

# Curable Sexually Transmitted Infection Treatment Interventions to Prevent HIV Transmission in Sub-Saharan Africa

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**Abstract:** *Introduction:* Sub-Saharan Africa (Africa) remains the most severely HIV affected region in the world. As there will not be a cure or vaccine against HIV for many years, primary HIV prevention remains key to HIV control. Primary prevention currently includes treatment of curable sexually transmitted infections (STIs). Here, the evidence for curable STI treatment as an HIV prevention strategy in Africa is reviewed.

*Results:* Despite data on the plausible biological mechanisms from laboratory studies and the relative risks from epidemiological studies suggesting that classical STIs do increase the risk of HIV acquisition and transmission, the impact of curable STI treatment on HIV transmission measured in RCTs has varied markedly. Syndromic STI treatment was shown to be an effective strategy in a population with an early HIV epidemic, but neither syndromic STI treatment, nor mass STI treatment were effective in mature HIV epidemics. Among sex workers with relatively low rates of STI, presumptive STI treatment also failed to reduce HIV incidence.

*Discussion:* Rational health policy requires that scarce resources be allocated to interventions with the best cost-effectiveness even if relative impact at population level is modest. Curable STI treatment is likely to prevent a decreasing fraction of new HIV infections as the HIV epidemic expands, but, because of increasing HIV incidence it may remain cost-effective for HIV prevention in many African countries.

**Keywords:** Sexually transmitted diseases, epidemiology, HIV, AIDS, cost effectiveness, primary prevention, Sub-Saharan Africa.

## INTRODUCTION

Sub-Saharan Africa remains the most severely HIV affected region in the world with around two thirds of the world's HIV infected people, but just over 10% of the world's population. In the region as a whole, HIV prevalence is stabilising at around 7% of the adult population, but this hides great heterogeneity between and within countries in the region. In some countries in East Africa, most notably Uganda, HIV prevalence has been falling for many years, whereas in Southern Africa prevalence continues to rise, albeit at a much slower rate than in the recent past. In West Africa HIV prevalences have remained relatively low by comparison [1].

In sub-Saharan Africa the predominant route of HIV transmission was quickly identified as heterosexual intercourse among those reporting high numbers of sexual partners or contact with sex workers [2-4]. This was recently challenged by a group of researchers who hypothesised a larger role (40% or more) for parenteral transmission [5]. However the hypothesis has since been found to be unlikely, both intellectually [6, 7] and empirically, when tested in increasing numbers of studies across sub-Saharan Africa [8-11]. As there will not be a cure or vaccine against HIV for

many years [12], HIV control in sub-Saharan African countries will continue to rely on primary prevention. The increasing coverage of anti-retroviral therapy [1] will reduce morbidity and increase survivorship among those who receive it, but its impact on HIV incidence is far less certain [13, 14].

Primary prevention activities seek to reduce unprotected sexual contact between HIV discordant individuals and if unprotected contact occurs, to reduce the probability of transmission [15]. Prevention activities to reduce unprotected sexual contact include information, education and communication interventions that promote risk reduction, such as delayed debut, fewer sexual partners, one partner at a time and condom use [16, 17]. Prevention activities to reduce the probability of transmission if unprotected contact does occur include STI treatment. It was recognised early in the HIV pandemic, that because classical STIs (defined here as all STIs except HIV) were common in the sub-Saharan Africa and control was poor, if classical STIs increased the probability of HIV transmission, then improving STI control might be an effective HIV prevention strategy [18].

## CLASSICAL SEXUALLY TRANSMITTED INFECTIONS IN THE SUB-SAHARAN AFRICA

The Sub-Saharan Africa has the highest rates of classical STIs per capita worldwide. For 1999, WHO estimated that in the sub-Saharan Africa, the prevalence of the curable bacterial STIs gonorrhoea, chlamydia, syphilis and

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trichomoniasis alone was 12%, and that there were 69 million new cases of these STIs annually [19]. Chancroid has been a common cause of genital ulcers in sub-Saharan Africa, but its prevalence appears to have been falling in recent years [20]. The rates of viral STIs are also very high in sub-Saharan Africa as compared to other regions of the world. The prevalences of *Herpes simplex virus* type-2 (HSV-2) typically range between 30% and 70% [21-23].

