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TREATMENT OF SEXUALLY TRANSMITTED INFECTIONS FOR HIV PREVENTION: END OF THE ROAD OR NEW BEGINNING?

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Introduction

HIV prevention research, programmes and policy have been crucibles of controversy and no issue has been more controversial than the control of other sexually transmitted infections (STIs) as a strategy for HIV prevention. Observational data have provided clear and consistent evidence of the importance of STI interventions in limiting HIV spread, while the results of randomised controlled trials (RCTs) have been mixed. In the absence of widespread understanding of the reasons for these seemingly contradictory findings, debate continues to rage about what role STI control should play in HIV prevention [Gray & Wawer 2008].

Two decades ago, ample observational data were already available to support the concept that biological interactions between HIV infection and other STIs could result in substantial epidemiological synergy, causing mutually reinforcing spirals of infection [Wasserheit, 1992]. Subsequent observational studies confirmed and extended these early findings by demonstrating that this epidemiological synergy could operate by increasing both susceptibility and infectiousness for both HIV and other STIs. More recent research has elucidated multiple biological mechanisms potentially underpinning these interactions, including mucosal disruption, HIV target cell recruitment and activation, altered cytokine production, reduced CD4 counts, impaired HIV-specific cytotoxic lymphocyte function, enhanced HIV replication, increased HIV viral load in plasma, vaginal fluids and semen, and an imbalance of the protective lactobacilli-dominated vaginal flora [Cohen and Pilcher 2005, Kaul et al 2007].

These findings provided a strong foundation for the plausibility of STI control as an HIV prevention strategy. STIs are more common among those with riskier sexual behaviour and so tend to cluster in the same subgroups of the population as those at risk of HIV infection. Moreover, STI prevalences were high in many countries during the expansion of the HIV epidemic, due at least in part to the poor quality of treatment services. This led to the hypothesis that improved STI treatment would reduce the prevalence of STIs among HIV-discordant partners and hence reduce HIV transmission.

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Subsequently, nine RCTs have been conducted to evaluate this approach to HIV prevention. They examined three different management approaches to a broad spectrum of curable and incurable STIs in a variety of populations with different levels of risk behaviours and STI prevalence, in the context of HIV epidemics that ranged from concentrated to generalised. In contrast to the consistent observational data, only one of these highly diverse RCTs demonstrated the efficacy of STI treatment in HIV prevention, while the other eight showed no significant effect.

In this paper, we briefly review the observational evidence for the cofactor effects of different STIs on HIV acquisition and transmission. We then summarise the results of the nine RCTs that have been carried out and discuss the explanations for their contrasting findings. Finally, we examine the implications of these results for HIV prevention policy, programmes and future research. While our primary focus is on STIs, we also briefly consider the role of bacterial vaginosis (BV) and vaginal candidiasis.

Evidence from observational studies

The substantially increased risk of HIV acquisition associated with both curable STIs and genital herpes has been robustly demonstrated in observational studies. A recent meta-analysis of 31 longitudinal studies demonstrated a 4-fold increased risk of HIV infection with any laboratory-documented STI (aOR 3.9, 95% CI: 2.8-5.3) [Sexton et al 2005]. Adjusted effect estimates were higher for any genital ulcer disease (aOR 2.8, 95% CI: 2.3-3.3) than for any non-ulcerative STI (aOR 1.7, 95% CI: 1.4-2.0) and consistently fell in the 2 to 3-fold range for herpes, syphilis, chancroid, gonorrhoea and chlamydia. These relative risks, generally measured over extended follow-up periods during which STIs will only have been present for a limited period, may imply considerably higher STI cofactor effects on HIV acquisition per sexual contact [Hayes et al 1995].

The results for herpes are consistent with a further meta-analysis of 25 cohort and nested case-control studies of prevalent HSV2 infection adjusted for age and sexual behaviour that provided summary estimates of the relative risk of HIV acquisition of approximately 3 in general population cohorts (women: aRR 3.4, 95% CI: 2.4-4.8; men: aRR 2.8, 95% CI: 2.1-3.7) and 1.5 in higher risk cohorts of female sex workers (aRR 1.5, 95% CI: 0.75-3.0) and men who have sex with men (aRR 1.6, 95% CI: 1.2-2.0) [Glynn et al 2009]. Studies of incident HSV2 infection suggest even stronger cofactor effects, although determination of the temporal relationship of incident HSV2 and HIV1 infection in these cohort studies is problematic.

While the observational studies do not provide direct estimates of the increased risk of HIV transmission associated with other STIs, numerous studies suggest that HIV infectiousness is increased by STIs, as indicated by increased frequency and quantity of HIV shedding in genital secretions. A meta-analysis of 39 studies evaluating the impact of STIs on genital tract HIV-1 DNA or RNA in co-infected individuals revealed a 2 to 3-fold increase in frequency of HIV shedding with urethritis (OR 3.1, 95% CI: 1.1-8.6), cervicitis (OR 2.7, 95% CI: 1.4-5.2), gonorrhoea (OR 1.8, 95% CI: 1.2-2.7) and chlamydia (OR 1.8, 95% CI: 1.1-3.1 [Johnson & Lewis 2008]. While HIV shedding was also increased 50-80% among subjects with vaginal discharge and genital ulcers, these differences were not statistically significant. Finally, HSV2 infection appears to significantly increase HIV plasma viral load (PVL), an established determinant of transmission risk [Quinn et al 2000]. A meta-analysis of 11 studies showed that HSV2 co-infection increased PVL by almost a quarter log (difference in mean PVL 0.22 log₁₀ copies/ml, 95% CI: 0.04-0.40) [Barnabas et al 2009].

