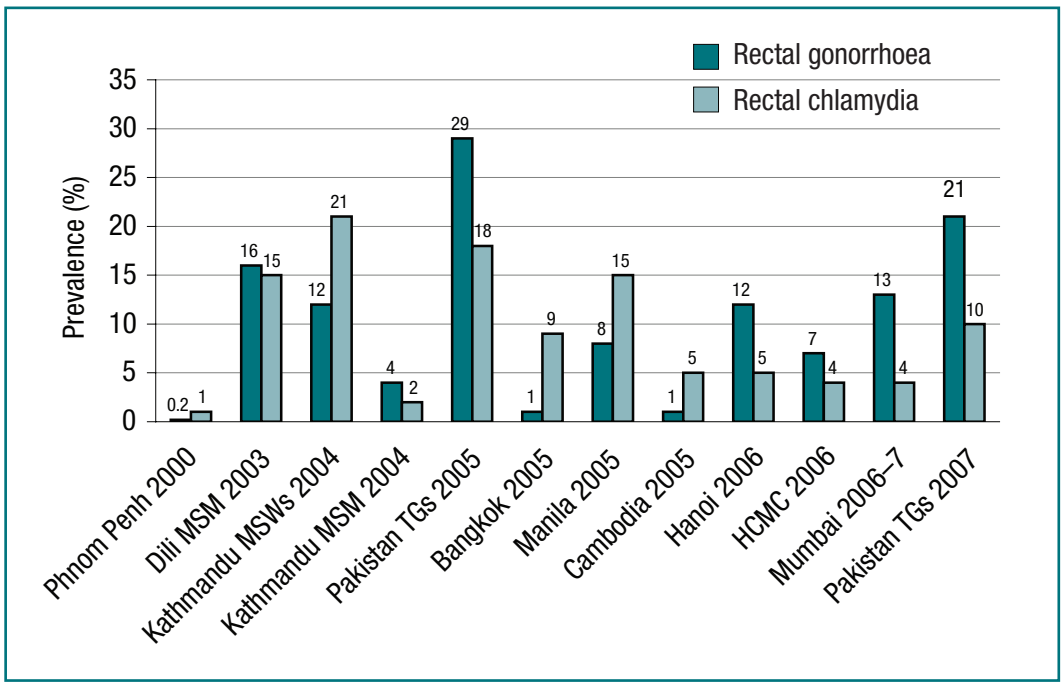
The results of studies on the prevalence of anorectal infections among MSM and male sex workers (MSWs), a review of the epidemiology of STIs among MSM in the United Kingdom, and a discussion of the management of anorectal infections were presented, to inform a discussion on the inclusion of anorectal infections in the WHO *Guidelines for the management of sexually transmitted infections* (*1*). Participants at the meeting prepared a draft algorithm for the management of anorectal infections.

Current knowledge and discussion

Prevalence of anorectal infections in Asia

Studies from the Asia region among MSM, MSWs and transgendered men reveal high prevalence rates of STIs, including rectal gonorrhoea and *Chlamydia*, although there is great variation between countries, within countries, and between individual diseases. The prevalence of rectal gonorrhoea and *Chlamydia* ranged from 0.2% to 29% and 1% to 21% respectively (see Figure 5) (Neilsen G, presentation at consultation).

Figure 5. Prevalence of rectal gonorrhoea and Chlamydia among MSM in Asia, 2000–2007



In most of the studies it was found that, among MSM, the prevalence of rectal gonorrhoea and *Chlamydia* is much higher than the prevalence of urethral infections. For instance, in the Philippines, the prevalence of urethral gonorrhoea and *Chlamydia* ranged from 1.2% to 3.5% and 8.5% to 11.2% respectively, while corresponding values for rectal infections were 10.8–18.4% for gonorrhoea and 14.6–18.4% for *Chlamydia*. Other STIs, including HIV infection, were also common (see Table 2) (Neilsen G, presentation at consultation).

