Choosing an Effective and Affordable Antibiotic Regimen for Sexually Transmitted Diseases (STD) Patients in Malawi

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2. Behets FM-T, Liomba G, Lule G, Dallabetta G, Hoffman IF, Hamilton HA, Moeng S, Cohen MS. Sexually transmitted diseases / human immunodeficiency virus control in Malawi: a field study of genital ulcer disease.

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Abstract

At the STD clinic at Queen Elizabeth Central Hospital, Blantyre, a total of 1295 male patients with complaints of either urethral discharge and/or dysuria (urethritis), or genital ulcer disease (GUD) were enrolled in the study. Gonococcal urethritis was diagnosed in 415 (80.3%) and nongonococcal urethritis (NGU) in 59 (11.2%) of 517 males enrolled with urethritis. *Haemophilus ducreyi* cultures were positive for 204 (26.2%) of the 778 patients enrolled with GUD. The syphilis seropositivity rate (RPR and MHA-TP reactive) was 10.7% for the urethritis patients and 17.0% of 758 examined sera among the GUD patients. Reactive syphilis serology and/or positive DFA was found for 228 (33.5%) of 681 GUD patients. HIV seroprevalence was 44.2% among the urethritis patients and 58.9% among the GUD patients.

For patients with urethritis, trimethoprim 320 mg/sulfamethoxazole 1600 mg PO for 2 days (TMPSMX), or the combination of amoxicillin 3 gm, probenecid 1 gm, and clavulanate 125 mg PO once (APC), failed to cure gonorrhoea effectively. Amoxicillin 3 gm, and clavulanate 125 mg, PO once with doxycycline 100 mg BID for 7 days (APC-D), gentamicin 240 mg IM once (GENT), and ciprofloxacin 250 mg PO once (CIPRO) cured 92.9% to 95% of gonorrhoea. APC-D treatment did not generate less NGU at follow-up. For the patients with GUD, cotrimoxazole DS (960 mg) PO twice daily for seven days (TMPSMX) was ineffective for the treatment of chancroid-proven GUD. Erythromycin 250 mg three times daily for 7 days (ERY250), erythromycin 500 mg three times daily for seven days (ERY500), ciprofloxacin 250 mg once daily for 5 days (CIP1D) and ciprofloxacin 500 mg (CIP5D) stat dose appear to be equally effective for chancroid proven GUD. Although HIV serostatus did not effect cure of urethritis, HIV infection clearly impaired healing of GUD. All patients presenting with urethritis or GUD complaints should be treated syndromically using a simple algorithm, and screened for syphilis seroreactivity for appropriate treatment and counselling.

Introduction

Recent cross-sectional and prospective studies provide compelling evidence that sexually transmitted diseases (STDs) are an independent risk factor for HIV transmission.[1,2] Ulcerative diseases have been shown to increase the risk of HIV transmission three to five-fold in prospective studies.[3,4] Non-ulcerative STDs, such as gonorrhea, chlamydia, and trichomonas also increase the risk of HIV transmission.[5] Estimations of the attributable risk of STDs on HIV infections in Africa range from 8% to 33%, indicating that a substantial proportion of HIV infections might be eliminated by control of other STDs.[6]

Malawi has one of the highest HIV prevalences in the world. In 1992, 27.2% of urban antenatal women[7] and 7.6% of rural antenatal women were HIV seropositive.[8] In 1989, 62% of 705 outpatients presenting to the outpatient department at Kamuzu Central Hospital in Lilongwe with signs/symptoms of STDs were HIV positive.[9]

Effective STD control requires both proper diagnosis and effective treatment. Syndromic approaches to the management of STDs using simple algorithms have been developed and advocated by the World Health Organization.[10] It is essential that recommended treatments are not only effective, but compatible with national health budgets.[11] Knowledge of local factors such as common aetiologies for specific syndromes, and effectiveness of antibiotic regimens is crucial for the optimal implementation of syndromic approaches.

Data on sexually transmitted disease aetiology and antimicrobial sensitivities in Malawi are scarce. This study was undertaken to first determine the aetiology of both genital ulcer disease and urethritis in males and then to test the efficacy of several antibiotic regimens in preparation for the adoption of updated national STD management guidelines.

