The syndromic management of vaginal discharge using single-dose treatments: a randomized controlled trial in West Africa

Jacques Pépin,[a] François Sobela,[b] Nzambi Khonde,[b] Thomas Agyarko-Poku,[b] Soumaila Diakité,[b] Sylvie Deslandes,[a] Annie-Claude Labbé,[c] Mohamed Sylla,[b] Comfort Asamoah-Adu,[b] & Eric Frost[a]

Objective To evaluate whether single-dose treatments are as effective as standard therapy in the syndromic management of vaginal discharge.

Methods A randomized controlled effectiveness trial compared single-dose tinidazole plus fluconazole (TF) with treatment for 7 days with metronidazole plus 3 days of treatment with vaginal clotrimazole (MC) among 1570 women presenting with vaginal discharge at primary health care institutions in Ghana, Guinea, Mali and Togo. Participants were randomly allocated to one of the two treatments by research nurses or physicians using precoded envelopes. Effectiveness was assessed by symptomatic response on day 14.

Clinical identifier ClinicalTrials.gov NCT00313131.

Findings The two treatment regimens had similar effectiveness: complete resolution was seen in 66% (TF) and 64% (MC) and partial resolution in 33% (TF) and 34% (MC) of participants ($P = 0.26$). Effectiveness was similar among subgroups with vulvovaginal candidiasis, *Trichomonas vaginalis* vaginitis or bacterial vaginosis. The two treatment regimens had a similar effectiveness among human immunodeficiency virus (HIV)-infected (TF: $n = 76$, 71% complete resolution, 28% partial; MC: $n = 83$, 72% complete resolution, 25% partial, $P = 0.76$) and HIV-uninfected women (TF: $n = 517$, 68% complete, 32% partial; MC: $n = 466$, 65% complete, 33% partial, $P = 0.20$). Cervical infections with *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Mycoplasma genitalium* were uncommon among women not involved in sex work, were associated with bacterial vaginosis or *T. vaginalis* vaginitis, and did not alter response to treatment with agents active against vaginal infections. Four-fifths of women not relieved by a single dose of TF had a favourable response when MC was administered as second-line treatment.

Conclusion Single-dose TF is as effective as multiple-dose MC in the syndromic management of vaginal discharge, even among women with HIV-infection. Given its low price and easier adherence, TF should be considered as a first-line treatment for vaginal discharge syndrome.

Bulletin of the World Health Organization 2006;84:729-738.

Voir page 736 le résumé en français. En la página 736 figura un resumen en español.

يمكن الاطلاع على الملخص بالعربية في صفحة 737.

Introduction

Despite the contradictory results of large trials in East Africa, the syndromic management of sexually transmitted infections (STI) remains a public health priority: whether or not it reduces transmission of human immunodeficiency virus (HIV), this intervention relieves patients' symptoms, lowers the risk of complications and reduces transmission of etiological agents.[1–5] Within core groups such as sex workers (SW) and their clients, STI could be important cofactors of HIV transmission even if this is less marked in the general adult population.[6] Furthermore, effective management of STI among SW can enhance the credibility and acceptability of interventions aimed primarily at increasing the use of condoms.

Syndromic management implies the simultaneous treatment of two or more infections: the higher cost of drugs is more than compensated by savings on diagnostic assays, but adverse effects are more frequent and adherence to multiple-dose regimens can be suboptimal.[1,2] Whereas strategies for the syndromic management of STI in men are standardized and very effective, this is not yet the case for vaginal discharge, which is by far the most common STI syndrome among women.[1,2] In the majority of cases, this syndrome is caused by either bacterial vaginosis (BV), *Trichomonas vaginalis* (TV) vaginitis, vulvovaginal candidiasis (CA) or any combination thereof. In West Africa, classical agents of cervicitis (*Neisseria gonorrhoeae* (NG) or *Chlamydia trachomatis* (CT)) are found in only 5–10% of women who are not SW and 10–25% of SW seeking treatment for a vaginal discharge.[7–11] To these pathogens must be added *Mycoplasma genitalium*, recently identified as an agent of cervicitis in West Africa.[10] The emergence of a generic drug industry in the developing world has led to a significant reduction in the cost of STI syndromic management, even with single-dose drugs.[12–14] To determine whether single-dose therapy would be as effective as standard therapy in the context of African primary health care institutions providing care to populations with a relatively high prevalence of HIV, we

[a] Department of Microbiology and Infectious Diseases, University of Sherbrooke, Centre Hospitalier Universitaire de Sherbrooke, 3001, 12ème Avenue Nord, Sherbrooke, Quebec, Canada, J1H 5N4, Canada. Correspondence to Dr Jacques Pépin (email: jacques.pepin@usherbrooke.ca).

[b] West Africa Project to Combat AIDS, Accra, Ghana; Lomé, Togo; Conakry, Guinea; Bamako, Mali.

[c] Hôpital Maisonneuve-Rosemont, Montreal, Canada.

Ref. no. **06-029819**

(*Submitted: 10 January 2006 – Final revised version received: 18 April 2006 – Accepted: 5 May 2006*)

conducted a randomized controlled trial comparing the effectiveness of single-dose tinidazole/fluconazole to that of a 7-day course of metronidazole plus intravaginal clotrimazole for 3 days.

Methods

Sites and data collection

This multicentre study involved nine health-care facilities in four West African countries:

- in Ghana, the STI clinics of Accra-Adabraka and Kumasi-Suntreso;
- in Guinea, the Madina and Carrière health centres, Conakry;
- in Mali, the Korofina and Soutoura health centres, Bamako; and
- in Togo, the STI clinics of Amoutivé and Agoé Nyivé (Lomé) and the health centre of Adakpamé.

The study protocol was approved by the national ethics committee of each country and by the institutional review board of the Centre Hospitalier Universitaire de Sherbrooke, Canada. It was designed as an effectiveness trial, done under conditions similar to those routinely seen in these facilities. Between January 2004 and April 2005, we recruited women who consulted the health centre for a vaginal discharge, regardless of HIV status or involvement in transactional sex, who were local residents and consented to participate. We excluded SW who sought active screening for STI, pregnant women, those whose main complaint was lower abdominal pain and those allergic to one of the study drugs. Women not eligible for the study were treated according to the algorithms routinely used in the health facility.