No data are available from the Asia region on other rectal infections, such as, for instance, anal syphilis, LGV, or anal human papillomavirus (HPV) infection, or on the prevalence of anorectal infections in women. The wide range in prevalence of rectal gonococcal and chlamydial infection found in MSM and MSWs might suggest that, while in some situations presumptive treatment could be justified, that is clearly not always the case. However, it is equally clear that anorectal infections are common among MSM, and especially so in transgendered men.

In other parts of the world, and especially in more affluent countries, STI and HIV epidemics among MSM are not being controlled, despite the availability of well-established services and relatively lower levels of stigmatization.

Table 2. Rates of selected STIs among MSM, MSWs, and transgendered men (TG) in various Asian countries, 2000–2007

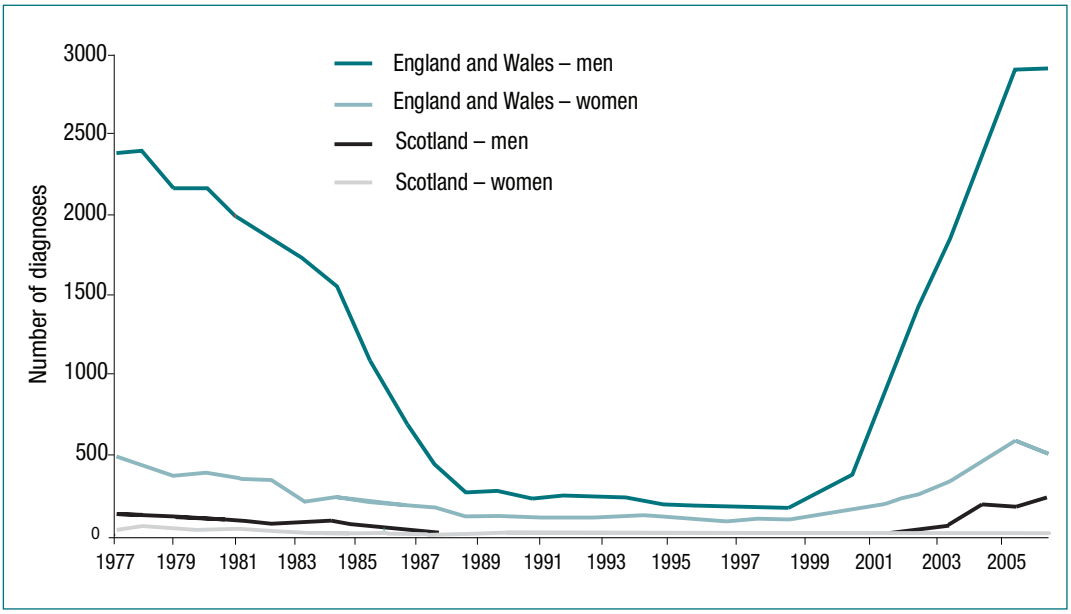
	Syphilis (active) (%)	Urethral GC (%)	Rectal gonorrhoea (%)	Urethral Chlamydia (%)	Rectal Chlamydia (%)	HIV (%)	HSV-2 (%)
Cambodia, MSM, 2000	5.5	4.8	0.2	7.2	1	14.4	—
Cambodia, MSM, 2005	0.4–1.4	0.4–0.8	1.1–1.3	1.4–2.9	1.2–9.1	2–7.9	—
East Timor, MSM, 2003	15.5	2.7	16.1	0	14.9	0.9	29.1
Nepal, MSW, 2004	2.4	1.2	12	1.2	20.5	4.8	28.9
Nepal, MSM, 2004	1.5	2.2	3.6	2.2	1.5	3.6	8.4
Philippines, MSM, 2004–2005	0–6.2	1.2–3.5	7.7–10.8	8.5–11.2	14.6–18.4	0	—
Pakistan, MSW, 2005	3.3–35.6	3.3–6.8	0–17.5	1.2–1.5	0–10.4	0–4.1	—
Pakistan, TG, 2005	11.5–60.2	3–4	0–29.4	0–1.5	0–18.3	0.5–1.5	—
Pakistan, MSW, 2007	4.5–45a	0–0.5	4.5–20.8a	0–0.4	3.7–10.4a	0–2.8a	7–54[a]
Thailand, MSM, 2005	—	10.4	1.3	7.8	9.1	—	—
Viet Nam, MSM, 2005–2006	0.1–1.7	1.7–3.1	6.7–11.5	5–7.6	3.8–5.4	—	—
Mumbai, India, MSM, 2006–2007	—	10	13	1	4	—	—

[a] Highest rates of range were in transgendered men.