Methods

This study took place between September 1992 and March 1993. The study population consisted of males presenting to the outpatient department of Queen Elizabeth Central Hospital in Blantyre with signs or symptoms of either genital ulcer disease (GUD) or urethritis (U), but not both. Signs and symptoms of urethritis were defined as either a purulent or mucoid discharge and/or dysuria. GUD was defined as any genital lesion that is denuded of the normal epithelium[12,13]. Those patients who denied receiving antibiotics during the previous 2 weeks, who were able to return for a follow up visit, and who gave informed consent were eligible. During the initial visit, demographic, historical and behavioral

data were gathered by a nurse clinician and the patients were examined.

Urethritis patients: For patients classified with urethritis, the patient's symptoms and the characteristics of the discharge were noted. Urethral swabs were obtained for 1) Gram stain, 2) *Neisseria gonorrhoeae* culture and 3) EIA chlamydia antigen detection. Blood was drawn for syphilis serologies. For N. gonorrhoeae detection, urethral specimens were inoculated directly onto Thayer Martin media and immediately placed in candle extinction jars. They were incubated at 36 degrees C for 24-48 hours. Gram stains were done on oxidase positive colonies looking for characteristic morphology. A patient was considered to have gonococcal urethritis if either the initial urethral Gram stain showed gram-negative intracellular diplococci or the culture was positive. Chlamydia antigen detection was carried out using EIA (Antigenz EIA, Shield Diagnostics, LTD, UK). A patient was diagnosed with nongonococcal urethritis (NGU) when the gonorrhea culture was negative and at least 5 polymorphonuclear leukocytes per HPF were seen on urethral smear, or if there were less than 5 polymorphonuclear leukocytes/HPF with a positive chlamydia antigen test and no laboratory evidence of gonorrhea.

Patients with urethritis were randomized to one of the following five treatment arms:

1. Amoxicillin 3 gm, probenecid 1 gm, and clavulanate 125 ng, PO once (APC).
2. Amoxicillin 3 gm, probenecid 1 gm, clavulanate 125 mg PO once, and doxycycline 100 mg BID for 7 days (APC-D).
3. Gentamicin 240 mg IM once (GENT).
4. Ciprofloxacin 250 mg PO once (CIPRO).
5. Trimethoprim 320 mg/sulfamethoxazole 1600 mg PO for 2 days (TMPSMX).

Genital Ulcer patients: For each study participant in the genital ulcer disease group, location and size of the three largest ulcers were sketched onto a pictograph of the male genitals and characteristics of the ulcers such as tenderness, presence of yellow base, ragged edges, and induration were recorded. Ulcers were cleaned with sterile saline prior to specimen collection. A microscopic slide was applied directly to the lesion and fixed using acetone for direct immunofluorescent staining (DFA) of *Treponema pallidum* with fluorescein labelled specific monoclonal antibody (Baltimore Biologic Labs, USA). Swabs from the ulcer base were immediately rolled onto enriched gonococcal agar-based and enriched Mueller Hinton agar-based media in tandem for culture of *Haemophilus ducreyi*. Plates were stored in candle extinction jars before transportation to the laboratory for incubation in humid microaerophilic conditions at 34o C for 48 hours. They were inspected up to 4-5 days for growth of indicative colonies which were evaluated for characteristic cohesiveness when pushed over the agar surface, Gram stain, oxidase, and catalase.

GUD patients were randomized to one of the following treatment regimens:

1. Erythromycin 250 mg PO TID for seven days and benzathine penicillin 2.4 million units IM once (ERY250).
2. Erythromycin 500 mg PO TID for seven days and benzathine penicillin 2.4 million units IM once (ERY500).
3. Cotrimoxazole (Double Strength 960 mg) PO BID for seven days and benzathine penicillin 2.4 million units IM once (TMPSMX).
4. Ciprofloxacin 250 mg PO once daily for 5 days and benzathine penicillin 2.4 million units IM once (CIP5D).
5. Ciprofloxacin 500 mg PO once and benzathine penicillin 2.4 million units IM once (CIP1D).

For all study participants (urethritis and GUD), blood was collected by venipuncture for screening of sera with rapid plasma reagin (RPR) (Macro-Vue, Becton-Dickinson, USA). RPR reactive sera were diluted to determine endpoint reactivity and were tested with microhaemagglutination for *Treponema pallidum* (MHA-TP) (SeraTec Treponemal Antibody, Fujeribio, Miles, USA).