At the initial visit, a questionnaire was used to gather information on demographic and behavioural characteristics, current complaints and the recent intake of antimicrobials. During gynaecological examination, the presence of vulvar inflammation, the characteristics of the discharge and signs of cervicitis (mucopurulent cervical discharge, pus on the swab, cervical bleeding after sampling and cervical inflammation) were noted. Two samples were obtained from secretions in the vaginal fornix and two from the endocervix, after cleaning the latter. The first vaginal sample was deposited in the Amplicor transport medium (Roche, USA) and used for the detection of *Trichomonas vaginalis*; the second was used to deposit secretions on a slide which was Gram-stained to detect the presence of BV (Nugent score ⩾7)[15] and/or yeasts compatible with *Candida albicans*. The first cervical sample, deposited in the Amplicor medium, was tested by polymerase-chain reaction (PCR) for the presence of NG, CT and *Mycoplasma genitalium* (MG);[7,10] the second was used to measure the leukocyte count per high-power field (hpf) as the mean of five counts. HIV serology was performed on capillary blood using an algorithm of two different enzyme immunoassays (Detect-HIV, Adaltis, Canada and Genie II HIV-1/HIV-2, Bio-Rad, France) and INNO-LIA HIV I/II Score (Innogenetics, Belgium) was used for the confirmation of discordant results between the first and second enzyme immunoassays.

Participants were identified only by a study number. Laboratory assays, including HIV serology, were performed anonymously. Women wishing to know their HIV status received pre-test counselling and a properly identified sample of venous blood was obtained. Processing of this sample, post-test counselling, and eventual referral to a facility providing treatment with antiretrovirals were performed as routinely done for patients not participating in the study.

Randomization

Randomization, stratified according to whether or not the woman was a sex worker, was conducted in each participating centre by the research nurses or physicians, using pre-coded envelopes. Participants were randomly assigned to a group receiving either tinidazole 2 g, single dose and fluconazole 150 mg, single dose or metronidazole 500 mg twice a day for 7 days and clotrimazole vaginal cream for 3 days. Women found to have at least one sign of cervicitis were given ciprofloxacin (500 mg, single dose) and azithromycin (1 g, single dose); those with a genital ulcer received ciprofloxacin (500 mg twice a day for 3 days) and benzathine penicillin (2.4 M units intramuscular, single dose). Fluconazole, tinidazole and, when necessary, ciprofloxacin and azithromycin, were swallowed by the patient under direct observation. Patients allocated to the group receiving metronidazole and clotrimazole used these drugs at home. Because the study aimed to measure effectiveness, generic drugs bought in West Africa were used. It would have been impractical to use placebos. Given the low prevalence of gonococcal and chlamydial infections anticipated among non-SW,[10] no attempt was made to treat their male partners.

Follow-up and outcomes

Participants were asked to come for a follow-up visit on day 14. A questionnaire verified the subjective response to treatment, which was the primary outcome. A clinical examination was performed to document whether there was an objective resolution of the vaginal discharge (secondary outcome). Vaginal and cervical samples were obtained for Gram staining: other secondary outcomes were the disappearance of *C. albicans* and the resolution of BV in vaginal secretions. Participants still complaining of vaginal discharge were given oral metronidazole (500 mg twice a day for 7 days) and clotrimazole cream (for 3 days) and asked to come back on day 28. If this second treatment led to no improvement, the choice of therapy was then left to the discretion of local health-care workers.

Sample size and statistical analyses

Aiming for 90% power, an alpha of 0.05, assuming that 50% of participants would have BV, that 25% of all women would be lost to follow-up and that the effectiveness of a 7-day course of metronidazole in women with BV would be 90%, we needed 381 women with BV in each group to show that the difference in effectiveness between metronidazole and tinidazole would be inferior to 10%. We aimed to enrol 1524 participants. Data were analysed with Stata 8.0 software. Categorical variables were compared using the χ^2 or Fisher's test. Logistic regression was used for multivariate analysis.

Clinical identifier

ClinicalTrials.gov NCT00313131.

Results

A total of 811 women were randomly assigned to receive tinidazole/fluconazole, and 759 to receive metronidazole/clotrimazole (Table 1 and Trial profile (Fig. 1)), suggesting that the randomization procedure was not always respected. Nevertheless, the groups were well balanced and no significant difference was seen between them in age, sex work, duration of discharge, prior treatment, presence of other symptoms, signs of

Table 1. **Baseline characteristics of the two treatment groups**

	Metronidazole + clotrimazole (%) (*n* = 759)	Tinidazole + fluconazole (%) (*n* = 811)
Country		
Ghana	352 (46)	350 (43)
Guinea	124 (16)	141 (17)
Mali	74 (10)	89 (11)
Togo	209 (28)	231 (28)
Age (years)		
11–20	192 (25)	216 (27)
21–30	391 (52)	404 (50)
>30	176 (23)	191 (24)
Sex worker (SW)		
Yes	281 (37)	304 (37)
No	478 (63)	507 (63)
Number of sex partners during last 3 months (non-SW only)		
None	68 (14)	87 (17)
One	388 (82)	406 (80)
⩾2	20 (4)	13 (3)
Duration of vaginal discharge (days)		
⩽7	314 (41)	323 (40)
8–14	169 (22)	173 (21)
⩾15	274 (36)	312 (39)
Other symptoms		
Low abdominal pain	258 (34)	297 (37)
Dyspareunia	242 (32)	248 (31)
Dysuria	121 (16)	140 (17)
Vulvar pruritus	625 (82)	685 (84)
Prior treatment of current episode of vaginal discharge	224 (30)	233 (29)
Signs of cervicitis on examination		
Cervical discharge	228 (30)	223 (27)
Pus on cervical swab	206 (27)	198 (24)
Cervical bleeding after sampling	98 (15)	96 (14)
Cervical inflammation	127 (17)	153 (19)
Cervical motion tenderness	164 (22)	195 (24)
Also given ciprofloxacin + azithromycin for presumed cervicitis	408 (54)	414 (51)
Also given ciprofloxacin + benzathine penicillin for genital ulcer	34 (4)	46 (6)
Leukocytes on cervical secretions (per hpf)[a]		
<10	540 (71)	602 (74)
10–29	131 (17)	130 (16)
⩾30	85 (11)	77 (10)
Presence of pathogens		
Non-sex workers		
Vaginosis on Gram stain	234 (49)	224 (44)
Yeast cells on Gram strain	168 (35)	172 (34)
Trichomonas vaginalis	30 (6)	32 (6)
Chlamydia trachomatis (CT)	6 (1)	13 (3)
Neisseria gonorrhoeae (NG)	8 (2)	6 (1)
Mycoplasma genitalium (MG)	11 (2)	12 (2)
CT, NG or MG	24 (5)	29 (6)
Human immunodeficiency virus (HIV)	33 (8)	35 (8)

(Table 1, cont.)