### STI TREATMENT STRATEGIES IN THE SUB-SAHARAN AFRICA

Although the symptoms of many STIs are similar, the drugs used to treat infections differ markedly. Therefore laboratory, not clinical diagnosis is required to identify the underlying aetiology and prescribe the correct treatment. This is not practical in most of the sub-Saharan Africa due to cost and lack of suitably equipped laboratories. Therefore 'syndromic management' is recommended for the treatment of STIs in resource poor settings [17, 24]. Syndromic management is based on the idea that if the underlying aetiology of a symptom cannot be identified, then treat all common and important causes of that symptom [24].

In many [25], but not all [26], developing countries syndromic management has been effective in reducing STI rates. It does however have its limitations. It cannot address asymptomatic infections, which are common particularly among women. Therefore an alternative strategy, 'mass treatment' of STIs was also proposed. This strategy targets the whole population with a cocktail of drugs against all common STIs, whether each individual is infected or not. It therefore treats both asymptomatic and symptomatic infections, although substantial over-treatment is inevitable. A more limited strategy in which high risk groups such as CSWs are targeted, is known as the periodic presumptive treatment [27].

Regardless of the strategy used however, the effectiveness of the treatment for STIs as an HIV control strategy will depend, in part, on the existence and magnitude of the 'STI cofactor effect', i.e. the increased risk of HIV transmission between HIV discordant sexual partners if either partner is (co-)infected with classical STIs.

### CLASSICAL SEXUALLY TRANSMITTED INFECTIONS AS COFACTORS FOR HIV TRANSMISSION

The interactions between classical STIs and HIV have been the subject of repeated review over the past two decades [28-31]. There is now a large body of evidence from laboratory, clinical and epidemiological studies supporting the hypothesis, first voiced in 1984, that classical STIs may facilitate the spread of HIV [3].

The highest quality epidemiological evidence is available from longitudinal studies that attempt to adjust for confounding by sexual behaviour and other risk factors. Cross-sectional studies are of limited utility as the direction of causation cannot be determined with any certainty. It is also desirable to have a clinical or microbiological diagnosis of infection with STIs, as self-reported STI symptoms are notoriously poor indicators of STIs, particularly for non-ulcerative STI in women [32].

### The Effect of STIS on Susceptibility to HIV Infection

Numerous studies have measured the effect of STIs on susceptibility to HIV infection. A systematic review and meta-analysis of longitudinal studies including STIs diagnosed by clinical or microbiological criteria, or self-report, was carried out by Rottingen and colleagues [28]. Their conclusions were cautious because of the many biases that may affect these data, including strong evidence of reporting/publication bias against smaller studies that did not find an association. Despite this they reported that the effects of genital ulcer disease on susceptibility to HIV acquisition may be larger than the effects of non-ulcerative STI symptoms (discharge, inflammation and pelvic inflammatory disease) and may be larger for males than for females [28].

A more recent systematic review and meta-analysis of effects of HSV-2 seroprevalence on HIV acquisition from prospective studies, found the overall relative risk to be similar in males and females (RR= 2.7, 95%CI= 1.9-3.9 and RR= 3.1, 95%CI= 1.7-5.6, respectively) [33]. The effects of HSV-2 seroprevalence on susceptibility to HIV infection reported by these two reviews did not differ significantly.

These results must be interpreted with caution however, as they remain subject to bias. In addition to the evidence of publication bias, residual confounding by unmeasured, or poorly measured risk factors would tend to inflate the measured effects [34]. Whilst study exposure periods that are longer than the duration of the STI would tend to dilute the effect [35], as would non-differential misclassification of STIs [36], non-differential misclassification of STIs may help explain the smaller effect detected for women than men by Rottingen *et al.* Their review included studies that classified STI based on reported symptoms. This may have diluted the effects measured for women relative to men, as STI symptoms are a less sensitive indicator of STI infection for women than men. In the review by Freeman and colleagues, HSV-2 infection was only classified by serological testing and the effects among males and females were similar.

In summary, the many biases prevent strong conclusions from being drawn, but these epidemiological studies do support the hypothesis that STI markers in HIV susceptibles are associated with an increased risk of HIV acquisition and that the magnitude of this STI cofactor effect may increase in line with the clinical severity of the STI symptoms.