Patients were asked to return for follow-up 8-10 days after the initial visit. A physical exam was performed. For urethritis patients, the presence of discharge was evaluated and repeat urethral Gram stain and *N. gonorrhoeae* cultures were obtained. Chlamydia EIA's were repeated only if the patients symptoms persisted. For GUD patients, the degree of ulcer healing was documented and a blood sample for syphilis serology was collected. Detection of herpes antigen using EIA (Herpcheck, Dupont, USA) was carried out on non-healing ulcers. Upon completion of the study, linked anonymous testing for HIV antibodies using Wellcozyme EIA (Wellcome, UK) was carried out on stored sera. Reactive sera underwent repeat testing.

Results

A total of 1,295 patients were enrolled in the study; 517 patients with urethritis (U) and 778 with genital ulcer disease (GUD). GUD was responsible for 60% of all visits to this STD clinic during the period of the study. Basic demographic and behavioural data are listed in Table 1.

For the urethritis patients, purulent discharge was observed among 71.4% of the patients, 27.2% had mucoid discharge, and 1.3% had no visible secretion. Scrotal pain was reported by 29.1% of the patients and scrotal swelling by 1.8%. Four hundred fifteen (80.3%) of 517 patients had gonococcal urethritis, and 59 (11.5%) had nongonococcal urethritis. Chlamydia antigen was found in 26 (5.2%) of the 497 specimens tested; the total chlamydia and gonococcal co-infection rate was 2.4%. Gonococcal urethritis was diagnosed in 63.1% of patients with mucoid discharge compared with 86.3% in patients with purulent secretion (OR: 0.27, 95% CI: 0.16 - 0.45; p = .008). Sixty one (12.2%) of 502 evaluated sera were RPR reactive, the overall proportion of RPR and MHA-TP positive sera was 10.7%.

Among the GUD patients at enrolment, 328 (42.2%) presented with one ulcer, 192 (24.7%) with two, 123 (15.8%) with three and the remaining 134 (17.3%) with at least four ulcers. The mean diameter of all largest ulcers was 8.4 mm (median: 5 mm, range 1-90 mm). Swollen inguinal nodes were reported by 96 (16.6%) of 579 patients of which 70 (72.9%) were reportedly painful, 30 (31.2%) bilateral, and 6 (6.2%) suppurative.

Haemophilus ducreyi cultures were positive (growth on at least one of the two media) for 204 (26.2%) of 778 ulcer patients. A reactive RPR test was found in 137 (18.0%), positive syphilis serology (reactive RPR and MHA-TP) in 129 (17.0%) of 758 examined sera. Among 676 evaluated slides holding ulcer base material, 136 (20.1%) showed treponemes using direct fluorescent staining (DFA). Reactive syphilis serology and/or positive DFA was found in 228 (33.5%) of 681 patients. Fifty four (23.7%) of these 228 males with laboratory evidence of syphilis had also laboratory confirmed chancroid.

Clinical presentation, including ulcer characteristics, lymphadenopathy characteristics, and duration of symptoms, did not allow accurate classification by aetiology. However, 23 (21.5%) of 107 chancroid ulcers were friable compared to 12 (9.2%) of 130 syphilitic ulcers (OR: 2.69, 95% CI: 1.29-5.61). Sixty-four (59.8%) of 107 chancroid ulcers were recorded as deep compared to 63 (48.5%) of 130 syphilitic ulcers (OR 1.58, 95%C1: 0.94-

2.66; p=.08). Other differences in characteristics such as raised borders, seen more often in syphilitic lesions (45.4% vs. 34.6%), yellow base more common in chancroid lesions (66.4% vs 59.2%), and more than one ulcer associated more frequently with chancroid (66.9% vs. 58.6%), were also not statistically significant at the 0.05 level.