	Metronidazole + clotrimazole (%) (*n* = 759)	Tinidazole + fluconazole (%) (*n* = 811)
Sex workers		
Vaginosis on Gram stain	135 (48)	136 (45)
Yeast cells on Gram stain	67 (24)	74 (24)
Trichomonas vaginalis	46 (16)	49 (16)
Chlamydia trachomatis	23 (8)	19 (6)
Neisseria gonorrhoeae	25 (9)	28 (9)
Mycoplasma genitalium	27 (10)	29 (10)
CT, NG or MG	60 (21)	64 (21)
HIV	77 (28)	75 (25)

[a] hpf = high power field.
P-value was >0.05 for all comparisons.

cervicitis or the presence of various pathogens including HIV. As expected, the prevalence of NG, CT, MG, TV and HIV was higher in SW than others, whereas candidiasis was less common. In both SW and non-SW, BV was found in almost half of participants. Among non-SW, HIV prevalence varied from 3.6% in Ghana (13/359) to 9.6% in Guinea (13/135) and 10.7% in Togo (42/394).

The association between MG and cervicitis being relatively novel,[10,16] we first tested for this association with cervicitis, initially defining cervicitis as a leukocyte count on cervical secretions ⩾10/hpf. In a logistic regression analysis that adjusted for age and the presence of other pathogens, presence of MG was associated with cervicitis (adjusted odds ratio (AOR): 2.0, 95% confidence interval (CI): 1.3–3.2, P = 0.004) as was NG (AOR: 2.2, 95% CI: 1.3–3.6, P = 0.003) and CT (AOR: 1.7, 95% CI: 1.0–3.0, P = 0.05). Subsequent analyses thus considered women in whom any of these three pathogens was present, alone or in combination, as having cervical infections. Interestingly, if we used a higher (⩾30 leukocytes/hpf) cut-off point to define cervicitis, NG (AOR: 2.4, 95% CI: 1.3–4.6, P = 0.007) and MG (AOR: 2.0, 95% CI: 1.1–3.7, P = 0.02) remained associated with cervicitis but not CT (AOR: 1.2, 95% CI: 0.5–2.7, P = 0.66). Women among whom at least one agent of cervicitis was found were more likely to also have BV and TV vaginitis than those without cervical infections (Table 2).

Four-fifths of participants attended the follow-up visit on day 14 (metronidazole/clotrimazole: 591/759, 78%; tinidazole/fluconazole: 653/811, 81%) (Trial profile (Fig. 1)). The proportion of women who reported either a complete resolution of the discharge or partial improvement on day 14 was similar in the two treatment groups (Table 3). Both treatments had similar effectiveness when analysis was restricted to subgroups: women with BV, those with candidiasis, those with trichomoniasis and women with cervical infections (NG, CT and/or MG). The two treatments had the same overall effectiveness among HIV-infected participants as among those who were seronegative. The presence of a visible vaginal discharge on day 14 was highly correlated with the patient's own perception of response to treatment: 93% (14/15) of women reporting no improvement had a visible discharge on day 14 as did 86% (358/418) of those reporting partial improvement, compared to 15% (116/759) of those reporting complete resolution (P <0.001). There was no difference between treatment groups for the presence of a vaginal discharge on examination on day 14, neither overall nor when examining the subgroups described above (data not shown).

Among women with vaginitis, we examined the presence of abnormal findings on day 14 and their relation with subjective or objective improvement of the discharge. Among women with BV on enrolment who were seen on day 14, 165/542 (30%) still had a Nugent score of 7 or more, but this was as frequent in those with complete resolution of discharge (90/319, 28%) as in those with only partial or no improvement (72/215, 33%) (P = 0.23), as well as among those with (75/240, 31%) or without a visible discharge (86/293, 29%) (P = 0.70). However, among women with candidiasis on enrolment, yeasts were more frequently found on day 14 among those with partial or no improvement of symptoms (81/166, 49%) than those with complete resolution (48/193, 25%) (P <0.001), and were also more common among those with a visible discharge

Fig. 1. **Trial profile**

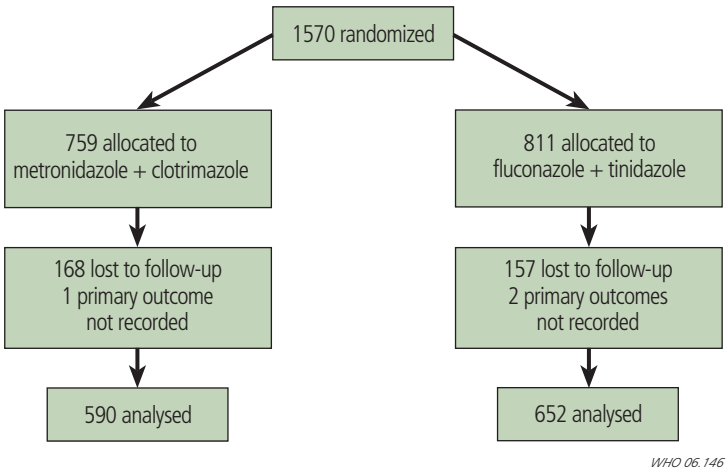

Table 2. **Associations between cervical and vaginal infections on day 0**

Findings on day 0	Bacterial vaginosis/total (%)	Candidiasis/total (%)	*Trichomonas vaginalis*/total (%)	Any agent of vaginitis (%)
Presence of NG,[a] CT[b] and/or MG[c]				
Yes (n = 179)	111 (62)	43 (24)	42 (23)	138 (77)
No (n = 1406)	626 (45)	439 (31)	118 (8)	912 (65)
P-value	0.001	0.06	<0.001	0.001

[a] NG = *Neisseria gonorrhoeae.*
[b] CT = *Chlamydia trachomatis.*
[c] MG = *Mycoplasma genitalium.*

(88/189, 47%) than those without any discharge (40/169, 24%) (P<0.001). Taking as a secondary outcome the presence of yeasts on day 14, there was no difference between treatment groups among the HIV seronegatives or among those with HIV infection (data not shown).