Prevalence of sexually transmitted infections among men who have sex with men in the United Kingdom

In the United Kingdom, for instance, among MSM there has been an increase in the number of new diagnoses of HIV infection since the late 1990s, even though diagnoses of AIDS and AIDS-related deaths in MSM decreased rapidly after the introduction of antiretroviral therapy in 1996. Diagnoses of syphilis among MSM in genitourinary medicine (GUM) clinics sharply reduced in the late 1970s and 1980s, and remained at low levels until the late 1990s (see Figure 6). Since then the incidence of syphilis in men in England and Wales has increased to levels that are higher than before the AIDS epidemic. Diagnoses of other STIs, too, have increased consistently since the late 1990s (see Figure 7).

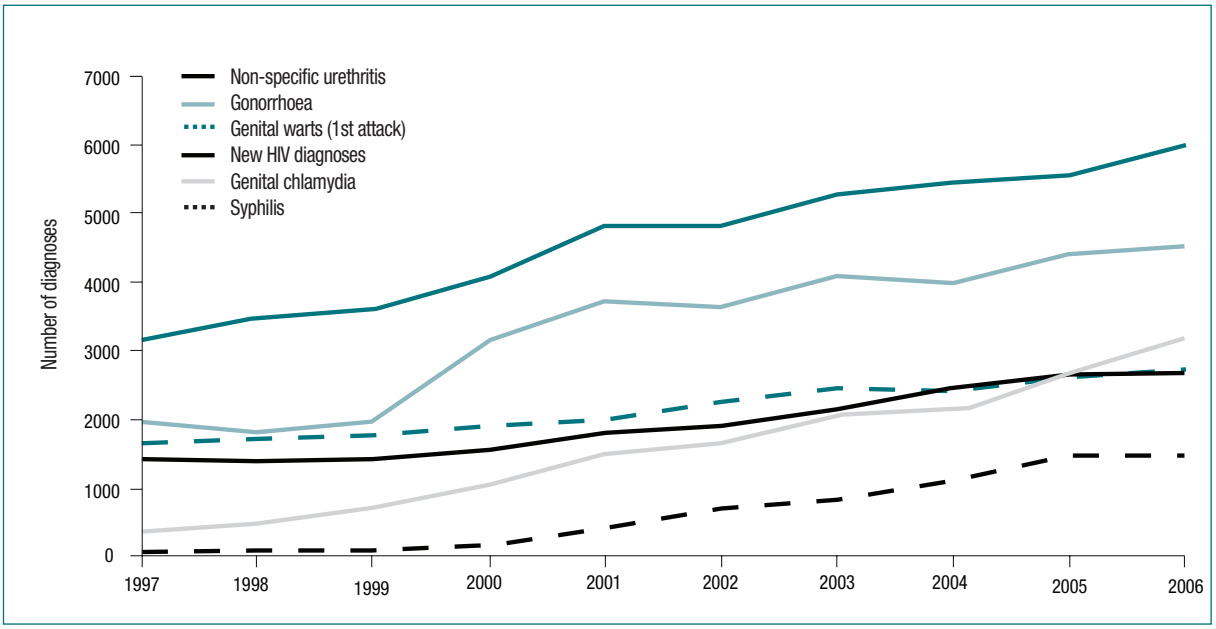
Figure 6. Diagnoses of syphilis (primary, secondary, early latent) in genitourinary medicine clinics by sex: England and Wales; Scotland