At follow-up, 63.8% (330/517) of urethritis patients and 70.2% (546/778) of GUD patients returned. Most of the behavioural and demographic characteristics did not differ between patients who returned and those who were lost to follow-up. However, the GUD patients who did not return for follow-up were significantly more likely to be circumcised (OR: 1.56, 95% C1: 1. 15-2.12; p = 0.005), to report having taken pills for their current GUD (OR: 2.22, 95% C1: 1.80-2.75; p = 0.001) or to report a lower number of days since their last sexual contact (p<.001). Patients with urethritis who reported a previous use of pills for the current episode were less likely to return for follow-up (OR: 0.59, 95%C1: 0.40-0.85; p=.005). There was no difference in follow-up rates between treatment arms for both urethritis and GUD patients. Mean duration of time between enrolment and follow-up visit was 9 days, median 8 days, range 1-46.

Cure rates for all urethritis patients based on the occurrence of laboratory documented urethritis at follow-up are shown in Table 2. Occurrence of NGU/PGU at follow-up was not lower in patients treated with APC-D, the only regimen with doxycycline. Chlamydia antigen was detected in only three (5.8%) of 55 patients presenting with persistent symptoms at follow-up visit. Cure rates defined by absence of laboratory confirmed urethritis at follow-up visit did not differ significantly between HIV seropositive (64.2%) and HIV seronegative patients (65%). Similarly, clearance of symptoms as reported by patients at follow-up did not differ significantly between HIV seropositive and HIV seronegative patients.

The effect of therapy and the cure rates based on laboratory-proven gonorrhea are as follows: APC-D (92.9%), GENT (95%), CIPRO (93.2%), APC (66.7%) and TMPSMX (48.3%). The treatment arm receiving trimethoprim/sulfamethoxazole was discontinued before the completion of the study due to the unacceptably low effectiveness rate.

For the GUD patients, response to therapy evaluated at follow-up visit is given in Table 3. Forty four males showed unequivocal evidence of treatment failure at follow-up (Delta-D<=0). Of those patients, 34 (77.3%) were HIV seropositive compared to 204 (55.9%) of the 365 males who responded best (Delta-D >=75). In logistic regression analysis, positive HIV serostatus and larger original diameter independently reduced the likelihood of healing (p = .003 and p = .007) respectively. Reported other treatment prior to the initial visit, GUD aetiology, and time between initial visit and follow-up visit did not influence cure. Herpes antigen was found in 6 out of 26 (23. 1 %) evaluated non-healing ulcers. Among the 44 treatment failures, 6 patients presented at follow-up with an ulcer which had increased by at least 100% (Delta-D <= -100), all were HIV seropositive, but none of the four males evaluated had a positive herpes antigen test.

HIV-1 antibodies were detected in 228 (44.2%) of 516 patients with urethritis and 445 (58.9%) of 756 GUD patients (p<.001). Among patients with urethritis, the highest HIV seroprevalence was found among patients with a positive syphilis serology (71.7%) compared to those with negative syphilis serology (40.9%) (OR: 3.6, 95% Cl: 2.01 - 6.65; p <.001).
Employed men were more likely to be seropositive than unemployed (47.5% vs 36% in urethritis patients, p=.020; 61% vs 52% in GUD patients, p=.016). Men reporting alcohol use showed a higher HIV rate than men who did not report alcohol use (55.2% vs 31.7% in urethritis patients, p<.001; 63% vs 53.6% in GUD patients, p=.016). Although reported sexual contact with a bargirl and lack of circumcision were associated with a higher HIV seroprevalence, these differences were not statistically significant at the .05 level.

Table 1.
Characteristics of patients presenting with either urethritis or genital ulcer disease at the STD clinic, Queen Elizabeth Central Hospital, Blantyre.

Mean age (years)	27.0
Mean years of education completed	5.5
Employed	69.7%
Married	46.2%
Single	46.8%
Divorced/widowed	7.0%
Circumcised	11.4%
Mean duration of symptoms (days)	12.4
Previously sought treatment	57.1%
from pharmacist	22.4%
from traditional healer/herbalist	28.6%
from other clinic/private doctor	16.4%
other types of care	23.0%
History of STD in past 2 years	23.5%
Sex with bargirl in last month	63.0%
>I sexual partner in last month	13.4%
Drinks alcohol	56.4%