### The Effect of STIS on HIV Infectiousness

In contrast, there are very few longitudinal studies that measured the effect of STIs or symptoms of STIs on the infectiousness of HIV, primarily because this requires collecting data on both sexual partners. Table 1 shows the longitudinal 'couple studies' that measured the effects of concurrent STI/ HIV infection on the risk of transmission to their HIV negative partner.

In Haiti, between 475 initially HIV discordant couples, in most of which the seropositive partner was male (81%), the unadjusted risks of HIV transmission were higher if the HIV infected partner had clinically diagnosed GUD (RR= 2.9, 95%CI= 1.0-9.2) or serologically diagnosed active syphilis (RR= 2.3, 95%CI= 1.1-4.6), but not clinically diagnosed discharge (RR= 0.9, 95%CI= 0.1-6.9) [37].

**Table 1. Longitudinal Studies Measuring the Effects of Sexually Transmitted Infections on HIV Infectiousness**

Population	Cases/ Controls	STI/ Symptom in HIV Infected	Diagnostic	Unadjusted E95% CI	Adjusted Effect (95% CI)	Adjustment	Ref.							
Haiti, 475 couples. 81% of HIV+ were M	20	GUD	Clinical	2.9 (1.0-9.2)	-	-	[37]							
		Discharge	Clinical	0.9 (0.1-6.9)	-									
		Active syphilis	Serological	2.3 (1.1-4.6)	-									
Uganda, 167 couples	30	GUD	Symptoms	-	1.6 (0.6-4.2)	-	[41]							
		Any symptom	Symptoms	-	1.5 (0.7-3.3)									
Uganda, 415 couples. 55% of HIV+ were M	90	GUD	Symptoms	-	0.9 (0.5-1.7)	Blood viral load, age, circumcision, number of partners, sex	[40]							
		Dysuria	Symptoms	-	1.1 (0.5-2.1)									
		Discharge	Symptoms	-	1.8 (0.9-3.5)									
		Syphilis	Serological	-	0.7 (0.3-1.3)									
		Gonorrhoea	PCR	-	1.2 (0.2-3.8)									
		Chlamydia	PCR	-	0.2 (0.0-1.0)									
		Trichomoniasis	Culture	-	1.8 (0.8-3.9)									
		Bacteria vaginosis	Microscopy	-	0.9 (0.5-1.8)									
Uganda, 174 monogamous couples. 56% of HIV+ were M	38	GUD	Symptoms	-	2.6 (1.0-5.7)	Blood viral load, age, sex	[39]							
		Dysuria	Symptoms	ns	-									
		Discharge	Symptoms	ns	-									
		Syphilis	Serological	ns	-									
		Gonorrhoea	PCR	ns	-									
		Chlamydia	PCR	ns	-									
		Trichomoniasis	Culture	ns	-									
		Bacteria vaginosis	Microscopy	ns	-									
Zambia 317 couples	109/208						[42]							
								137 HIV+ F	43/94	STI	Symptoms	1.7 (1.0-2.7)*	-	-
										Syphilis	Serology	1.7 (1.1-2.8)*	-	-
	Trichomoniasis	-	0.8 (0.3-2.2)*	-	-									
	180 HIV+ M	66/114					Blood viral load							
									Genital inflammation	-	-	ns	-	
									STI	Symptoms	1.1 (0.7-1.6)*	-	-	
	Syphilis	Serology	0.8 (0.4-1.5)*	-	-									
	Genital inflammation	-	-	sig	Blood viral load, acts/ 3m, age									
Uganda, 235 monogamous couples	68	GUD	Symptoms	2.2 (1.1-4.5)	2.0 (1.0-4.0)	Blood viral load, age.	[38]							

F: female, GUD: genital ulcer disease, 'HIV+': HIV seropositive, M: male, ns: not significant (value not stated), PCR: polymerase chain reaction, sig: significant (value not stated), - : not stated, \*: not directly reported, calculated from data in paper.

The most recent study from investigators in Rakai, Uganda is the most convincing evidence for an effect of STI symptoms on HIV infectiousness [38]. Among 235 monogamous couples (confirmed by sequencing of the transmitted HIV strain), GUD in the seropositive partner was found to double the probability of transmission (adjusted RR= 2.0, 95%CI= 1.0-4.0), after adjusting for the blood HIV viral load and age of the seropositive partner. The earlier studies from this population showed that other STI markers were not associated with HIV transmission after adjusting for the blood HIV viral load [39-41].

