SHORT REPORT

Risk factors associated with failure of syndromic treatment of sexually transmitted diseases among women seeking primary care in Addis Ababa

D Wolday, Z G-Mariam, Z Mohammed, H Meles, T Messele, W Seme, A Geyid, S Maayan

Sex Transm Infect 2004;**80**:392–394. doi: 10.1136/sti.2003.005660

Objective: To determine risk factors associated with the failure of syndromic management of sexually transmitted diseases (STDs) among women seeking treatment in primary healthcare centre in Addis Ababa, Ethiopia.

Methods: Women with symptomatic STDs seeking care in a health centre were prospectively enrolled. A total of 259 women were interviewed and underwent clinical examination; 106 were enrolled and received syndromic STD treatment and 91% returned for follow up. Logistic regression analysis was used to identify risk factors associated with treatment failure.

Results: Of the 106 women enrolled and presenting with symptomatic STDs 67% were HIV seropositive. Syndromic STD treatment did not result in clinical improvement in 30% of the women. Having genital ulcer disease, genital ulcer disease with genital discharge, genital warts, bacterial vaginosis and plasma HIV-1 load >10 000 copies RNA/ml or being HIV seropositive were all significantly associated with treatment failure. In multivariate analysis, however, only genital ulcer disease was significantly associated with treatment failure.

Conclusion: In our setting, the association between HIV and genital ulcer disease caused by herpes may, therefore, be the reason for the failure of treatment.

Ethiopia has one of the highest HIV prevalences in sub-Saharan Africa. HIV prevalence is between 14% and 20% among urban pregnant women, 12% in patients treated for STDs, and 74% in commercial sex workers.[1 2] The World Health Organization (WHO) recommends syndromic treatment of STDs in developing countries at the primary healthcare level.[3] However, the effectiveness of syndromic treatment approach for STDs in Ethiopia has not been validated. Indeed, the performance outcome of the syndromic STD treatment in Addis Ababa City has been characterised by low sensitivity and specificity.[4] In this study, we assessed risk factors associated with the failure of syndromic treatment of STDs.

PATIENTS AND METHODS

Study population

Study subjects were recruited at Tekle-Haymanot Health Centre in Addis Ababa, Ethiopia, between June and September 2001. The health centre serves a heterogeneous urban population in the centre of the city. Demographic characteristics, sexual history, and other relevant information were collected. Subjects were eligible for the study if they presented with symptoms suggestive of STDs, such as genital discharge or ulcers, and if they had had no antibiotic treatment for at least 2 weeks before enrolment. All women presenting with symptomatic STDs were offered voluntary HIV counselling and testing. The project was approved by institutional and national ethical committees.

Gynaecological examination was performed at entry visit and after syndromic STD treatment. During the speculum examination, cervical and vaginal secretions were collected for microbiological investigations. Blood was obtained for virological and immunological assays. At entry, women with clinical signs of STDs were treated based on a syndromic approach. A programme to improve syndromic case management in 18 Addis Ababa health centres was launched by the regional health bureau in collaboration with the non-governmental organisation Médecins Sans Frontières, Belgium.[5] The protocol was adopted based on the WHO syndromic treatment algorithm.[3] Under the programme, drugs are dispensed in the form of pre-packaged treatments, known as syndrome selective packaging. The packet contained the full course treatment for a STD syndrome, condoms, instruction leaflet, and a partner referral card.

Women with genital discharge syndrome, and a negative risk assessment were treated with metronidazole (single oral dose 2 g) and nystatin (intravaginal 100 000 IU for 14 days). Those with genital discharge, but a positive risk assessment (age <20 years, partner with STD, having multiple sexual partners), were treated additionally with doxycycline (oral 200 mg divided in two doses for 7 days) and spectinomycin (2 g single intramuscular injection). Women presenting with genital ulcer disease were treated with benzanthine benzylpenicillin (single intramuscular injection) and erythromycin (1.5 g divided in three doses daily for a total of 7 days). Patients were checked, on average, 2 weeks after syndromic treatment to assess compliance and clinical outcome. Treatment failure was defined when women have persistence of the symptoms and have clinical signs of genital infections at follow up visit despite treatment. Women who did not improve after syndromic treatment and those with infections that were not recognised at enrolment received pathogen specific treatment, and were asked to return 2 weeks following re-treatment.

Laboratory investigations

HIV test was performed by HIVSPOT and enzyme immunoassay (EIA). Positive specimens were confirmed by western blot. Plasma HIV-1 load was quantified by nucleic acid based amplification assay. HIV levels below the lower detection limit of the assay were considered at 80 copies/ml. CD4+ count was determined by FACScan.