Discussion

In this study, among patients presenting with complaints of urethral discharge and/or dysuria (urethritis), infection with *Neisseria gonorrhoeae* was confirmed in 80.3%. *Chlamydia trachomatis* (as determined by direct antigen detection using EIA) was not a major pathogen. A similarly low prevalence of chlamydia (3.4-4%) was found among pregnant women in Blantyre[14] . Among patients symptomatic at follow-up visit we also detected few carriers of chlamydia antigen. We did not screen for other organisms associated with NGU such as *Ureaplasma urealyticum and Trichomonas vaginalis.*

Although interpretation of laboratory diagnosis is complicated, we conclude that among the patients with GUD, chancroid contributed at least as much as did syphilis. Indeed, *Haemophilus ducreyi* was isolated for 26% of the patients but the sensitivity of this technique in our field conditions is unknown. Other investigators have reported that *Haemophilus ducreyi* culture detects at most 80% of chancroid cases[15]. In Malawi, isolation of *H. ducreyi* was newly introduced for the purpose of this study so that lack of experience might have affected yield. Furthermore, 60% of the men reported having sought treatment for their GUD prior to study enrolment. Although previous treatments did not result in cure, they could interfere with microbial recovery. We noticed on several occasions the use of topical applications which might hamper laboratory diagnosis.

Reactive syphilis serology and/or positive DFA was found in 33.5% and 11.7% of the GUD and urethritis patients, respectively. Sensitivity rates between 77% and 99% and specificity between 93% and 99% have been reported for RPR in primary syphilis[16]. Although direct microscopic examination of ulcer material in GUD patients is supposed to allow the most definitive

Table 2.
Cure rates of urethritis according to occurrence of laboratory confirmed urethritis at follow-up visit.

Therapy	Number of patients	% Cured[2]	% NGU/PGU[3]	% GU[4]
APC	71	56.3	15.5	28.2
APC-D	68	73.5	20.6	5.9
GENT	53	73.6	22.6	3.8
CIPRO	70	61.4	28.6	10.0
TMPSMX	35	51.4	5.7	42.9
Overall	297	65.6	20.2	14.2

Regimens:

APC	Amoxicillin 3 gm, probenecid I gm, and clavulanate 125 mg PO once
APC-D	Amoxicillin 3 gm, probenecid I gm, and clavulanate 125 mg PO once and doxycycline 100 mg BID for 7 days
GENT	Gentamicin 240 mg IM once
CIPRO	Ciprofloxacin 250 mg PO once
TMPSMX	Trimethoprim 320 mg/sulfamethoxazole 1600 mg PO for 2 days

[2]No Gram negative intracellular diplococci in urethral smear, <5 white blood cells per high power field (HPF), negative GC culture.
[3]Nongonococcal urethritis or postgonococcal urethritis because at least 5 WBC/HPF or chlamydia antigen positive and no gonococcal urethritis.
[4]Gonococcal urethritis defined as Gram negative intracellular diplococci in urethral smear and/or GC culture positive.

Table 3.
Response to therapy for all GUD patients categorized by % change of diameter for largest ulcer (Delta-D) at follow-up visit

Therapy	NO HEALING OR WORSE Delta-D <=0 N (%)	SOME HEALING Delta-D >0-<50 N (%)	MARKED HEALING Delta-D >=50-75 N (%)	ALMOST OR COMPLETE Delta-D >=75 N (%)
ERY250	14 (11.3)	8 (6.4)	21 (16.9)	81 (65.3)
ERY500	6 (5.4)	6 (5.4)	23 (20.7)	76 (68.5)
TMPSMX	14 (13.1)	5 (4.7)	15 (14.0)	73 (68.2)
CIP5D	6 (5.8)	8 (7.7)	13 12.5)	77 (74.0)
CIPID	4 (4.7)	6 (7.1)	12 (14.1)	63 (74.1)
Overall	44 (8.3)	33 (6.2)	84 (15.8)	370 (69.7)

Regimens:

ERY250	Erythromycin 250 mg PO three times daily for seven days and benzathine penicillin 2.4 million units IM
ERY500	Erythromycin 500 mg PO three times daily for seven days and benzathine penicillin 2.4 million units IM
TMPSMX	Cotrimoxazole DS (960 mg) PO twice daily for seven days and benzathine penicillin 2.4 million units IM
CIP5D	Ciprofioxacin 250 mg PO once daily for 5 days and benzathine penicillin 2.4 million units IM
CIPID	Ciprofloxacin 500 mg PO and benzathine penicillin 2.4 million units IM

diagnosis of treponemal infection, a negative DFA test does not exclude syphilis as age or condition of the lesion, prior treatment as well as suboptimal specimen collection and laboratory techniques influence the outcome of the test[16]. Under ideal conditions, routine syphilis screening should be performed on all STD patients not routinely receiving penicillin.