In Zambia, between 137 initially discordant couples with a seropositive female partner, the unadjusted risks of HIV transmission were higher if the female reported STI symptoms in the past 5 years (RR= 1.7, 95%CI= 1.0-2.7), or had a positive RPR test, (RR= 1.7, 95%CI= 1.1-2.8), but not *Trichomonas* infection (RR= 0.8, 95%CI= 0.3-2.2). In the

same study, among 180 initially discordant couples with a seropositive male partner 'genital inflammation' (not defined) was found to be significantly associated with HIV transmission after adjustment for the blood viral load, but the risk was not reported. Reported STI symptoms in the past 5 years or a positive RPR test were not significantly associated with HIV transmission to the female partner [42].

In summary, these studies do (weakly) support the hypothesis that HIV infected individuals, co-infected with STIs are at increased risk of transmitting HIV to their susceptible partner(s) and the effect may be stronger for markers of ulcerative STI than non-ulcerative STI.

### Biological Plausibility

The biological mechanisms that may explain how classical STIs enhance the spread of HIV infection are provided by a number of clinical and laboratory studies [29, 43-45].

Ulcerative STI such as HSV-2, chancroid and syphilis, and to a lesser extent inflammatory STI such as gonorrhoea, chlamydia and trichomoniasis, may weaken the physical barrier to infection among HIV uninfected individuals and the shedding of HIV among HIV infected individuals. However, any association between HIV shedding into the genital tract and STIs is likely to be confounded by the level of HIV immunosuppression. More highly HIV immunosuppressed individuals are likely to shed more HIV than less highly HIV immunosuppressed individuals and also be more susceptible to STI infection. Studies that have adjusted for the level of HIV immunosuppression, do show higher rates of HIV shedding among males and females with GUD, cervicitis, urethritis, gonorrhoea and chlamydia [46-50].

In addition, infection with an STI induces an immune response in the host. This includes the recruitment of CD4 macrophages, the primary target cells of HIV, to the site of infection. Among HIV uninfected individuals this response increases the number of cells HIV can infect, increasing susceptibility. Levine and colleagues showed that higher numbers of CD4 cells were present in the cervix of women with gonorrhoea, chlamydia, or trichomoniasis infection, than among women without these STIs [51].

There is also evidence suggesting the replication of HIV virus within infected cells may be enhanced by co-infection with classical STIs. Albrecht and colleagues showed that HIV replication increased in epithelial cells coinfecting with HSV-2 [52] and Mole and colleagues showed HIV transcription and plasma viral load rose during episodes of HSV-2 ulcerations [53].

Many of the shedding studies cited above used a cross sectional design. Therefore the increased shedding in the presence of STI may have been because HIV infected individuals were more susceptible to classical STIs (reverse causality). However, intervention studies have shown treatment of GUD, urethritis, cervicitis, gonorrhoea, chlamydia and trichomoniasis reduce shedding of HIV [43, 47, 50, 54-57], whilst others studies have not [58]. These studies are important because they show that the association between STIs and HIV shedding is causal and not entirely due to confounding, or reverse causality. The investigators of the study that found no effect of STI treatment, concluded that this was likely to be because of a high prevalence of GUD due to (incurable) HSV-2 infection [59].

Taken together, the likely biological mechanisms from laboratory studies and the relative risks from epidemiological studies suggest that classical STIs do increase the risk of HIV acquisition and transmission, and ulcerative STIs may have a stronger effect than non-ulcerative STI, and that gonorrhoea and chlamydia may have a stronger cofactor effect than trichomoniasis and bacteria vaginosis.

## **CURABLE STI TREATMENT INTERVENTIONS TO PREVENT HIV TRANSMISSION IN THE SUB-SAHARAN AFRICA**

The effectiveness of curable STI treatment for HIV prevention depends not only on STI cofactor magnitudes, but also on the prevalences of the various curable and incurable STIs in a population at a particular time, and the

effectiveness of the STI treatment in curing these STIs [31]. Therefore, the effectiveness of the STI treatment for HIV control cannot be estimated from the biological or observational epidemiological studies discussed above, but is best learnt from intervention trials that prospectively measure HIV incidence.