Observational studies also support the hypothesis that STI treatment can reduce HIV infectiousness. Studies in Malawi and Kenya have demonstrated substantial declines in GVL

within two weeks of treatment for gonorrhoea, chlamydia and trichomoniasis in both men and women [Cohen et al 1997, Price et al 2003, McClelland et al 2001, Wang et al 2001].

The evidence that vaginal infections that are not primarily sexually transmitted (such as BV and vaginal candidiasis) are cofactors in HIV transmission is less clear than the evidence for classical STIs but is mounting. The initial studies showing a link between BV and HIV were cross-sectional, making it difficult to draw conclusions about a temporal relationship [Myer et al 2005a]. However, four prospective studies have consistently shown significant associations between BV and subsequent acquisition of HIV in women, with hazard ratios ranging from 1.4 to 2.3 [Taha et al 1998, Martin et al 1999, Myer et al 2005b, van de Wijgert et al 2008]. It is important to note that one of these studies showed that both BV and intermediate flora as defined by Nugent score (each compared with normal flora) were associated with HIV acquisition in women; the hazard ratios were almost identical [van de Wijgert et al 2008].

The evidence for vaginal candidiasis is slightly less consistent, with four of six prospective or nested case-control studies showing a positive association with HIV acquisition, with adjusted relative risks ranging from 1.8 to 3.3 [Laga et al 1993, Kapiga et al 1998, Taha et al 1998, Martin et al 1999, Hester et al 2003, van de Wijgert et al 2008].

While the effects of vaginal infections on HIV acquisition in women are generally less strong than for classical STIs, the population attributable fractions (PAF) are likely substantial due to the high prevalences of these infections. A recent analysis of data from Zimbabwe and Uganda showed that the PAF for vaginal infections (defined as BV or intermediate flora by Nugent score or vaginal candidiasis by wet mount) was lower than that for HSV2 but substantially higher than those for any of the other STIs [van de Wijgert et al 2009]. Taken together, the evidence thus far suggests that any deviation from normal lactobacilli-dominated vaginal flora increases women's vulnerability to HIV and other STIs. The evidence also suggests that most of these relationships are bidirectional – women who are already HIV-infected or have other STIs are also much more likely to have imbalances in vaginal flora.

Trials of STI control for HIV prevention

The data from observational studies provide strong evidence that the acquisition and transmission of HIV infection are enhanced in the presence of other STIs. This led to recommendations that improved STI treatment should form one component of HIV prevention and control programmes in countries or communities in which STIs remain common. The effects of such interventions, however, are difficult to predict as they depend on a wide range of factors, including the prevalence and distribution of different STIs in the population, the coverage and effectiveness of STI treatment before and after intervention, and the exact magnitudes of STI cofactor effects on HIV susceptibility and infectiousness, which are likely to vary between STIs and between men and women. Mathematical modelling has been used to estimate the potential population-level effects of such interventions, taking into account indirect effects on onward transmission of HIV (and STIs) as well as the direct protective effects on treated individuals, but depend on a large number of assumptions and on parameter values that are not known with any accuracy.

The most convincing evidence of the effectiveness of such interventions therefore comes from RCTs in which specific approaches to improved STI control have been evaluated in different study populations and empirical data on impacts on HIV incidence have been measured. Nine such trials have been published to date, and their results are briefly reviewed here. We begin with the six trials that have assessed the effects of treating curable STIs, and

then consider the three trials that have looked specifically at the impact of herpes suppressive therapy. The results of all nine trials are summarised in Figure 1.

Treatment of curable STIs

Cluster randomised trials—Four of the six trials of various approaches to the treatment of curable STIs examined population-level STI treatment interventions that aimed to provide effective treatment to a large proportion of STI patients, both HIV infected and uninfected, in the general population and to measure the population-level impact on HIV incidence (Table 1). These trials attempted to capture the effects of STIs on both HIV acquisition and transmission, as well as the direct and indirect (“herd”) effects achieved through a population-wide intervention. They did this by using a cluster randomised trial (CRT) design in which large communities were randomly allocated to intervention or control arms, and HIV incidence in the entire population, or a sample of the population, was measured through prospective follow-up.

The Mwanza trial examined the effect of improved STI services at government health units using syndromic management and found a reduction in HIV incidence in the general population of around 40% which was highly significant [Grosskurth et al 1995]. Significant reductions were also seen in the prevalence of active syphilis in both sexes and of symptomatic urethritis in males [Mayaud et al 1997]. In the other trials, there was no significant reduction in HIV incidence, although reductions in some STIs were observed in Rakai and Masaka (STIs were not measured in Manicaland) [Wawer et al 1999, Kamali et al 2003, Gregson et al 2007].