A large number of MSM remain unaware of their HIV status, and MSM are disproportionately affected by HIV and other STIs: in the United Kingdom, 44% of all diagnosed HIV infections, 23% of diagnoses of gonorrhoea, and 68% of diagnoses of syphilis are in MSM. In addition, while approximately 7–11% of MSM are HIV infected, these men also have 50% of gonorrhoea, 52% of syphilis, and 74% of LGV in the country. Thus, among MSM in the United Kingdom there has been no reduction in new HIV diagnoses and no reduction in incidence of HIV; one-quarter of MSM living with HIV infection remain undiagnosed; and there has been an increase in STIs between 1997 and 2005, especially syphilis, hepatitis C, and LGV.

Increased rates of STIs among MSM are associated with increases in high-risk sexual behaviours. Between 1990 and 2000, the percentage of men reporting homosexual sex (oral, anal, or any other genital contact) increased significantly, from 1.5% to 2.6%. Over that same period, among men who had homosexual sex in the past five years, the proportion reporting anal sex increased from 47.5% to 64.4% (P=0.027) (*37*). Among men surveyed in gay bars in London, United Kingdom, the proportion reporting unprotected anal intercourse in the last year increased from 32% in 1996 to 50% in 2005 (*38*). Two trends have been observed. First, there is evidence of serosorting among MSM in the United Kingdom: the practice of seeking sexual partners with the same HIV status. Serosorting among HIV-infected men permits such men to have unprotected anal intercourse without the risk of contracting a primary infection with HIV. Second, the internet is increasingly used to identify (seroconcordant) sexual partners (*39*), and the percentage of responders that met their first sexual partner through the internet increased from 2.6% in 1993 to 61% in 2002. This poses both challenges (the initial meeting place is virtual) and, possibly, opportunities for interventions. Lastly, it is important to note that even within a group with high rates of risky sexual behaviour, there is a subgroup with very high rates of risky behaviour: while 75% of HIV-infected MSM reported fewer than 35 new sexual contacts in the last year, 25% reported 35 or more new sexual contacts. These 25% were responsible for 79.3% of all reported new sexual contacts.

Figure 7. Diagnoses of HIV and selected STIs among MSM, United Kingdom



The internet, but also international travel and 'sex tourism', recreational drug use, and reported increases in sex-on-premises in bars and clubs, all facilitate the expansion of social and sexual networks, and the rapid acquisition of new partners.

In summary, before the introduction of antiretroviral therapy, marked declines in bacterial STIs were seen among MSM in the United Kingdom. There is broad consensus that this was the result of effective generalized and targeted public education and health-promotion strategies, resulting in widespread adoption of condom use and reductions in the number of new sex partners, and selective mortality of individuals with high-risk lifestyles. Since the introduction of antiretroviral therapy in the late 1990s, however, rates of many bacterial STIs returned to or exceeded pre-HIV rates, and HIV incidence has increased. Within the core group of high-risk men, there is another core with very-high-risk behaviours.

Management of anorectal infections

Infections of the anogenital region can be divided into:

- *anal infections:* infections of the external anus and anal canal, involving the stratified squamous epithelium, e.g. HPV, HSV, syphilis;
- *proctitis*: infections from the dentate line to the rectosigmoid junction, e.g. gonorrhoea, *Chlamydia*, HSV;
- *proctocolitis*: infections of the rectum and colon, e.g. *Shigella*, *Campylobacter*, *Salmonella*, cytomegalovirus, amoebiasis.

For the purposes of this report, these infections were all grouped under anorectal infections. Studies into sexually transmitted aetiologies of anorectal infections generally reveal the presence of a substantial number of infections of unknown origin. Thus, in a study among MSM with proctitis in San Francisco, USA, the following causative infections were identified: gonorrhoea in 20%, *Chlamydia* in 11%, HSV in 13%, syphilis in 1%, *Chlamydia* and gonorrhoea in 7%, HSV and gonorrhoea in 2%, gonorrhoea, *Chlamydia*, HSV, and syphilis in 1%, and none in 45% (*40*).