The highest quality evidence for the effectiveness of HIV prevention interventions is available from randomised controlled trials (RCTs) [60]. In addition, as shown above much uncertainty remains about the importance of STI cofactors for the transmission of HIV [34, 35] and therefore evidence for the effectiveness of curable STI treatment interventions should include direct ascertainment of HIV incidence and not be limited to intermediate outcomes, such as reductions in classical STI rates, or STI symptoms that may be subject to reporting bias [61]. Further, as is shown below, even the impacts on HIV of similar STI treatment interventions have been shown to vary markedly between populations [62-65] and therefore the evidence used to evaluate the effectiveness of these strategies is limited to studies in sub-Saharan Africa. Therefore the focus of this section is on the available evidence from RCTs of curable STI treatment interventions in sub-Saharan Africa that included an objectively measured HIV outcome.

To date five high-quality randomised controlled trials of curable STI treatment interventions with an HIV endpoint have been completed in sub-Saharan Africa (Table 2).

### **1. Improved Syndromic STI Disease Case Management in Mwanza, Tanzania**

In an early HIV epidemic with low but rising HIV prevalence, the first HIV prevention RCT in Mwanza, Tanzania integrated improved STI disease treatment services into the existing primary health care system between 1991 and 1994 [62]. It was designed to be an effectiveness trial that would be feasible in resource poor settings. The treatment algorithms used for the intervention were adapted from existing WHO guidelines by adding second and third line treatment regimens [66]. Health centre and dispensary staff was trained to perform clinical examinations and how to correctly use the redesigned syndromic treatment algorithms. The regular delivery of drug supplies was ensured and regularly monitored [66]. During the intervention, the rural population was educated about the importance of rapid treatment of STI symptoms. Partners of STI disease patients were strongly encouraged to refer recent sexual contacts for treatment, who were then also offered treatment for the same syndrome as the index STI disease patient even if asymptomatic [66].

The proportions that seroconverted over two years were 1.2% in the intervention communities and 1.9% in the comparison communities, and the HIV incidence rate ratio (IRR) was 0.62, 95% CI= 0.45–0.85 [62, 67].

### **2. Mass STI Treatment in Rakai, Uganda**

Across the lake in Rakai, Uganda, in a mature HIV epidemic with high, but stable or falling HIV prevalence, a community based, randomised, controlled, single-masked trial of home-based mass STI treatment was carried out between 1994 and 1996 [68]. It was not designed to be feasible in resource poor settings, but to be an efficacy trial,

**Table 2. Summary of Randomised Trials of Curable STI Treatment Interventions with an HIV Endpoint in Sub-Saharan Africa**

Population	HIV Prevalence	Intervention	Outcome	Ref.
Mwanza, Tanzania, 12 communities, 12,537 adults, 1991-4	Low and rising	Improved ST	Reduction in prevalence of low and high titre TP and symptomatic urethritis and the incidence of high titre TP. Reduction in HIV incidence, IRR = 0.62, 95% CI= 0.45–0.85.	[62, 81]
Rakai, Uganda, 10 communities, 13,623 adults, 1994-6	High and stable or falling	Periodic mass STI treatment	Reduction in low titre TP prevalence and TV prevalence. No reduction in HIV incidence, IRR= 0.97, 95% CI= 0.81–1.16.	[68]
Masaka Uganda 18 communities, 12,819 adults 1994-2000	High and stable or falling	IEC and IEC + improved ST	Significantly increased condom use in both intervention arms. IEC arm: Reduced HSV-2 incidence. IEC+ST arm: significant reduction in TP incidence, NG prevalence and reported vaginal discharge, but no reduction in HIV incidence, IRR= 1.00, 95% CI= 0.63–1.58.	[63]
Nairobi, Kenya, 466 F CSWs, 1998-2002	High	Periodic presumptive STI treatment	Reduction in incident NG, CT and TV. No reduction in HIV incidence, IRR= 1.2, 95%CI= 0.6-2.5.	[71]
Manicaland, Zimbabwe, 12 rural and peri-rural communities, 1998-2003	High and falling	Community-based peer education, condom distribution, income-generation, improved ST and counselling services	No community level reduction in any classical STI outcomes. No reduction in HIV incidence, IRR= 1.27, 95% CI= 0.92–1.75.	[70]