The effect seen in Mwanza, and the differences in effect between trials, were very unlikely to have occurred by chance and it is therefore important to examine possible explanations for these differences. There are four main differences between the trials and study populations which may be important.

HIV epidemic phase: The Mwanza trial was the first to be carried out and was conducted in a study population with an expanding HIV epidemic, as shown by the low prevalence:incidence ratio, while the other three trials were carried out in mature epidemics. Modelling studies have shown that the proportion of HIV infections attributable to the cofactor effects of curable STIs declines during the epidemic, as the virus spreads widely in the population beyond subgroups at high risk of STIs [White et al 2008]. In mature epidemics, much transmission takes place within stable partnerships in which STIs are relatively uncommon and the cumulative probability of HIV transmission is quite high even in the absence of STIs. This dynamic is particularly apparent in settings in which STI services were strengthened as part of HIV prevention programmes, as was recommended by the World Health Organization (WHO), UNAIDS and the US Centers for Disease Control and Prevention by the mid 1990s.

Control group interventions: Intervention effects on HIV (and STIs) in trials may be diluted because of interventions provided to the control group. In the Mwanza trial, the control group received existing STI services, which were shown in a special study [Buvé et al 2001] to be of poor quality until the syndromic treatment intervention was extended to control communities at the end of the trial. By contrast, control groups in the other three trials received somewhat more active services, including syndromic treatment services provided at local health units in all three sites, treatment of symptomatic STIs and referral of RPR-positive individuals for treatment at 10-monthly intervals in Rakai, condom social marketing and project VCT services in Masaka, and condom social marketing and limited health education in Manicaland. Despite this, there was evidence of differences in STI

prevalences between study arms in Rakai and Masaka, and so the intensity of control interventions cannot fully explain the difference in HIV impact. STIs were not measured in the Manicaland trial, but it is worth noting that Zimbabwe was one of the first countries to establish effective syndromic management services in the 1980s.

Prevalence of STIs: The impact of STI control interventions on HIV incidence will vary depending on the prevalence of STIs in HIV-discordant partnerships. A detailed study was carried out by investigators of the Mwanza, Rakai and Masaka trials to compare data on STI prevalence with careful adjustment for the different sampling procedures and diagnostic tests used in these studies [Orroth et al 2003]. This study demonstrated that prevalences of some STIs were substantially higher in the Mwanza study population at the time of the trial than in Rakai and Masaka. For example, baseline prevalences of high-titre active syphilis were 6.3% and 5.6% in women and men in Mwanza, but only 1.4% and 2.3% in Rakai and 0.7% and 1.2% in Masaka. These differences mirrored reported risk behaviour which also appeared to be higher in the Mwanza study population. Subsequent analyses have shown that there were substantial decreases in risk behaviours in Uganda during the 1990s, which were probably partly responsible for declining HIV incidence. Such decreases had probably not occurred in Mwanza by the time this trial was carried out from 1990 to 1994. Data on STIs were not reported in the Manicaland trial, but reductions in risk behaviour have also been seen in Zimbabwe and the trial publication notes that prevalences of curable STIs including gonorrhoea, chlamydia and syphilis were low [Gregson et al 2007].

Intervention strategy: A further difference between the four trials was in the STI treatment approaches adopted in the intervention arms. Syndromic management was shown to be effective in Mwanza but not in Masaka and Manicaland, while both syndromic management and mass treatment showed no effect in the trial populations in Uganda. These findings suggest that intervention differences could not explain the contrasting results, and stochastic simulation modelling of the Tanzanian and Uganda trials supports this conclusion [Korenromp et al 2005].

Individually randomised trials—The two remaining trials were carried out among female sex workers in Abidjan and Nairobi (Table 1). These were individually randomised trials aimed at measuring the effect of STI control interventions on HIV acquisition in individual HIV-negative women. They therefore differ intrinsically from the four trials discussed above which capture effects on HIV infectivity as well as susceptibility, and also capture indirect and population-level effects. The Abidjan trial was not powered for HIV incidence and so, although the observed effect was a 30% reduction, this could easily have been due to chance [Ghys et al 2001]. The control group in this trial also received a relatively intensive intervention, including monthly provision of syndromic management, condoms and prevention counselling. The investigators report that HIV incidence during the trial was considerably lower than previously and suggest that this may be ascribed to the intervention, although this included counselling and condom provision as well as STI screening and treatment. Similar findings were obtained in an earlier study in Kinshasa [Laga et al 1994].

The findings of the Nairobi trial were more surprising, as substantial effects were seen on incidence rates of STIs but no effect on HIV [Kaul et al 2004]. This study was powered on an assumed HIV incidence of 15%, but the actual incidence was much lower at 3-4%, so this study was also underpowered. Thus, only 35 HIV seroconversions were observed, and a reduction in HIV incidence of up to 40% could not be confidently excluded. HIV prevention activities (including STI treatment) were quite intensive in both arms of the trial, which perhaps helps to explain the lower than expected incidence, and the investigators comment

on the low prevalence of curable ulcerative STIs, including chancroid and syphilis, in this sex worker population which had been the target of preventive interventions for many years.