Of 433 women without complete resolution on day 14 who were then treated with metronidazole/clotrimazole, 358 (83%) attended a further follow-up visit on day 28: more than 80% of these women reported a complete resolution of the discharge on day 28, regardless of the treatment received on day 0 and regardless of the presence of objective evidence of vaginosis or candidiasis on day 14 (Table 4).

Finally, we examined whether the presence of signs of cervicitis on examination was correlated with cervical infections (Table 5). Signs of cervicitis were not associated with the presence of NG, CT and/or MG. However, among SW the presence of NG, CT and/or MG was correlated with the leukocyte count in cervical secretions, a higher prevalence being seen as soon as the leukocyte count was >3/hpf. The presence of spermatozoa on Gram stains of vaginal secretions was correlated with the presence of NG, CT and/or MG. We examined the performance of determining the indication for providing treatment for cervical infections based on the presence of a leukocyte count ⩾4/hpf. Among SW this approach had a sensitivity of 64% (79/123) and a positive predictive value of 30% (79/264). Among non-SW the sensitivity was 53% (28/53) and the positive predictive value only 7% (28/413).

Discussion

A combination of single-dose tinidazole/fluconazole was as effective as the longer standard course of metronidazole (7 days)/clotrimazole (3 days) in women presenting with vaginal discharge to primary health care facilities in four West African countries. The effectiveness of the two treatments was similar when examining all women, but also among subgroups selected according to the presence of various etiological agents. Importantly, the two treatments were equally effective in HIV-infected women.

Bacterial vaginosis was the most common etiology of vaginal discharge, both among SW and non-SW, in line with previous studies.[17,18] We defined BV using the Nugent score which, compared to the Amsel criteria, is simpler, more reproducible, and has reasonable sensitivity and specificity.[15,19–21] The standard treatment of BV is a 7-day course of metronidazole; single-dose metronidazole is slightly less effective.[2,20–23] The effectiveness of single-dose metronidazole in women with BV is lower among those who are seropositive for HIV than in those who are seronegative.[18] BV, an infection characterized by frequent relapses after initial improvement, has been the limiting step in the overall management of vaginal discharge with single-dose therapies. Given its longer half-life (12–14 hours versus 6–7 hours for metronidazole),[24] tinidazole would be expected to be more effective as a single-dose therapy. It is better tolerated than metronidazole[25,26] and very cheap (wholesale price per 2 g dose ≈ US$ 0.07). Studies of single-dose tinidazole in women with BV have shown a wide range of effectiveness (51–97%)[27–30] but used different definitions of BV and cure. Experts now agree that the goal of BV treatment is symptomatic relief.[20] In this regard, single-dose tinidazole was equivalent to a week of treatment with metronidazole, even among HIV-infected women.

The prevalence of TV among symptomatic participants in the present study was low, mirroring the results of populational surveys of asymptomatic women which documented a prevalence of only 3% in Cotonou (Benin), compared to 18–34% in Yaoundé (Cameroon), Kisumu (Kenya) and Ndola (Zambia).[31] To treat *T. vaginalis* infections, WHO and others recommend as first choice, single-dose metronidazole (2 g),[2,22,23] which has an effectiveness comparable to that of a 5–7 day course of the same drug.[25,26] Tinidazole was compared to metronidazole in early randomized trials;[32,33] a meta-analysis of these suggested that single-dose tinidazole was superior to single-dose metronidazole.[25] We showed that single-dose tinidazole was as effective against TV as 7 days of metronidazole.

Previously, in sub-Saharan Africa, the treatment of vaginal candidiasis relied on nystatin, with unsatisfactory results. Nystatin was replaced with azole-containing creams, with better results. A generic clotrimazole pessary remains little used. Single-dose oral fluconazole offers an interesting alternative, as it can be combined with single-dose tinidazole and given under direct observation.[34] Generic fluconazole is now cheaper (US$ 0.13 for 150 mg) than the clotrimazole pessary (US$ 0.84).[12–14] Whether vulvovaginal candidiasis is more common or more likely to recur among HIV-infected women is controversial, and there was little information on the effectiveness of single-dose fluconazole in HIV-infected women.[35] We found no difference in effectiveness between fluconazole and clotrimazole in HIV-infected participants, and no difference in response between HIV-infected and HIV-negative women with candidiasis.

Signs of cervicitis on examination were not reliable predictors of cervical

Table 3. **Subjective response to treatment as assessed on day 14 according to treatment group and the presence of various pathogens on day 0**

Treatment group	Symptomatic response on day 14			*P*-value
	Complete resolution (%)	Partial resolution (%)	No improvement (%)	
Overall				
Metronidazole/clotrimazole	377 (64)	203 (34)	10 (2)	
Tinidazole/fluconazole	432 (66)	215 (33)	5 (1)	0.26
Candidiasis present on day 0				
Metronidazole/clotrimazole	110 (57)	78 (40)	5 (3)	
Tinidazole/fluconazole	120 (58)	85 (41)	1 (0.5)	0.23
Bacterial vaginosis present on day 0				
Metronidazole/clotrimazole	179 (62)	101 (35)	7 (2)	
Tinidazole/fluconazole	188 (63)	110 (37)	1 (0.5)	0.09
***T. vaginalis* present on day 0**				
Metronidazole/clotrimazole	37 (62)	22 (37)	1 (2)	
Tinidazole/fluconazole	43 (66)	21 (32)	1 (2)	0.87
NG,[a] CT[b] and/or MG[c] present on day 0				
Metronidazole/clotrimazole	47 (77)	14 (23)	0 (0)	0.50
Tinidazole/fluconazole	50 (70)	20 (28)	1 (1)	
HIV seronegatives				
Metronidazole/clotrimazole	304 (65)	154 (33)	8 (2)	
Tinidazole/fluconazole	350 (68)	164 (32)	3 (1)	0.20
HIV-infected				
Metronidazole/clotrimazole	55 (72)	19 (25)	2 (3)	0.76
Tinidazole/fluconazole	59 (71)	23 (28)	1 (1)	
Ghana				
Metronidazole/clotrimazole	154 (73)	51 (24)	5 (2)	0.21
Tinidazole/fluconazole	165 (77)	48 (22)	1 (0.5)	
Guinea				
Metronidazole/clotrimazole	88 (75)	29 (25)	0 (0)	0.24
Tinidazole/fluconazole	92 (68)	44 (32)	0 (0)	
Mali				
Metronidazole/clotrimazole	40 (55)	32 (44)	1 (1)	0.65
Tinidazole/fluconazole	54 (61)	33 (37)	2 (2)	
Togo				
Metronidazole/clotrimazole	95 (50)	91 (48)	4 (2)	0.29
Tinidazole/fluconazole	121 (57)	90 (42)	2 (1)	

[a] NG = *Neisseria gonorrhoeae.*
[b] CT = *Chlamydia trachomatis.*
[c] MG = *Mycoplasma genitalium.*

infections. Of 560 non-SW women with ⩾1 sign of cervicitis given ciprofloxacin/azithromyin, only 30 (5.4%) had a cervical infection. Most women with cervical infection also had vaginitis, which most likely prompted their consultation; indeed, presumably because of their association with sexual activity, BV and TV were more common among women with cervical infections. Only 53 (5.4%) of non-SW were infected with NG, CT and/or MG; of these only 18 and 28 had ⩾10 and ⩾4 leukocytes/hpf, respectively. In light of these low prevalences, attempting to identify non-SW with cervical infections seems pointless.