Symptoms associated with anorectal infections are the following: pain, itching, discharge, bleeding, sensation of rectal fullness, tenesmus, constipation, and mucus streaking of stools. In addition to an external examination of the anus and proctoscopy, the following laboratory tests can be employed: Gram-stained smear for *N. gonorrhoeae* and for leukocytes, culture of *N. gonorrhoeae*, NAAT for *Chlamydia* and LGV, PCR and/or culture for HSV-2, and dark-ground microscopy for *T. pallidum*. However, the performance of many tests on rectal specimens is not well established, and test kits are usually not

licensed for use on rectal specimens. Drug choice, dosage, and duration of treatment are in general not different from those for infections at other anatomical locations.

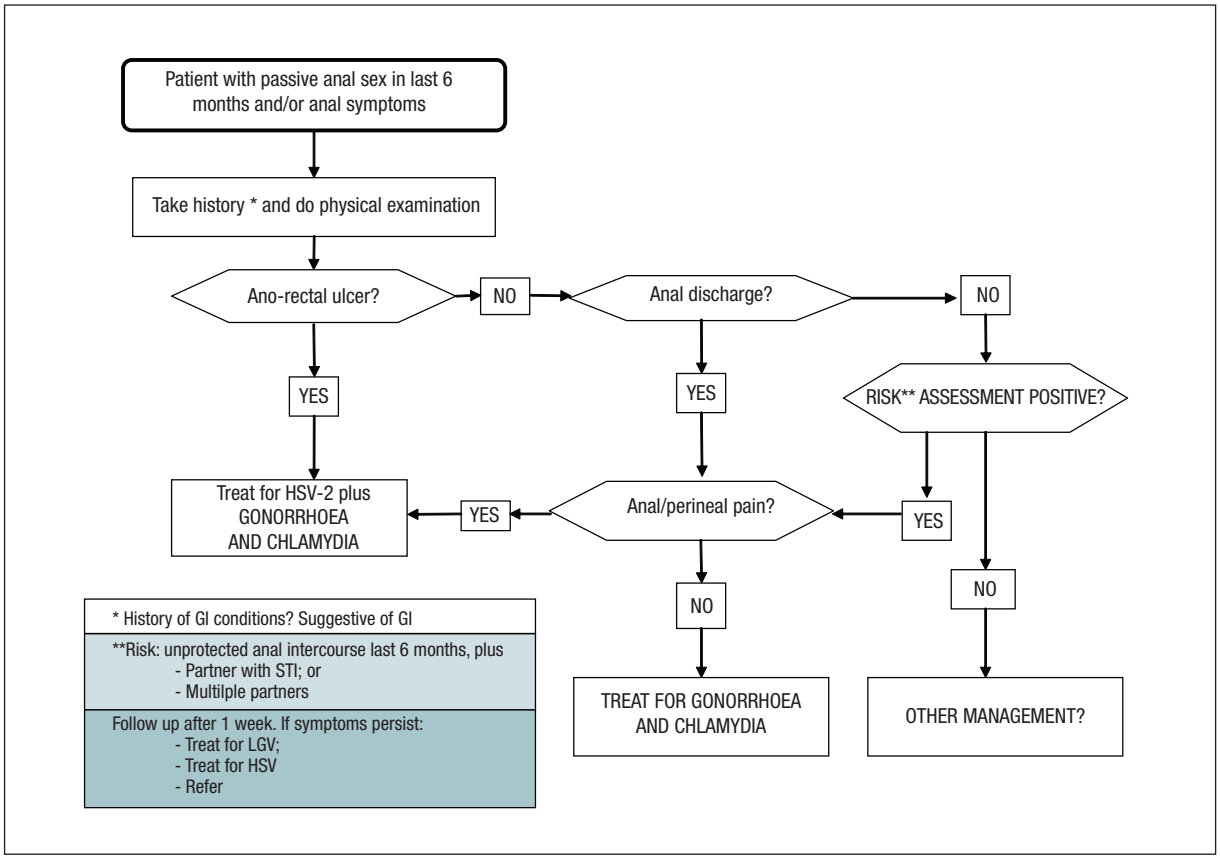
Asymptomatic anorectal infections are thought to be not uncommon, although data are scarce. Risk groups for asymptomatic anorectal infections are MSM, male and female sex workers, male-to-female transgendered individuals, and men and women who have had receptive anal intercourse with men identified with STIs. Specific risk behaviours associated with anorectal infections include receptive anal sex, oro-anal contact, fisting, fingering, nudging, dipping, and sharing of sex toys.