In addition to the syndromic diagnosis of STDs, pathogen specific diagnosis of certain STDs was performed. Serology

Abbreviations: RPR, rapid plasma reagin; TPPA, *Treponema pallidum* passive particle agglutination

for syphilis was done using rapid plasma reagin (RPR) test and *Treponema pallidum* passive particle agglutination (TPPA) assay. Those reactive to both were considered as having active syphilis. *Neisseria gonorrhoeae* was detected by Gram stain confirmed by culture (modified Thayer-Martin medium), and by ligase chain reaction. *C trachomatis* was detected by ligase chain reaction. *T vaginalis* was detected by wet mount and/or by culture using In Pouch TV and bacterial vaginosis was detected by quantitative morphology of Gram stained slides based on Nugent's criteria.[6]

Statistical analyses

Proportions were compared using the χ^2 test or Fisher's exact test where appropriate. Median CD4 counts and HIV load between the different groups were compared using Mann-Whitney U test. Univariate logistic regression analysis was used to identify predictors of increased likelihood of treatment failure. Multivariate logistic regression was used to ascertain whether associations persisted after adjustment for confounding factors. A p value of less than 0.05 was considered statistically significant.

RESULTS

Of the total of 259 women screened, 128 (49%) did not have symptomatic STDs on presentation. Of the remaining 131 women, eight did not come for enrolment, six were excluded because of advanced AIDS, five were not willing to undergo HIV testing, six were excluded because of extensive tuberculosis, gynaecological malignancies and hysterectomy. A total of 106 (81%) women were enrolled. The age of the women ranged from 17 to 51 years (median, 27) and 71 (67%) were HIV-1 seropositive. The most common syndrome was genital discharge and bacterial vaginosis was common in this population. The syndromic diagnosis, however, either missed or led to overdiagnosis of many of the infections (table 1).

The median time of follow up was 17 (interquartile range, 15–19) days after completion of treatment. Of the 106 women enrolled, 91% returned for a follow up visit and 95% of them reported taking all the medications prescribed. Overall, syndromic STD treatment did not result in clinical improvement in 30% of the women. While treatment failure was only 14% among the 29 HIV seronegative women, it was 37% among the 67 HIV seropositive women. Having genital ulcer disease, genital ulcer disease with genital discharge, genital warts, bacterial vaginosis, and plasma HIV-1 load >10 000 copies RNA/ml or being HIV seropositive were all significantly associated with treatment failure (table 2). In contrast, genital discharge, cervicitis, *Neisseria gonorrhoeae*, *Candida albicans*, syphilis, presence of leucocytes in cervix, or CD4 cell decrease were not associated with treatment failure. In multivariate analysis, however, only genital ulcer disease was significantly associated with treatment failure. Because of the collinearity of several variables significant in univariate regression analysis (HIV-1 seropositivity, CD4 count, and plasma HIV-1 load), we did not create models adjusting for these confounding factors.

DISCUSSION

We found that the performance outcome of the syndromic STD treatment approach resulted in either undertreatment or overtreatment of STDs. In the primary care centre where the current study has been done, in the year 2000 alone, 9755 cases have been managed under the programme.[4] Given the fact that more than 50% of the cases are misdiagnosed, the continued use of the current syndromic treatment approach is not warranted.

The underlying reason for the differential response to syndromic therapy might be attributed to the differences in the frequency of potentially untreatable or recurrent genital infections. Treatment failure of 61% in women with genital ulcer disease in our study is higher than the 19% reported for Malawian men with genital ulcer disease.[7] These might be attributed to differences in gender, genital ulcer disease aetiologies, drug susceptibility of the offending organisms, or differences in the stage of HIV infection. Indeed, the data support the contention that the effects of syndromic STD treatment depend on the prevalence of curable STDs in a given population.[8 9] We have previously documented that herpes simplex virus type 2 (HSV-2) seroprevalence was strongly associated with history of genital ulcer syndrome (OR = 5.32, CI = 2.39 to 11.8, p = 0.0001) and HIV-1 seropositivity (OR = 5.25, CI = 1.42 to 19.35, p = 0.01) in women in Addis Ababa.[10] Moreover, recent observation (Girma A *et al*, personal communication) showed that more than 75% of genital ulcerations among women are due to HSV-2. Treatment of HSV-2 is not included in the syndromic management algorithm of genital ulcer disease in Ethiopia. The association between HIV and genital ulcer disease caused by herpes may, therefore, be the reason for the failure of treatment rather than the presence of HIV alone. Moreover, a decrease in STDs following syndromic management[11] may not result in parallel reduction in HIV prevalence in a given geographical setting. None the less, HSV-2 has become an important cause of genital ulcer disease in HIV infected people,[7] thus antiherpes therapy should be included in syndromic management algorithms.