Treatment of genital herpes to reduce HIV acquisition—Two of the three randomised placebo-controlled trials of the effect of herpes suppressive therapy on HIV incidence have examined the impact of HSV suppression on HIV acquisition, and neither demonstrated a protective effect on HIV incidence (Table 2). The first trial was conducted in an occupational cohort of 821 HSV2-seropositive, HIV-negative women at high risk of HIV infection (working in bars and other food and recreational facilities) in Tanzania [Watson-Jones et al 2008]. HIV incidence was 4.4% in the acyclovir arm compared with 4.1% in the placebo arm (RR=1.08, 95% CI: 0.64-1.83). Tablet adherence was similar in both arms (90% adherence reported in 51% and 52% of person-years in the acyclovir and placebo arms respectively). Adherence may have been suboptimal since there was a lower than expected impact on HSV genital shedding (4.3% in the acyclovir arm vs. 4.5% in the placebo arm; OR=0.98, 95% CI: 0.50-1.91).

The second trial enrolled 3,172 participants, including 1,358 women from 3 sites in Africa (Johannesburg, Harare and Lusaka) and 1,814 MSM from Peru and the US [Celum et al 2008]. HIV incidence was 3.9% in the acyclovir arm compared to 3.3% in the placebo arm (RR=1.16, 95% CI: 0.83-1.62). Acyclovir had a significant effect on the incidence of genital ulcers (RR=0.53, 95% CI: 0.46-0.62) and an even greater effect on ulcers due to HSV2 based on PCR (RR=0.37, 95% CI: 0.31-0.45). Overall adherence to expected doses was 85% in the acyclovir arm and 86% in the placebo arm.

There is compelling epidemiological and biological evidence supporting the hypothesis that HSV2 increases susceptibility to HIV [Wald & Link 2002, Pujades et al 2002, Corey et al 2004, Freeman et al 2006, Kapiga et al 2007] and, therefore, HSV suppressive therapy would be expected to reduce HIV incidence. Increased presence and persistence of HIV target cells may explain the lack of impact of HSV2 suppression on HIV susceptibility. The first study to demonstrate increased HIV target cells due to HSV2 infection was a cross-sectional study of endocervical specimens from HIV-negative women at high risk in Nairobi, which indicated that HSV2 seropositive women had a 10-fold increase in endocervical immature dendritic cells expressing DC-SIGN and a 3-fold increase in CCR5-positive CD4 cells compared with HSV2 seronegative women [Rebbapragada et al 2007]. A longitudinal study of 8 healthy, HIV-negative subjects with recurrent genital HSV2 that obtained sequential biopsies of HSV2 lesions on and off suppressive therapy demonstrated persistence of a cellular infiltrate 8 weeks after healing of the ulcer on HSV suppressive therapy [Zhu et al 2009]. Notably, HIV target cells (CCR5 positive CD4 T cells and mixed plasmacytoid and myeloid dendritic cells) were increased compared to control skin biopsies and persisted during 8 weeks of antiviral therapy and after HSV antigen was cleared. Thus, the results of the two trials may be explained by enhanced recruitment of HIV target cells during HSV2 reactivations that persist during HSV suppressive therapy. This would imply that a preventive HSV2 vaccine or more potent therapies to suppress HSV2 reactivation and associated genital tract inflammation would be needed to reduce the effect of HSV2 on HIV susceptibility.

Treatment of genital herpes to reduce HIV transmission—A number of proof-of-concept trials have been conducted among HIV-positive individuals to determine if HSV suppressive therapy can reduce HIV genital shedding and HIV plasma viral load (PVL), proxy markers for HIV transmission. Reductions in genital HIV RNA of 0.2-0.5 log₁₀ copies/ml and PVL (0.25-0.5 log₁₀ copies/ml) have been seen in randomised trials of valacyclovir 500mg bd or acyclovir 800mg bd given for periods of up to 3 months [Nagot et al 2007, Dunne et al 2008, Zuckerman et al 2009, Baeten et al 2008]. Three trials of

acyclovir 400 mg bd showed weaker or no effects on HIV genital load [Cowan et al 2008, Delany et al 2009, Tanton et al (in press)], although one trial using this regimen did see a reduction in PVL [Delany et al 2009]. However, suboptimal adherence may have been an important factor in some of these trials, which confounds the ability to directly compare the relative reductions in PVL between trials. Differences in trial designs (parallel randomisation or cross-over design), study populations and duration of follow-up may also be factors to consider in comparing trial outcomes.

A critical question was whether the reduction in HIV levels observed in the proof-of-concept trials would be sufficient to reduce HIV transmission. The Partners in Prevention HSV/HIV study was a multi-centre, randomised, placebo-controlled trial of 3408 HIV-1 serodiscordant couples designed to answer this question (Table 2). The trial enrolled couples in which the HIV-infected partner was co-infected with HSV2, had a CD4 count >250 cells/mm³ and did not meet national ART initiation guidelines at enrolment. The HIV/HSV2-seropositive partner was randomised to acyclovir 400 mg bd or placebo. The HIV-uninfected partner could be either HSV2 seropositive or seronegative. The study was conducted in 14 sites in 7 countries in East and Southern Africa. Overall adherence was high, with 85% of expected doses taken. Although acyclovir suppressive therapy reduced HIV PVL by an average of 0.25 log₁₀ and genital ulcers due to HSV2 by 73%, HIV transmission was not significantly reduced (RR=0.92, 95%CI: 0.60-1.41) [Celum, in press]. A modest reduction in HIV disease progression of 16% was observed, as measured by time to CD4<200, ART initiation (excluding short-term ART use for prevention of mother-to-child transmission) and non-traumatic causes of death [Lingappa, in press]. These results suggest that a greater reduction in plasma HIV levels than 0.25 log₁₀ is necessary to reduce HIV transmission risk, which is an important gauge for future evaluation of treatment of co-infections and of therapeutic HIV vaccines to reduce HIV infectiousness.