Only a single randomized controlled trial on the syndromic management of anorectal infections has been published to date. In this study, which enrolled 129 MSM, aetiological diagnosis of anorectal infections was compared with syndromic treatment for syphilis with doxycycline. The results showed a faster resolution of the infection with syndromic treatment, except in cases where HSV was present (*41*). Guidelines for the management of anorectal infections have been prepared by the International Union against Sexually Transmitted Infections (IUSTI), in collaboration with WHO (*42*), and by CDC (*43*). The following syndromic treatment of symptomatic patients is recommended: azithromycin 1 g stat for *Chlamydia*, or doxycycline 100 mg twice daily for 7 days (the latter extended to 21 days if a NAAT is positive for *Chlamydia*); with cefixime 400 mg for gonorrhoea; and with aciclovir or valaciclovir for HSV.

In many developing countries, rates of anorectal infection in MSWs are comparable to rates of infection in female sex workers. In resource-constrained settings, where diagnostic options are limited, asymptomatic infections can be identified by proctoscopy, possibly with Gram-stained smear and count of the number of polymorphonucleated leukocytes. It should be noted, however, that little or no data exist to validate the use of microscopy in the diagnosis of anorectal infections. A practical approach might be periodic presumptive treatment for high-risk males, or presumptive treatment at first visit.

Issues with regard to an algorithm for the management of anorectal infections include: identification of persons at risk, identification of risk behaviours in persons at risk, proctoscopy skills (and availability of a proctoscope), differentiation between anorectal infection and other pathology, entry points for the

Figure 8. Draft management algorithm for anorectal syndrome.



management protocol, and, lastly, thresholds for adding HSV or syphilis treatment. Given the dearth of research on this subject, a number of research topics were presented, as follows: aetiological studies in different settings, prevalence of anorectal infections in high-risk women, prevalence of infectious versus non-infectious causes of anorectal symptoms, validation of laboratory tests on rectal specimens, validation of treatment for anorectal infections, and evaluation of syndromic management of anorectal infections. A draft algorithm for syndromic management of anorectal infections was prepared during the meeting (see Figure 8).

Conclusions and recommendations

The health-care needs of MSM are diverse and cover a broad spectrum of diseases and conditions, and the development of guidelines to comprehensively meet those needs was beyond the scope of the consultation. There is, however, mounting evidence that the prevalence of both symptomatic and asymptomatic anorectal infections in MSM and MSWs is high. While not all anorectal morbidity is due to sexually transmitted pathogens, STIs are a frequent cause of anorectal infections. It is highly recommended that syndromic management of anorectal infections be included in the WHO *Guidelines for the management of sexually transmitted infections* and that the proposed algorithm for the management of anorectal infections be validated in different settings. It is also recommended that research be conducted to better understand the nature and prevalence of both symptomatic and asymptomatic anorectal infections, in high-risk men and women, to validate laboratory tests on rectal specimens and to validate the treatment of anorectal infections.

Update on treatment of early syphilis

Rationale

Both the 2002 WHO STI Treatment Guidelines as well as the 2006 CDC STD Treatment Guidelines recommended benzathine penicillin G, 2.4 MU by intramuscular injection for the treatment of early syphilis, with doxycycline 100 mg orally twice daily (or tetracycline 500 mg orally four times a day) for 14 days as an alternative regimen for penicillin-allergic non-pregnant patients. At the time, insufficient data were available to recommend the use of azithromycin 2 g orally in a single dose as an alternative to penicillin treatment. Azithromycin, as a single-dose, oral treatment, offers many advantages over either parenteral penicillin or multiday doxycycline treatment.