Earlier studies have shown that HIV infected men with concomitant STDs had increased shedding of HIV-1 and that effective treatment reduced HIV shedding.[12] Whether syndromic treatment of STDs is effective in reducing HIV

Table 1 Distribution of laboratory diagnosed infection by syndromes

	Syndromic STD diagnosis* (n = 106)	
Laboratory diagnosed infection	Genital discharge (n = 87)	Genital ulcer disease (n = 19)
Neisseria gonorrhoeae	11 (12.7%)*	3 (15.8%)
Chlamydia trachomatis	1 (1.2%)	0 (0.0%)
Bacterial vaginosis†		
Intermediate	14 (16.1%)	3 (15.8%)
Moderate or severe	22 (25.3%)	6 (31.6%)
Candida albicans	14 (16.1%)	4 (21.1%)
Trichomonas vaginalis	1 (1.2%)	0 (0.0%)
Active syphilis‡	10 (11.5%)	2 (10.5%)

*Only 46% had laboratory identified infections.
†Nugent's score: intermediate flora (score 4–6), and moderate or severe bacterial vaginosis (7–10).[5]
‡Seropositive by RPR and TPPA.
11 women with genital ulcer syndrome had additional genital discharge; and 22% and 21% women with genital discharge and genital ulcer disease, respectively, had multiple laboratory identified infections.

Table 2 Risk factors associated with treatment failure of syndromic management of STDs (n = 96)

Variables	Treatment failure		OR (95% CI)	Adjusted OR (95% CI)
	No/total	%		
Clinical syndromes				
Genital discharge	22/73	30.1	0.99 (0.36 to 2.73)	–
Cervicitis	16/47	34.0	1.43 (0.60 to 2.43)	–
Genital ulcer	11/18	61.1	5.24 (1.77 to 15.49)	4.12 (1.35 to 12.58)*
Genital discharge and ulcer	7/10	70.0	6.79 (1.61 to 28.55)	5.06 (1.17 to 21.84)*
Genital warts	4/5	80.0	10.56 (1.13 to 99.11)	7.81 (0.82 to 74.36)
Laboratory findings				
HIV positive	25/67	37.3	3.72 (1.16 to 11.97)	2.46 (0.71 to 8.49)
Neisseria gonorrhoeae	3/12	25.0	0.74 (0.19 to 2.97)	–
Chlamydia trachomatis	1/1	100.0	–	–
Bacterial vaginosis†				
Intermediate	6/21	28.6	1.44 (0.44 to 4.68)	–
Moderate or severe	13/29	44.8	2.93 (1.06 to 8.06)	1.27 (0.42 to 3.81)
Candida albicans	6/15	40.0	1.68 (0.54 to 5.26)	–
Trichomonas vaginalis	0/1	0.0	–	–
Active syphilis‡	2/12	16.7	0.42 (0.09 to 2.06)	–
Past syphilis	5/23	21.7	0.57 (0.19 to 1.71)	–
Cervical leucocytes (⩾10 hpf)	3/16	18.8	0.48 (0.13 to 1.83)	–
CD4 count				
<200 cells $\times 10^6$/l	11/27	40.7	1.94 (0.76 to 4.97)	–
Per 100 cells $\times 10^6$/l decrease	–	–	1.18 (1.00 to 1.39)	–
Plasma HIV load				
⩾10 000 copies/ml	22/50	44.0	1.83 (1.04 to 3.22)	1.57 (0.86 to 2.87)
Per $\log_{10}$ copies/ml increase	–	–	3.67 (0.94 to 14.38)	–

*Adjusted for HIV serostatus.
†Nugent's score: intermediate flora (score 4–6), and moderate or severe bacterial vaginosis (7–10).[5]
‡Seropositive by RPR and TPPA.

shedding in genital secretions is hardly known. Our preliminary results show that syndromic STD treatment failure can result in persistent genital shedding of HIV-1.[13] Its implication, however, remains to be addressed.

Although the WHO recommends syndromic treatment of STDs in developing countries at the primary healthcare level,[3] accurate diagnosis and treatment of STDs is important in limiting the transmission of HIV infection. The recognition of treatable co-factors that may influence the sexual transmission of HIV will have important implications for HIV control programmes.