Implications for policy

Following the publication of the Mwanza trial, improved STI treatment was widely accepted as an essential component of HIV control, and introduced into national programmes in many countries in sub-Saharan Africa and elsewhere. As we have seen, a number of subsequent trials failed to show effects of a range of STI control strategies on HIV incidence, and this led to a reduced emphasis on this HIV prevention strategy by some countries and agencies. We believe that this is an inappropriate response to the available data, for several reasons.

RCTs may fail to demonstrate a significant positive effect for three reasons. The basic concept may be wrong; the concept may be right, but the specific intervention may not work; and/or aspects of the trial design and conduct may preclude detection of an effect that does, in fact, exist. Careful examination of the observational and intervention studies of STI treatment for HIV prevention strongly supports the underlying concept that STI control has an important role to play in HIV prevention, but reveals that insufficiently potent interventions were tested in the herpes suppression trials, and design or implementation factors limited interpretability of several of the trials of treatment of curable STIs.

With respect to the basic concept, the biological and epidemiological evidence that STIs enhance HIV acquisition and transmission remains compelling. There is little doubt that individuals with an untreated STI are at increased risk of acquiring HIV if they are HIV-negative and exposed to an HIV-infected partner, or of transmitting HIV if they are HIV-positive.

Yet we clearly have much to learn about how to intervene. For example, the emerging data on the prolonged persistence of HIV target cells in the genital inflammatory response to HSV2 reactivation despite standard acyclovir doses that achieve suppression of clinical

herpetic disease strongly suggest that failure to demonstrate a significant effect in the HSV2 suppression trials was largely due to testing antivirals that partially suppressed HSV2 reactivation but not the associated genital inflammatory response that includes HIV target cells. Indeed, the detailed biological mechanisms mediating increased HIV susceptibility and infectiousness with most other STIs are just beginning to be elucidated. We have assumed that the same STI treatment regimens that have been proven to control clinical manifestations, sequelae and onward transmission would be equally effective in interrupting these STI-HIV interactions even though the underlying mechanisms may differ substantially.

Furthermore, issues in RCT design and conduct plagued several of the trials evaluating the role of treatment of curable STIs in HIV prevention (Table 1). Firstly, curable STIs were not common in the largely low risk, general population cohorts enrolled in all three of the CRTs that were conducted in late phase HIV epidemics and that showed no significant effect of STI treatment on HIV incidence. Second, HIV prevention services beyond the local standard of care were introduced in the comparison arms of each of these trials, and in the two individually randomised trials that also demonstrated no intervention effect with treatment of curable STIs, reducing the ability of investigators to detect a difference between the intervention and control groups. Finally, both of the individually randomised trials of interventions for curable STIs were inadequately powered to evaluate HIV incidence.

A particularly difficult area of debate is the population-level effect on the HIV epidemic that will be provided by STI treatment under different circumstances. Rational consideration of this question must consider the full range of available evidence, including the results of observational studies, mathematical modelling and intervention trials. We have seen that only four trials measured the impact of STI control interventions on population-level HIV incidence, and one of these showed a substantial 40% reduction in HIV while the other three showed no significant effect. These findings are often described as if the results are contradictory. However, we posit that the effect of an indirect intervention of this kind, in which control of one infection aims to prevent the transmission of another, would be expected to vary substantially between different populations depending on HIV epidemic phase and the prevalence of curable and incurable STIs. The results of the four trials are consistent with this framework since they demonstrate a substantial effect of STI treatment in an expanding epidemic with high population prevalences of STIs, but no significant effects in populations with a mature epidemic and lower STI prevalences. Mathematical modelling studies carried out by a collaborative team including the investigators of three of the trials showed that the trial findings in Mwanza, Rakai and Masaka were consistent with the expected impact of the STI control interventions in these different population settings [White et al 2004, Korenromp et al 2005].

The three trials in areas with mature epidemics were carried out in countries (Uganda and Zimbabwe) where STI treatment services using the syndromic approach were already in place and where there was evidence of a decline in HIV incidence. Although it is difficult to attribute incidence reductions to specific interventions, it is likely that improved STI treatment may have played some part in the declining HIV incidence seen in several countries. Trials have not been carried out in the many other parts of sub-Saharan Africa where HIV incidence remains at a high level and where STI treatment services are inadequate. However, mathematical modelling studies have shown that while the relative impact of treatment of curable STIs is expected to fall as the epidemic expands, its absolute impact in terms of HIV cases averted may remain substantial [White et al 2008].