Control of NG, CT and MG in the general population of African countries requires these infections to be controlled among SW: decreasing transmission to their clients will ultimately reduce infections among women not involved in transactional sex. Effective single-dose treatments for gonorrhoea and chlamydia are available, although the emergence of ciprofloxacin-resistant gonococci in South Africa is a matter for concern.[36] There are two possible approaches for managing cervical infections among SW. Early in an intervention, when condom use is low and prevalences of cervical infections are high, administering drugs active against agents of cervicitis to all SW will have a sensitivity of 100% and a positive predictive value equal to the prevalence. Later on, when prevalence of cervical infections decreases, the ecological disadvantages (selective pressure for resistance) become a consideration: treatment active against agents of cervical infections might then be given only to SW with ⩾4 leukocytes/hpf in cervical

Table 4. **Subjective response to a second treatment (metronidazole and clotrimazole given on day 14) as assessed on day 28 according to various characteristics**

	Symptomatic response on day 28			*P*-value
	Complete resolution (%)	Partial resolution (%)	No improvement (%)	
Treatment received on day 0				
Metronidazole/clotrimazole	142 (81)	31 (18)	2 (1)	1.00
Tinidazole/fluconazole	148 (81)	33 (18)	2 (1)	
Bacterial vaginosis on day 14				
Absent	210 (80)	51 (19)	3 (1)	0.68
Present	72 (84)	13 (15)	1 (1)	
Yeast cells on day 14				
Absent	176 (79)	42 (19)	4 (1)	0.28
Present	106 (83)	22 (17)	0 (0)	
HIV				
Negative	243 (84)	44 (15)	3 (1)	0.70
Positive	33 (80)	7 (14)	1 (2)	

secretions. However, this implies that roughly half of SW receive ciprofloxacin/azithromycin and that Gram stains are available. The development of affordable, sensitive, specific, rapid, user-friendly and equipment-free tests to diagnose gonococcal and chlamydial infections in women has been a laborious process, further complicated by the recent identification of *M. genitalium* as a third agent of cervicitis.[10,16] The development of cheap dipsticks that would detect the presence of leukocytes might be more easily attainable.

Cross-sectional and cohort studies have examined the association between HIV and vaginitis.[37–42] A meta-analysis estimated that the risk of acquiring HIV was increased 1.4–2.2-fold by BV, TV and candidiasis.[40] Although there is no evidence that adequate treatment of BV reduces the risk of HIV, the high prevalence of BV suggests that its population attributable fraction of incident HIV among women could be substantial.[37] HIV vaginal shedding is higher in women with candidiasis, and is reduced by treatment of candidiasis and TV.[43,44]

Conclusions

Among non-SW at low risk for HIV, the goal is symptomatic relief and single-dose tinidazole/fluconazole could be used as the initial treatment for vaginal discharge, because it is convenient, well tolerated and cheap (wholesale price: US$ 0.20). Most women who do not respond to tinidazole/fluconazole are cured when given as second-line

Table 5. **Associations between various characteristics and the presence of cervical infections with *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT) and/or *Mycoplasma genitalium* (MG)**

Findings on day 0	Sex workers	Non-sex workers
	Presence of NG, CT or MG/total (%)	Presence of NG, CT or MG/total (%)
Cervical discharge		
Absent	88/421 (21)	36/698 (5)
Present	36/164 (22)	17/287 (6)
Pus on cervical swab		
Absent	85/408 (21)	37/757 (5)
Present	39/177 (22)	16/227 (7)
Cervical bleeding after sampling		
Absent	82/400 (21)	39/747 (5)
Present	15/48 (31)	10/146 (7)
Cervical inflammation		
Absent	96/446 (22)	47/843 (6)
Present	28/139 (20)	6/141 (4)
Cervical motion tenderness		
Absent	94/443 (21)	44/767 (6)
Present	30/142 (21)	9/217 (4)
Leukocytes on cervical secretions (per hpf)		
0–3	44/318 (14)	25/570 (4)
4–9	24/97 (25)	10/157 (6)
10–29	30/105 (29)	12/156 (8)
⩾30	25/62 (40)[a]	6/100 (6)
Spermatozoa		
Absent	108/534 (20)	47/940 (5)
Present	16/51 (31)	6/37 (14)[b]
Were given ciprofloxacin + azithromycin		
No	66/322 (20)	23/420 (5)
Yes	58/262 (22)	30/560 (5)

[a] $P<0.05$.
[b] $P<0.001$.

treatment a standard course of metronidazole/clotrimazole (wholesale price: US$ 1.06). Among SW, in addition to symptomatic relief, this visit to a health worker should be used as an opportunity for promotion of condom use and screening for cervical infections. ■

Acknowledgements
This study was funded by the Canadian International Development Agency through its West Africa Project to Combat AIDS and STI in West Africa, and by the United States Agency for International Development and Family Health International.

The following people made important contributions to this project: Canada, Josée Ducharme and Andrée Grondin, who interpreted the Gram stains; Guinea, Dr Thierno Mouctar Diallo and Dr Fatoumata Binta Bah (CS Carrière), Dr Thierno Amadou Koundouno (CS Madina); Mali, Dr Sidibé Garangué Souko (CS Soutoura) and Dr Fatoumata Binta Keita (CS Korofina); Togo, Dr Adom W. Kpao, Director of the National AIDS/STI Control Programme, Dr Kéré Banla Abiba, Director of the Institut National d'Hygiène (INH) and her staff.

Competing interests: none declared.