ACKNOWLEDGEMENTS

ENARP is a collaborative research project between EHNRI, the Amsterdam Municipal Health Service, the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, and the Academic Medical Centre of the University of Amsterdam. ENARP is a bilateral project financially supported the Netherlands Ministry of Foreign Affairs and the Ethiopian Ministry of Health. SM has also received financial support from the MASHAV, Jerusalem, Israel.
We thank the study participants for their kind collaboration, and the laboratory staff of ENARP and the microbiology section of EHNRI for their technical assistance.

CONTRIBUTORS

DW is the principal investigator responsible for all aspects of the study; ZG and ZM are co-investigators responsible for the clinical follow up of the patients and contributed to implementation of the study design; WD, HM, and ES are co-investigators and contributed to laboratory follow up, data entry, analysis, and writing of the manuscript; AG and WS were co-investigators who contributed to study research design, supervision of STD laboratory protocols, and write up; SM is co-principal investigator who contributed to the study design and write up; all investigators contributed to the editing of the final version of the manuscript.

Authors' affiliations

D Wolday, H Meles, T Messele, Ethio-Netherlands AIDS Research Project (ENARP), Ethiopian Health and Nutrition Research Institute (EHNRI), Addis Ababa, Ethiopia
Z G-Mariam, Department of Gynaecology and Obstetrics, Black-Lion Teaching Hospital, Addis Ababa, Ethiopia
Z Mohammed, Tekle-Haymanot Health Center, Addis Ababa, Ethiopia
W Seme, A Geyid, Microbiology Section, Ethiopian Health and Nutrition Research Institute (EHNRI), Addis Ababa, Ethiopia
S Maayan, AIDS Center, Hadassah University Hospital, Jerusalem, Israel

Conflict of interest: None.

Correspondence to: Dr D Wolday, Ethio-Netherlands AIDS Research Project (ENARP), Ethiopian Health and Nutrition Research Institute (EHNRI), PO Box 8297, Addis Ababa, Ethiopia; dawit@enarp.com

Accepted for publication 16 January 2004

REFERENCES

1 **Kebede D**, Aklilu M, Sanders E. The HIV epidemic and the state of its surveillance in Ethiopia. *Ethiop Med J* 2000;**38**:283–9.
2 **Aklilu M**, Messele T, Tsegaye A, *et al*. Factors associated with HIV-1 infection among sex workers of Addis Ababa, Ethiopia. *AIDS* 2001;**15**:87–96.
3 **World Health Organization/Global Programme on AIDS**. *Management of sexually transmitted diseases*, WHO/GPA/TEM/94.1. Geneva: WHO, 1994.
4 **Médecins Sans Frontières, Belgium**. *Report on the implementation of syndromic case management in the public health centres of Addis Ababa, Ethiopia*, Addis Ababa, 2000.
5 **Médecins Sans Frontières (Belgium)/Addis Ababa Health Bureau Joint Initiative**. *Sexually transmitted diseases syndrome therapeutic guidelines*, Addis Ababa, 1999.
6 **Nugent RP**, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *J Clin Microbiol* 1991;**29**:297–301.
7 **Behets FM**, Liomba G, Lule G, *et al*. Sexually transmitted diseases and human immunodeficiency virus control in Malawi: a field study of genital ulcer disease. *J Infect Dis* 1995;**171**:451–5.
8 **Grosskurth H**, Mosha F, Todd J, *et al*. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530–6.
9 **Wawer MJ**, Sewankambo NK, Serwadda D, *et al*. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. *Lancet* 1999;**353**:525–35.
10 **Mihret W**, Rinke de Wit TF, Petros B, *et al*. Seroprevalence of herpes simplex virus type-1 (HSV-1) and type-2 (HSV-2) among urban and semiurban Ethiopians: possible association with HIV status and sociodemographic factors. *Sex Transm Dis* 2002:175–81.
11 **Corbett EL**, Stekette RW, Kuile FO, *et al*. HIV-1/AIDS and the control of other infectious diseases in Africa. *Lancet* 2002;**359**:2177–87.
12 **Coombs RW**, Reichelderfer PS, Landay AL. Recent observations on HIV type-1 infection in the genital tract of men and women. *AIDS* 2003;**17**:*455*–80.
13 **Wolday D**, GebreMariam Z, Mohammed Z, *et al*. The impact of syndromic treatment of sexually transmitted diseases on cervical shedding of HIV-1. *AIDS* 2004;**18**:781–5.