There is growing recognition that, in the near to medium term, we will not have a single “magic bullet” to control HIV epidemics, and that combinations of partially effective

interventions will be needed. We recommend that national AIDS control programmes continue to ensure that effective treatment services are provided for curable STIs as one component of the HIV prevention response. As with any preventive intervention, STI treatment must be targeted to relevant populations and deployed with high levels of coverage. This means that STI detection and treatment services should be located in communities with substantial STI prevalence, and priority populations should include symptomatic individuals (regardless of HIV infection status), HIV-infected individuals not yet on antiretroviral therapy engaging in risk behaviours, sex workers and sexually active adolescents. Partner services should be an integral part of STI management. National Ministries of Health should monitor the adequacy of service delivery and take rapid action to ensure that provision is improved in areas where the quality of delivery is poor.

While most countries in sub-Saharan Africa have well-developed systems of HIV surveillance that can provide accurate estimates of HIV prevalence and incidence, there is a serious dearth of reliable data on the frequency of other STIs. Attention should be given to enhancing the monitoring of STI rates so that areas and populations with high prevalence can be identified and control measures can be strengthened. Potential approaches include STI screening together with HIV screening in antenatal care and surveillance programmes, HIV voluntary counselling and testing services, or national surveys such as the Demographic and Health Surveys (DHS). WHO is well placed to provide support and technical guidance in this area. A good example is provided by data from South Africa showing high prevalences of a range of STIs in pregnant women [Johnson et al 2005]. Clearly, such high prevalence in a population with high exposure to HIV infection is of serious public health concern and calls for concerted action.

Relaxation of STI control efforts could reverse the benefits that have been achieved by improved STI treatment services, leading to higher STI prevalences in the community, and subsequent adverse health effects and enhancement of HIV transmission. This is of particular concern in the declining HIV epidemics now being seen in several countries. Just as the impact of curable STIs on HIV spread decreases as HIV epidemics become generalized, it is likely to rebound as HIV epidemics settle into the next, endemic phase in which infection again becomes concentrated in higher risk groups with limited health care access [Wasserheit & Aral 1996].

Finally, STIs are an important cause of morbidity and mortality in their own right, and the effective diagnosis and treatment of curable STIs should be regarded as an essential component of primary health care. If effective and accessible clinical services for STIs are not available to those who need them, this will have serious consequences for the health of men, women and newborns.

Directions for future research

Future research must elucidate the biological mechanisms responsible for the STI-HIV interactions that facilitate HIV acquisition and transmission, and test new STI control strategies that target these mechanisms. Development of point-of-care STI diagnostics and evaluation of alternative partner service approaches (e.g. patient-delivered partner therapy) in low and middle income countries will also be critical to implementing STI treatment for HIV prevention in large scale programmes.

Strategies for the control of genital herpes

As discussed above, three trials have demonstrated unequivocally that herpes suppressive therapy using a currently available treatment regimen was ineffective in reducing the acquisition or transmission of HIV, although one demonstrated modest clinical benefits for

HIV/HSV2 dually infected persons. The evidence that genital herpes is an important cofactor that has a substantial effect on HIV transmission at individual and population levels remains compelling. There is a need for further detailed clinical research to investigate the biological mechanisms underlying this powerful cofactor effect and to better understand whether alternative approaches (e.g. higher doses of suppressive therapy in HIV/HSV2 dually infected persons or therapeutic HSV vaccines) could show a protective effect.

Modelling studies have shown that as HIV epidemics expand, genital herpes plays an increasing role in HIV transmission [White et al 2008]. Unless more effective treatment strategies can be devised, it seems that primary prevention of herpes is the most promising approach. The behavioural strategies promoted for HIV prevention, such as partner reduction and condom use, should also reduce the transmission of HSV2 infection leading to additional indirect effects on HIV transmission. However, HSV2 prevalence remains extremely high in most parts of sub-Saharan Africa, and it seems unlikely that behaviour change alone will be sufficient to substantially decrease HSV2 incidence and prevalence. Male circumcision only has a modest effect on HSV2 incidence and there is no evidence yet that any of the existing vaginal microbicides has a measurable effect on HSV2 infection. An effective HSV2 prophylactic vaccine would potentially be a valuable tool to reduce HIV transmission as well as the significant morbidity associated with genital herpes, and continued development and evaluation of such vaccines is an important research priority.

Interventions against bacterial vaginosis and other vaginal conditions

We have seen that there is increasing evidence that HIV acquisition is enhanced in the presence of BV, intermediate flora or vaginal candidiasis. BV treatment was included in the mass treatment intervention in Rakai without any measurable effect on HIV incidence, probably because the effects of current treatment regimens are short-lived and recurrence rates are very high [Wawer et al 1999]. Research is needed to increase our understanding of the aetiology of imbalances in vaginal flora, and to explore novel approaches to achieve healthy lactobacilli-dominant vaginal flora with no inflammatory immune activation over extended periods of time.