Current knowledge and discussion

The results of two studies were presented. An equivalence study, comparing a single dose of 2 g azithromycin with 2.4 MU of benzathine penicillin for the treatment of early syphilis revealed identical cure rates at 3, 6, and 9 months' follow-up (*44*). Cure rates at 9 months were 98% for azithromycin versus 96% for benzathine penicillin, with cure rates for HIV seronegative participants being 100% and 97% respectively for azithromycin and benzathine penicillin. Among HIV seropositive patients, cure rates were 94% and 95% for azithromycin and benzathine penicillin respectively.

A phase III equivalence trial comparing azithromycin 2 g orally in a single dose, with benzathine penicillin G 2.4 MU intramuscularly evaluated adverse events and cure rates at 6 months' follow-up. The total number of adverse events was similar in both treatment arms, with azithromycin causing a larger number of non-serious gastrointestinal side-effects, while penicillin was associated with slightly more serious adverse events and more cutaneous and administration-related side-effects. Cure rates at 3 and 6 months were identical in both arms: 74.4% and 75.7% at 3 months for azithromycin and penicillin respectively, and 77.6% and 78.5% at 6 months for azithromycin and penicillin.

Reports of clinical failure of azithromycin treatment for primary syphilis have been linked to the presence of a mutation that confers macrolide resistance to *T. pallidum*, even though it is not clear whether the presence of the mutation is always linked to reduced macrolide susceptibility. In view of what appears to be a slow increase in the identification of macrolide-resistant strains (*45*), it is important to monitor antibiotic susceptibility and the prevalence of macrolide-resistant strains when using azithromycin in the treatment of syphilis.

Conclusion and recommendations

The availability of a single-dose oral treatment for syphilis would greatly facilitate treatment of early syphilis. A non-penicillin drug would also offer treatment alternatives for pregnant women and patients who are allergic to penicillin. The studies presented suggest that not only is azithromycin 2 g orally in a single dose relatively well tolerated, but it is also equivalent to benzathine penicillin G 2.4 MU intramuscularly for the treatment of early syphilis. Based on this evidence, a number of participants proposed that azithromycin be recommended as an alternative treatment for early syphilis, especially for pregnant women, penicillin-allergic patients, and in situations where parenteral treatment is not practical.

The small number of studies presented and reports of azithromycin resistance, however, suggest that antibiotic susceptibility and the prevalence of macrolide resistance need to be carefully monitored when azithromycin is used for the treatment of early syphilis.

Meeting participants did not reach consensus on the inclusion of azithromycin for the treatment of syphilis and recommended that further studies on the prevalence of azithromycin resistance be conducted. Where azithromycin is used as an alternative treatment for early syphilis, it will be important to carefully monitor macrolide resistance.

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Annex 1: List of participants

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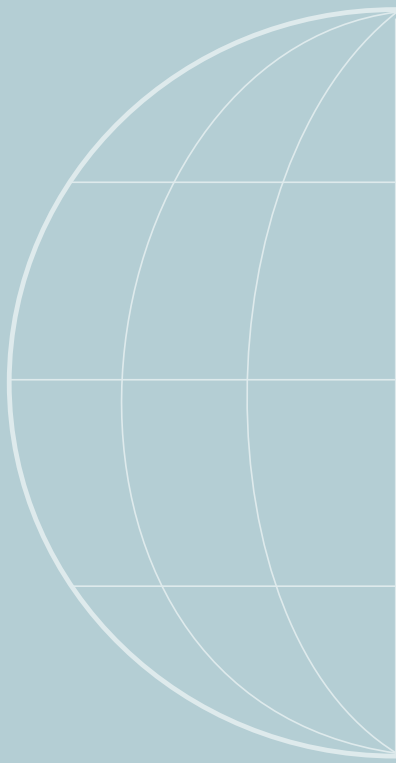

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