CSW: commercial sex worker, CT: chlamydia, F: female, HSV-2: *Herpes simplex virus type-2*, IEC: information, education and communication, NG: gonorrhoea, ST: syndromic treatment, TP: Syphilis, TV: trichomoniasis.

to provide further evidence that STI treatment could reduce STI prevalence and HIV incidence under optimal conditions in a sub-Saharan Africa population. By using a mass treatment strategy, both asymptomatic and symptomatic individuals would be treated. The STI treatments were selected primarily because they were single dose, to increase acceptability and compliance and not on their (higher) cost. This directly administered, single dose STI treatment was offered to individuals in the intervention communities regardless of their symptoms, three times at approximately 10-monthly intervals [68].

The incidence of HIV infection was 1.5 per 100 person-years in both the intervention and comparison communities, HIV IRR= 0.97, 95% CI= 0.81–1.16 [68].

### 3. Information, Education and Communication with and without Improved Syndromic STI Disease Case Management in Masaka, Uganda

In neighbouring Masaka District, Uganda, in a similar HIV setting as Rakai, a 3-arm, community based, randomised, controlled, trial of information, education and communication (IEC) with and without improved syndromic treatment (ST), was carried out between 1994 and 2000 [63]. Like the Mwanza trial, it was designed to be feasible in resource poor settings, to test whether an IEC intervention could reduce HIV incidence and to measure the extra impact gained by also improving the clinic-based syndromic treatment services. The design of the STI disease treatment intervention was based on that used for the Mwanza RCT, training health workers and ensuring a regular drug supply.

No significant difference was detected between HIV incidence in the three study arms, HIV IRR (ST+IEC arm)= 1.00, 95% CI= 0.63–1.58 [63].

### 4. Integrated Community and Clinic-based Intervention Including Clinic-based STI Disease Treatment in the Eastern Zimbabwe

In peri-rural Zimbabwe, in a population with a mature HIV epidemic and continuing high STI/ HIV prevalences [69], a RCT of a community level intervention of peer education, free condom distribution, income-generating projects, and clinic-based STI disease treatment and counselling services was tested. Although the intervention led to fewer reported risk behaviours and STI symptoms and lower HIV incidence among males attending programme meetings, it failed to lead to any significant community level impact on behavioural, STI or HIV outcomes (HIV IRR= 1.27, 95% CI= 0.9–1.7) [70]. The authors concluded that the intervention failed to lead to lower risk behaviour and STI cofactor prevalence in a large enough proportion of the population to have a detectable impact on HIV incidence at the population level.

### 5. Individual-level trial of periodic presumptive curable STI disease treatment in Nairobi, Kenya

In a mature, high HIV prevalence setting, a randomised, double blind, placebo controlled, individual-level trial of periodic presumptive STI treatment at monthly intervals was tested among female sex workers in Nairobi, Kenya between 1998 and 2002 [71]. The trial tested whether regular STI treatment could reduce STI and HIV incidence in a high risk population, who may be missed by interventions targeting the general population. The treatment was a 1 gram directly-observed, monthly oral dose of azithromycin or placebo. Both study arms received a high level of care including peer and clinic counselling on safer risk behaviour, free male condoms, treatment of symptomatic STI and screening and treatment of asymptomatic STI every 6 months.

The baseline prevalences of curable non-ulcerative STI were high. Incident HIV infection was associated with preceding incident infection with gonorrhoea (adjusted RR= 4.9, 95%CI= 1.7-14.3), or chlamydia (RR= 3.0, 95%CI= 1.1-8.9), or baseline HSV-2 infection (RR= 6.3, 95%CI= 1.5-27.1). Incidence was reduced in the treatment group for gonorrhoea (RR= 0.46, 95%CI= 0.31-0.68), chlamydia (RR= 0.38, 95%CI= 0.26-0.57) and trichomoniasis (RR= 0.56, 95%CI= 0.40-0.78) but not syphilis or bacterial vaginosis. Among the 341 initially HIV seronegative women who were followed up, no reduction in HIV incidence was detected (RR= 1.2, 95%CI= 0.6-2.5) [71]. This study found an association between preceding gonorrhoea or chlamydia infection and HIV incidence, an impact on gonorrhoea, chlamydia and trichomoniasis incidence, but no impact on HIV incidence.