Many women with vaginal infections do not have visible signs of inflammation and are asymptomatic, and many BV-associated bacteria are difficult to visualize by microscopy or to grow in culture. Novel molecular techniques are now enabling the detection of such bacteria, as well as bacteria that are present in small quantities, thereby allowing in-depth characterization of the vaginal flora [Fredricks et al 2005]. About 70-90% of BV patients are cured after standard treatment with metronidazole, but recurrence rates are high: 30-50% within 6 months [Austin et al 2005]. Candidiasis treatment with antimycotics is more effective: the cure rate is usually above 90% and recurrence rates are <5% [Pitsouni et al 2008]. Several other BV treatment strategies have been tried, including treatment with lactobacilli-based probiotics, maintenance therapy with antibiotics or combined antibiotics/antimycotics, and treatment of male sexual partners, but none of these were significantly better than treatment with metronidazole [Taha et al 2007, McClelland et al 2008, Abad and Safdar 2009]. While it seems daunting to achieve healthy lactobacilli-dominant vaginal flora in most women over extended periods of time, the new molecular techniques may improve our ability to target treatment interventions to specific micro-organisms and study their biological effects. This is an active area of current research. Furthermore, treatment interventions could be combined with interventions targeting intra-vaginal practices and other behaviours that may be associated with BV.

Improved strategies for the treatment of curable STIs

While syndromic management is highly effective for the treatment of STIs presenting as genital ulcer disease (apart from genital herpes) or male urethral discharge, it is not very effective for the clinical management of vaginal discharge. An important step forward would be the development of accurate and simple point-of-care tests to provide aetiological diagnoses for important STIs such as gonorrhoea and chlamydia, and it is hoped that research now in progress will soon lead to such tests. Alternative approaches to STI screening (e.g. self-sampling or self-testing) and partner notification and treatment are also called for.

Interactions between HPV and HIV

Evidence is accumulating that infection with human papillomavirus (HPV) may also be a risk factor for HIV acquisition [Auvert et al 2010]. HPV is a sexually transmitted agent with multiple genotypes, some of which are causally associated with cervical cancer. Further research is needed to confirm and quantify the association of HPV with HIV acquisition, and to determine whether this is linked to particular HPV genotypes, persistent or clearance of HPV infection, or cervical lesions. The incidence and prevalence of HPV infection are high in many high HIV-prevalence countries and, since there are effective prophylactic vaccines against some HPV types, the potential role of HPV vaccination as an HIV control strategy needs to be investigated.

Conclusion

Modelling studies have shown that STIs may have played a critical role in helping HIV to become established in new populations. They also show that the proportion of new HIV infections attributable to STIs remains substantial throughout the epidemic, although this effect is increasingly due to genital herpes rather than curable STIs. The development of effective interventions to reduce the prevalence of these cofactor STIs remains an important priority and we have indicated some of the key areas for future research.

We have gained tremendous insights from the last two decades of research on STI-HIV interactions. While there is strong evidence from observational and biological studies of the important effects of STIs on HIV acquisition and transmission, only one of nine RCTs of STI control interventions has shown a significant impact on HIV incidence, and this remains one of the few HIV prevention trials to demonstrate an effect on HIV in the general adult population [Grosskurth et al 1995]. As we have seen, there are disparate reasons for the failure of the remaining trials to show an effect, and it is inappropriate to group them together as if they were a set of homogeneous trials investigating the same question. Only four of the trials have tested the population-level effects of STI treatment, and only one of these was carried out in a population with high STI prevalence. This trial found an important effect. The two trials of sex worker interventions were underpowered for HIV incidence and only targeted effects on HIV acquisition in uninfected women. The three herpes suppressive therapy trials investigated the effects of an intervention strategy which now appears to be insufficient to adequately control the strong cofactor effect of HSV2 on HIV transmission, partly mediated by recruitment and persistence of HIV target cells during HSV2 reactivation.

In aggregate, the evidence suggests that the basic concept is sound and it is time to begin a new phase of exploration of how, when and in whom to include STI control as a key component of HIV prevention. This new phase should be driven by basic research on the biological mechanisms underpinning STI-HIV interactions so that we can design effective

treatment interventions, and evaluate them in trials that address issues that we have come to appreciate by reviewing the landmark studies that have been conducted to date.

From a policy perspective, treatment of curable STIs is an essential part of primary health care and should continue to be promoted as one component of HIV control programmes in communities in which the burden of STIs is substantial. While the population-level impact of such services will differ between settings, this is a cheap, simple and effective intervention when appropriately targeted and delivered. As with the provision of safe blood for transfusions and safe medical injections, provision of effective clinical care for STIs should be regarded as an essential contribution of the health care sector to the prevention of HIV.

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Figure 1.

Summary of results of nine randomised trials of STI treatment for HIV prevention. Studies are grouped as (i) community-randomised trials of population-level curable STI treatment interventions; (ii) individually-randomised trials of curable STI management in HIV-negative sex workers; (iii) individually-randomised trials of herpes suppressive therapy in HIV-negative or HIV-positive subjects. RR shows relative risk of HIV incidence in intervention arm compared with control arm.