Résumé

Prise en charge syndromique de la leucorrhée par des traitements sous forme de dose unique : essai contrôlé randomisé en Afrique de l'Ouest

Objectif Evaluer l'efficacité comparative des traitements par dose unique et du traitement standard pour la prise en charge syndromique de la leucorrhée.

Méthodes Un essai contrôlé randomisé a comparé l'efficacité d'une dose unique de l'association tinidazole/ fluconazole (TF) à celle d'un traitement de sept jours par le métronidazole, complété par trois jours sous clotrimazole vaginal (MC), chez 1570 femmes présentant une leucorrhée accueillies par des centres de soins de santé primaires au Ghana, en Guinée, au Mali et au Togo. Les participantes ont été réparties de manière aléatoire au moyen d'enveloppes précodées en deux groupes de traitement par les infirmières ou les médecins chargés de mener l'étude. L'efficacité thérapeutique a été évaluée d'après la réponse symptomatique au quatorzième jour.

Identificateur clinique ClinicalTrials.gov NCT00313131.

Résultats On a constaté une efficacité similaire pour les deux traitements : on a observé une résolution complète chez 66 % des participantes traitées par TF et chez 64 % de celles traitées par MC ainsi qu'une résolution partielle chez 33 % des femmes traitées par TF et 34 % des femmes traitées par MC ($p = 0,26$). Une efficacité analogue a également été constatée chez les sous-groupes présentant une candidose vulvovaginale, une vaginite à *Trichomonas vaginalis* ou une vaginose bactérienne. L'efficacité des deux traitements était similaire chez les femmes infectées par le virus de l'immunodéficience humaine (VIH) (TF : $n = 76$, résolution complète 71 %, résolution partielle 28 % ; MC : $n = 83$, résolution complète 72 %, résolution partielle 25 %, $p = 0,76$) et chez les femmes non infectées par le VIH (TF : $n = 517$, résolution complète 68 %, résolution partielle 32 % ; MC : $n = 466$, résolution complète 65 %, résolution partielle 33 %, $p = 0,20$). Les infections du col par *Neisseria gonorrhoeae*, *Chlamydia trachomatis* et *Mycoplasma* genitalium étaient peu fréquentes chez les femmes ne pratiquant pas le commerce du sexe, étaient associées à une vaginose bactérienne ou à une vaginite à *T. vaginalis* et ne modifiaient pas la réponse au traitement par des agents actifs contre les infections vaginales. Chez les quatre-cinquièmes des femmes qui n'avaient pas été soulagées par une dose unique de TF, on a observé une réponse favorable lors de l'administration de MC comme traitement de deuxième intention.

Conclusion L'association TF sous forme de dose unique est aussi efficace que l'association MC administrée en plusieurs doses dans la prise en charge syndromique de la leucorrhée, même chez les femmes infectées par le VIH. Compte tenu de son coût peu élevé et de l'observance plus facile, il faudrait envisager de classer l'association TF parmi les traitements de première intention de la leucorrhée.

Resumen

Manejo sindrómico del flujo vaginal mediante tratamientos de dosis única: ensayo controlado aleatorizado en África Occidental

Objetivo Determinar si los tratamientos de dosis única son eficaces como terapia estándar en el manejo sindrómico del flujo vaginal.

Métodos En un ensayo controlado aleatorizado se comparó la eficacia de una dosis única de tinidazol y fluconazol (TF) con la de un tratamiento con metronidazol durante 7 días seguido de clotrimazol vaginal durante 3 días más (MC) en un total de 1570 mujeres que acudieron con problemas de flujo vaginal a establecimientos de atención primaria de Ghana, Guinea, Malí y Togo. Utilizando sobres precodificados, enfermeras y médicos investigadores asignaron aleatoriamente a las participantes a alguno de los dos tratamientos. La eficacia se evaluó determinando la respuesta sintomática a los 14 días.

Identificador clínico ClinicalTrials.gov NCT00313131.

Resultados Los dos regímenes terapéuticos tuvieron una eficacia parecida: curación completa en el 66% (TF) y el 64% (MC) de los casos, y curación parcial en el 33% (TF) y el 34% (MC) de los casos ($P = 0,26$). La eficacia fue similar entre los subgrupos con candidiasis vulvovaginal, vaginitis por *Trichomonas vaginalis* o vaginosis bacteriana. Los dos regímenes terapéuticos tuvieron también parecida eficacia en las pacientes infectadas por el virus de la inmunodeficiencia humana (VIH) (TF: $n = 76$, curación completa en el 71% de los casos, y parcial en el 28% de los casos; MC: $n = 83$, curación completa en el 72% de los casos, y parcial en el 25%; $P = 0,76$) y las no infectadas por el VIH (TF: $n = 517$, curación completa en el 68% de los casos, y parcial en el 32%; MC: $n = 466$, curación completa en el 65% de los casos, y parcial en el 33%; $P = 0,20$). Las infecciones cervicouterinas por *Neisseria gonorrhoeae*, *Chlamydia trachomatis* y *Mycoplasma genitalium* eran infrecuentes entre las mujeres que no eran profesionales del sexo, se asociaban a vaginosis bacteriana o vaginitis por *T. vaginalis*, y no influían en la respuesta al tratamiento con productos activos contra las

infecciones vaginales. Las cuatro quintas partes de las mujeres que no respondían a una dosis única de TF presentaron una respuesta favorable al uso de MC como tratamiento de segunda línea.
Conclusión La dosis única de TF es tan eficaz como las dosis múltiples de MC en el manejo sindrómico del flujo vaginal, incluso entre las mujeres con infección por VIH. Teniendo en cuenta su bajo precio y el mayor cumplimiento del régimen, la combinación TF debería ser siempre una alternativa a considerar como tratamiento de primera línea del síndrome de flujo vaginal.