In summary, only the first randomised controlled trial detected a significant impact on the transmission of HIV [62]. Since then, four other RCTs of STI treatment interventions have all failed to show a significant reduction in HIV incidence in the sub-Saharan African populations [63, 68, 70, 71].

## DISCUSSION

Despite data on the plausible biological mechanisms from laboratory studies and the relative risks from epidemiological studies suggesting that classical STIs do increase the risk of HIV acquisition and transmission, the impact of curable STI treatment on HIV transmission measured in RCTs has varied markedly. Syndromic STI disease treatment was shown to be an effective strategy in a population with an early HIV epidemic [62], but neither syndromic STI disease treatment, nor mass STI treatment were effective in mature HIV epidemics [63, 68, 70]. Among sex workers with relatively low rates of STI, presumptive STI treatment also failed to reduce HIV incidence [71].

Unsurprisingly, the failure of the majority of the RCTs to reduce HIV incidence has led some researchers and policy-makers to question whether STI treatment should continue to be promoted as an HIV control strategy in generalised epidemics in Africa [72], particularly as suppressive therapy of the incurable STI HSV-2, has also failed to reduce HIV acquisition [73, 74].

This may be because the observed epidemiological associations are purely due to confounding [72], but this would be inconsistent with the data from clinical studies showing reductions in HIV shedding after curable STI treatment. Reanalysis of the data from the Mwanza, Rakai and Masaka [75] and mathematical modelling studies have suggested an alternative explanation for the failure of four of the five RCTs to detect an impact on HIV incidence [76, 77], and may provide some support for continuing to treat curable STIs for HIV prevention in many African countries [78].

The reanalysis of data from the Mwanza, Rakai and Masaka trials showed that there were higher rates of reported risk behaviour and higher rates of curable STI in Mwanza as compared to Rakai and Masaka at the time of the trials and this may explain, at least part of the contrasting results of these trials [75].

This hypothesis was tested in two mathematical modelling studies that showed that the contrasting impact could indeed be explained by behaviour change in Rakai and Masaka, in combination with the later stage of the HIV epidemic in Rakai and Masaka. Both factors combined to reduce the role of curable STIs in HIV transmission in Rakai and Masaka as compared to Mwanza, which would result in a smaller relative impact of curable STI treatment in Rakai and Masaka as compared to Mwanza [76, 77].

Subsequent modelling studies have suggested that throughout HIV epidemics in Africa, the contribution of STIs to HIV transmission may remain high, with 50% or more of HIV transmission attributed to STIs [79]. However, this relative stability in the overall population attributable fraction (PAF) conceals opposing trends in the contribution of curable and incurable STIs. The attributable-fraction for curable STIs is predicted to fall during HIV epidemics, while the attributable-fraction for HSV-2 is predicted to rise [79].

These findings may help to explain why the STI treatment strategies tested since the trial in Mwanza have failed to show a significant impact on HIV incidence. Even if the STI treatment interventions in Rakai, Masaka and Zimbabwe [68, 70, 80] had led to large reductions in STI rates, in these generalised HIV epidemics the relative impact on HIV incidence would have been relatively small and therefore undetectable.

This has important implications for the (cost-) effectiveness of interventions seeking to target curable STIs [78]. Over time the relative impact of STI treatment on HIV incidence is predicted to fall, which tends to increase the cost per HIV-infection-averted. However, in populations with a rapidly expanding HIV epidemic, this increase in cost is offset by the rapidly rising HIV incidence that increased the absolute impact of the intervention. It was suggested that that in African populations with mature HIV epidemics, curable STI treatment interventions may remain cost-effective and may even be cost-saving, particularly in populations in which safer sexual behaviours have not adequately controlled STIs and HIV incidence remains high [78].

Rational health policy requires that scarce resources be allocated to interventions with the best cost-effectiveness even if relative impact at population level is modest. Effective STI management is likely to prevent a decreasing fraction of new HIV infections as the epidemic expands, but is an inexpensive intervention with important collateral public health benefits and which effectively protects STI patients from the enhanced risk of HIV acquisition and transmission, and may remain cost-effective or even cost saving for HIV prevention in many African countries.

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