Table 1
Summary of randomized trials of the impact of interventions to treat curable STIs on HIV incidence

	Mwanza, Tanzania (Gen population)	Rakai, Uganda (Gen population)	Masaka, Uganda (Gen population)	Manicaland, Zimbabwe (Gen population)	Abidjan, Cote d'Ivoire (Sex workers)	Nairobi, Kenya (Sex workers)
Intervention	Improved syndromic treatment at health units	Mass treatment of all adults every 10m	Improved syndromic treatment at government and other clinics	Community peer education, condom provision, improved syndromic treatment	Intensive screening and treatment for STIs, monthly	Monthly presumptive treatment with azithromycin
Study design	CRT: 2 arms 12 communities 6 matched pairs	CRT: 2 arms 10 communities 5 matched pairs	CRT: 3 arms 18 communities 6 matched triplets	CRT: 2 arms 12 communities 6 matched pairs	RCT: 2 arms	RCT: 2 arms
Intended power (HIV incidence)	80% for 50% reduction from 1%	80% for 35% reduction from 2% (actual incidence 1.5%)	90% for 50% reduction from 1.5% (actual incidence 0.8%)	80% for 40% reduction from 2% (actual incidence 1.5%)	Not stated, but not powered for HIV incidence	80% for 50% reduction from 15% (actual incidence 3-4%)
Sample size	Random sample of adults (<90m from HC) 12,537 at baseline	All resident adults, 15,127 at baseline	All adults in villages near health centre, 14,554 at baseline	All adults (1 sampled from each marital gp), 9,454 at baseline	542 enrolled, 225 with f/up	466 enrolled, 341 followed for y
Follow-up	Baseline and follow-up after 2y	Baseline and follow-up after 10m and 20m	Baseline and two follow-up rounds, average f/up = 3.5y	Baseline and follow-up after 3y	Baseline and follow-up every 6m for 6-42m (mostly 1y)	Baseline and follow-up every 3m for 2y
Control group interventions	Current services Cohort: Treatment of symptomatic STIs and syphilis (RPR+) at b/l	Current services (incl. syndromic treatment) Surveys: treatment of symptomatic STIs, referral of RPR+	Community dev't interventions All 3 arms: condom social marketing, VCT	Current services (incl. syndromic treatment) Both arms: condom social marketing, IEC	Monthly visits with syndromic treatment Both arms: condoms, counselling	Monthly treatment for symptomatic STIs, lab screening every 6m Both arms: Condoms, counselling
Impact on HIV incidence	48:82 events RR=0.58 (0.42-0.79)	101:89 events RR=0.97 (0.81-1.16)	110:113 events RR=1.00 (0.63-1.58)	123:89 events RR=1.27 (0.92-1.75)	6:10 events RR=0.70 (0.25-1.9)	19:16 events RR=1.2 (0.6-2.5)
Impact on STIs (RR)	TPHA inc: 0.69 HT syphilis: 0.69 Urethritis (M): 0.87 Symp Ur (M): 0.51	Syph inc: 1.0 Active Syphilis: 0.80 TV: 0.59	HT syph inc: 0.58 NG: 0.28 CT: 0.99	No data	TV at 6m: 7%:14% NG/CT/GUD: NS	TV: 11.3%:20.4% NG: 4.7%:12.7% CT:6.9%:14.5% Syph: 3.9%:3.8% GUD: 0.9%:1.6%
HIV prevalence: incidence ratio	4.1:0.9 = 4.6	15.9:1.5 = 10.6	10:0.8 = 12.5	23:1.5 = 15.3	N/A	N/A
Context	Expanding epidemic High prevalence of STIs /risk behaviour	Mature epidemic Lower prevalence of STIs/risk behaviour	Mature epidemic Lower prevalence of STIs/risk behaviour	Mature epidemic Decreasing prevalence of STIs/risk behaviour	Rise in condom use, fall in STIs during f/up Reduced HIV inc	Rise in condom use, fall in clients during f/up, reduced HIV inc

Table 2
Summary of randomized trials of the impact of herpes suppressive therapy on HIV incidence

	Mwanza, Tanzania (Facility workers)	S Africa, Zimbabwe, Zambia (women) Peru, USA (MSM)	7 countries in East and Southern Africa (Discordant couples)
Intervention	Acyclovir 400mg bd	Acyclovir 400mg bd	Acyclovir 400mg bd
Study design	Placebo-controlled RCT	Placebo-controlled RCT	Placebo-controlled trial
Intended power (HIV incidence)	80% for 50% reduction from 10% (actual incidence 4-5% so sample size and follow-up extended)	90% for 50% reduction from 3.5% (actual incidence 3.6%)	90% for 50% reduction from 4% (actual incidence 2.8%)
Sample size	821 female food and recreational facility workers (HIV-/HSV2+)	1358 women in Africa 1814 MSM in Peru/USA (HIV-/HSV2+)	3408 discordant couples (HIV+ partner CD4 250 and HSV2+)
Follow-up	12-30 months depending on phase of enrolment	12-18 months	12-24 months
Control group interventions	Both arms seen every 3 months. Condoms, risk reduction counselling, VCT, treatment of curable STIs	Both arms seen monthly. Condoms, HIV counselling and testing, treatment of curable STIs.	Both arms: HIV+ partner seen monthly. HIV- partner seen every 3m: HIV counselling and testing, condoms
Impact on HIV incidence	27:28 events RR=1.08 (0.64-1.83)	75:64 events RR=1.16 (0.83-1.62)	41:43 events [/] RR=0.92 (0.60-1.41)
Adherence to acyclovir	90% adherence reported during 51-52% person-years	86% expected doses taken	85% expected doses taken

[/] Modified ITT analysis