ملخص

التدبير وفق المتلازمات للمفرزات المهبلية بالمعالجة بجرعة وحيدة: دراسة معشاة مضبوطة بالشواهد في غرب أفريقيا

الهدف: تقييم ما إذا كانت المعالجة بجرعة وحيدة تتمتع بنفس فعّالية المعالجة المعيارية في التدبير وفق المتلازمات للمفرزات المهبلية.
الطريقة: قارنت دراسة معشاة مضبوطة بالشواهد فعّالية جرعة وحيدة من التينيدازول والفلوكونازول مع فعالية المعالجة لمدة سبعة أيام بالميترونيدازول بالإضافة إلى ثلاثة أيام من المعالجة بالكلوتريمازول المهبلي، وشملت الدراسة 1570 امرأة تعاني من مفرزات مهبلية في مؤسسات الرعاية الصحية الأولية في كل من غانا وغينيا ومالي وتوغو. وقد وزع الأطباء أو الممرضات المشرفات على هذه الدراسة المريضات اللاتي شاركن في الدراسة ضمن واحد من النظامَيْن العلاجيَّيْن باستخدام مظاريف مسبقة الترميز، وأجري تقييم أعراض الاستجابة في اليوم الرابع عشر.
الرقم التعريفي السريري (الإكلينيكي): دراسات سريرية ((إكلينيكية)) (NCT00313131)
الموجودات: لقد كان للنظامَيْن العلاجيَّيْن نفس الفعَّالية؛ فقدشوهد الشفاء التام لدى 66% من الحالات المعالجة بجرعة وحيدة بالتينيدازول مع الفلوكونازول ولدى 64% من الحالات المعالجة بالميترينيدازول والكلوتيرمازول المهبلي، كما شوهد الشفاء الجزئي لدى 33% من الحالات المعالجة بجرعة وحيدة بالتينيدازول مع الفلوكونازول ولدى 34% من الحالات المعالجة بالميترونيدازول والكلوتريمازول المهبلي (وكانت قيمة الاحتمال 0.26). كما كانت الفعّالية متشابهة لدى المجموعات الفرعية التي تعاني من التهاب المهبل والفرج بالـمِبْيَضّات والتهاب المهبل بالمشعّرة المهبلية أو التهاب المهبل بالجراثيم. وقد كان للنظامَيْن العلاجيَّيْن نفس الفعالية لدى المصابات بالإيدز، فبالنسبة للمعالجة بجرعة وحيدة بالتينيدازول مع الفلوكونازول تحقق الشفاء التام لدى 71% والشفاء الجزئي لدى 28% من بين 76 مصابة، أما بالنسبة للمعالجة بالميترينيدازول والكلوتريمازول المهبلي، فقد تحقق الشفاء التام لدى 72% والشفاء الجزئي لدى 25% من بين 83 مصابة، (وقيمة الاحتمال 0.76). وبين غير المصابات بعدوى الإيدز وعددهن 517 مصابة، فقد تحقق الشفاء التام لدى 68% ممن عولجت بجرعة وحيدة بالتينيدازول مع الفلوكونازول، وتحقق الشفاء الجزئي لدى 32% منهن، كما تحقق الشفاء التام لدى 65% ممن عولجن بالميترينيدازول والكلوتيرمازول المهبلي وعددهن 466 مريضة، والشفاء الجزئي لدى 33% منهن، (وقيمة الاحتمال 0.20). ولم تكن العدوى بالكلاميديا الحثرية والمصورات التناسلية شائعة بين اللاتي لا يقترفن البغاء، ولكنها ترافقت مع التهاب المهبل الجرثومي أو التهاب المهبل بالمشعرات المهبلية، دون أن يغير ذلك من الاستجابة للمعالجة بأدوية فعَّالة ضد العدوى المهبلية. وقد تحسَّن أربعة أخماس النسوة اللائي لم يستجبن جيداً للمعالجة بجرعة وحيدة من التينيدازول مع الفلوكونازول بعد معالجتهن بالميترينيدازول والكلوتريمازول المهبلي كخطٍ علاجي ثانٍ.
الاستنتاج: إن المعالجة بجرعة وحيدة من التينيدازول والفلوكونازول تضاهي بفعاليتها المعالجة بجرعات متعددة من الميترينيدازول والكلوتريمازول المهبلي في تدبير المفرزات المهبلية، حتى لدى النساء المصابات بالإيدز، ونظراً لانخفاض سعر الجرعة الوحيدة وسهولة الامتثال لها ينبغي اعتبارها الخط الأول من المعالجة لمتلازمة المفرزات المهبلية.

References

1. Dallabetta G, Gerbase A, Holmes KK. Problems, solutions, and challenges in syndromic management of sexually transmitted diseases. *Sex Transm Infect* 1998;74: Suppl 1:S1-S11.
2. World Health Organization. *Guidelines for the management of sexually transmitted infections*. Geneva: WHO; 2003. Availble from: http://whqlibdoc.who.int/publications/2003/9241546263.pdf
3. Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Senkoro K, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;346:530-6.
4. Wawer MJ, Sewankambo NK, Serwadda D, Quinn TC, Paxton LA, Kiwanuka N, et al. Control of sexually transmitted disease for AIDS prevention in Uganda: a randomised community trial. Lancet 1999;353:525-35.
5. Kamali A, Quigley M, Nakiyingi J, Kinsman J, Kengeya-Kayondo J, Gopal R, et al. Syndromic management of sexually transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. *Lancet* 2003;361:645-52.
6. Kaul R, Kimani J, Nagelkerke NJ, Fonck K, Ngugig EN, Keli F, et al. Monthly antibiotic chemoprophylaxis and incidence of sexually transmitted infections and HIV-1 infection in Kenyan sex workers. A randomized controlled trial. *JAMA* 2004;291:2555-62.
7. Pepin J, Sobela F, Alary M, Deslandes S, Kintin F, Khonde N, et al. Low prevalence of cervical infections in women with vaginal discharge in West Africa: implications for syndromic management. *Sex Transm Infect* 2004; 80:230-5.
8. Alary M, Mukenge-Tshibaka, Bernier F, Geraldo N, Lowndes CM, Méda H, et al. Decline in the prevalence of HIV and sexually transmitted disease among female sex workers in Cotonou, Benin, 1993-1999. *AIDS* 2002;16:463-70.
9. Ghys PD, Diallo MO, Ettiègne-Traoré V, Kalé K, Tawil O, Carael M, et al. Increase in condom use and decline in HIV and sexually transmitted diseases among female sex workers in Abidjan, Côte d'Ivoire, 1991-1998. *AIDS* 2002;16:251-8.
10. Pepin J, Labbé AC, Khonde N, Deslandes S, Alary M, Dzokoto A, et al. *Mycoplasma genitalium*: an organism commonly associated with cervicitis among West African sex workers. *Sex Transm Infect* 2005:81:67-72.
11. Ndoye I, Mboup S, De Schryver A, Van Dyck E, Moran J, Samb ND, et al. Diagnosis of sexually transmitted infections in female prostitutes in Dakar, Senegal. *Sex Transm Infect* 1998;74 Suppl 1:S112-17.
12. Pépin J, Mabey D. Sexually transmitted infections in Africa: single dose treatment is now affordable. *Sex Transm Infect* 2003;79:432-4.
13. United Nations Children's Fund-Joint United Nations Programme on HIV/AIDS-World Health Organization-Medecins sans Frontieres. Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS. Geneva: UNICEF-UNAIDS-WHO-MSF; 2005. Available from:http://www.who.int/3by5/amds/sourcesAug05.pdf
14. International Dispensary Association. *Price indicator*. Amsterdam: International Dispensary Association; August 2005.

15. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardised method of Gram stain interpretation. *J Clin Microbiol* 1991;29:297-301
16. Manhart LE, Critchlow CW, Holmes KK, Dutro SM, Eschenbach DA, Stevens CE, et al. Mucopurulent cervicitis and Mycoplasma genitalium. *J Infect Dis* 2003;187:650-7.
17. Behets FMT, Andriamiadana J, Randrianasolo D, Rasamilalao D, Ratsimbazafy N, Dallabetta G , et al. Laboratory diagnosis of sexually transmitted infections in women with genital discharge in Madagascar: implications for primary care. *Int J STD AIDS* 2002;13:606-11.
18. Moodley P, Wilkinson D, Connolly C, Sturm AW. Influence of HIV-1 coinfection on effective management of abnormal vaginal discharge. *Sex Transm Dis* 2003;30:1-5.
19. Sobel J. Vaginitis. *N Engl J Med* 1997;337:1896-903.
20. Joesoef MR, Schmid GP, Hillier SL. Bacterial vaginosis: review of treatment options and potential clinical indications for therapy. *Clin Infect Dis* 1998; 28 Suppl 1:S57-S65.
21. Koumans EH, Markowitz LE, Hogan V, for the CDC BV Working Group. Indications for therapy and treatment recommendations for bacterial vaginosis in non-pregnant and pregnant women: a synthesis of data. *Clin Infect Dis* 2002;35 Suppl 2:S152-S172.
22. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *Morbidity and Mortality Weekly Report* 2002;51(RR-6):1-82. Available from: http://www.cdc.gov/std/treatment/rr5106.pdf
23. Clinical Effectiveness Group. UK national guidelines on sexually transmitted infections and closely related conditions. *Sex Transm Infect* 1999; 75: Suppl 1:S1-S88.
24. Chaikin P, Alton KB, Sampson C, Weintraub HS. Pharmacokinetics of tinidazole in male and female subjects. *J Clin Pharmacol* 1982;22:562-70.
25. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. *The Cochrane Database of Systematic Reviews.* Latest update: 22-6-2005.
26. Gulmezoglu AM, Garner P. Trichomoniasis treatment in women: a systematic review. *Trop Med Int Health* 1998;3:553-8.
27. Schindler EM, Thamm H, Ansmann EB, Sarnow E, Schindler AE. Treatment of bacterial vaginitis. Multicenter, randomized, open study with tinidazole in comparison with metronidazole. *Fortschr Med Orig* 1991;109:138-40.
28. Ekgren J, Norling BK, Degre M, Midtvert T. Comparison of tinidazole given as a single dose and on 2 consecutive days for the treatment of non-specific bacterial vaginosis. *Gynecol Obstet Invest* 1988;26:313-7.
29. Vutyavanich T, Pongsuthirak P, Vannareumol P, Ruangsri R, Luangsook. A randomised double-blind trial of tinidazole treatment of the sexual partners of females with bacterial vaginosis. *Obstet Gynecol* 1993;82:550-4.
30. Mohanty KC, Deighton R. Comparison of 2 g single dose of metronidazole, nimorazole and tinidazole in the treatment of vaginitis associated with *Gardnerella vaginalis. J Antimicrob Chemother* 1987;19:393-9.
31. Buvé A, Weiss HA, Laga M, Van Dyck E, Musonda R, Zekeng L, et al. The epidemiology of trichomoniasis in women in four African cities. *AIDS* 2001; 15 Suppl 4:S89-S96.
32. Sawyer PR, Brogden RN, Pinder RM, Speight TM, Avery GS. Tinidazole: a review of its antiprotozoal activity and therapeutic efficacy. *Drugs* 1976; 11:423-40.
33. Apte VV, Packard RS. Tinidazole in the treatment of trichomoniasis, giaridasis and amoebiasis. Report of a multicentre study. *Drugs* 1978;15 Suppl 1:43-8.
34. Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A. Oral versus intravaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *Cochrane Database Systematic Reviews*, latest update 22 May 2002.
35. Sobel J. Gynecologic infections in HIV-infected women. *Clin Infect Dis* 2000; 31: 1225-33.
36. Moodley P, Sturm AW. Ciprofloxacin-resistant gonorrhoea in South Africa. *Lancet* 2005;366:1159.
37. Schmid G, Markowitz L, Joesoef R, Koumans E. Bacterial vaginosis and HIV infection. *Sex Transm Infect* 2000;76:3-4.
38. Myer L, Denny L, Telerant R, de Souza M, Wright TC, Kuhn L. Bacterial vaginosis and susceptibility to HIV infection in South African women: a nested case-control study. *J Infect Dis* 2005;192:1372-80.
39. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;75:3-17.
40. Rottingen JA, Cameron DW, Garnett GP. A systematic review for the epidemiologic interactions between classic sexually transmitted diseases and HIV. How much is really known? *Sex Transm Dis* 2001;28:579-97.
41. Martin HL, Richardson B, Nyange PM, Lavreys L, Hillier SL, Chohan B, et al. Vaginal lactobacilli, microbial flora and risk of HIV-1 and STD acquisition. *J Infect Dis* 1999;180:1863-8.
42. Taha T, Hoover DR, Dallabetta GA, Kumwenda NI, Mtimavalye LA, Yang LP, et al. Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition of HIV. *AIDS* 1998;12:1699-706.
43. Mostad SB, Overbaugh J, DeVange DM, Welch MJ, Chohan B, Mandaliya K, et al. Hormonal contraception, vitamin A deficiency and other risk factors for shedding of HIV-1-infected cells from the cervix and vagina. *Lancet* 1997; 350:922-7.
44. Wang CC, McClelland RS, Reilly M, Overbaugh J, Emery SR, Mandaliya K, et al. The effect of treatment of vaginal infections on shedding of human immunodeficiency virus type 1. *J Infect Dis* 2001;183:1017-22.