At enrolment, complaints of dysuria and/or urethral discharge among our study participants were highly correlated with laboratory confirmed urethritis. Thus, we recommend the syndromic approach for management of patients presenting with complaints of urethritis using a simple algorithm no laboratory analyses. Our findings are not applicable applicable to asymptomatic patients who do require laboratory diagnosis for detection. In the present study, the importance of using effective therapy was illustrated at follow-up where we documented that 85% of the men who had gonococcal infection reported complete resolution or substantial improvement of symptoms.

Clinical signs and history did not allow accurate differentiation between syphilis and chancroid in patients with genital ulcers. In industrialized as well as in developing countries, a diagnosis based on history and physical examination is often not reliable[17]. In Malawi, first line STD case management cannot include comprehensive laboratory diagnosis because of limited resources. Therefore treatment of GUD must cover both chancroid and syphilis.

Prior to this study, clinically diagnosed chancroid was treated with trimethoprim/sulfamethoxazole in Malawi. With a failure rate of 19%, this antimicrobial can no longer be used. Erythromycin and ciprofloxacin seemed to be equally effective for treatment of chancroid. Trimethoprim 320 mg/sulfamethoxazole 1600 mg PO for 2 days (TMPSMX) or a combination of amoxicillin 3 gm, probenecid I gm, and clavulanate 125 mg PO once (APC) were both ineffective for the treatment of gonococcal urethritis. The failure rates were 51.7% and 33.3% respectively. The three other evaluated regimens: APC-D, GENT, and CIPRO all appear equally effective for gonococcal urethritis with failure rates ranging between 5% and 7.1%.

It is plausible that the urethritis cure rates we observed represent an under-estimate of the real cure rates. Indeed, our treatment cure rates might have been higher if all enrolled patients returned for follow-up since patients with prompt response to therapy might have been less likely to return for follow-up. Among patients with genital ulcer disease (which usually needs more time to cure than urethritis) we observed an overall follow-up rate of 70.2%, compared to 63.8% among patients with urethral discharge (p= 0.02).

The only doxycycline-inclusive regimen, APC-D, failed to show a lower NGU rate at follow-up than the other regimens although it reduced urethral symptoms best according to patient reporting. Poor response of Chlamydia trachomatis-negative NGU to antimicrobials[18] which are active against C. trachomatis has been described.

As expected, HIV seroprevalence was high among these patients. Higher socioeconomic status as measured by husband's education, was a risk factor for HIV infection among pregnant women in Blantyre[14]. Among our STD patients, we found that employed men and men reporting current alcohol use were at increased risk of being HIV seropositive. We also documented that more than two thirds of the male urethritis patients who had a positive syphilis serology were HIV seropositive. Although our sample size does not allow definitive conclusions, the finding that cure of uncomplicated gonorrhoea was not affected by concurrent HIV infection is encouraging. Our results also confirm the internecine HIV-GUD link: HIV infection clearly impaired healing of GUD and GUD was a risk factor for HIV. Urethritis patients who were found to be syphilis seropositive had no visible ulcer but may have had ulcers in the past. They were significantly more likely to be HIV seropositive compared to urethritis patients with a non-reactive syphilis serology.

In this study, over half of all participants presenting at the public STD clinic (where all services and drugs are provided free of cost) had first sought care elsewhere for their episode of an STD. Although we can only speculate about the reasons for this, it does demonstrate the frequency of inadequate care at the first visit. Among our study participants who had sought care elsewhere, more than one third reported having consulted a traditional healer or herbalist. Traditional healers have been reported to be perceived as less expensive,[19] more sympathetic, more confidential, and more easily accessible[19]

STD/HIV prevention and control efforts should be assertive and comprehensive: all members of the medical community need to be informed of the importance of STD control and of the recommended treatment of STDs. Educational campaigns targeting pharmacists, traditional healers/herbalists to ensure referral for proper STD care, as well as outreach to commercial sex workers and clients in bars should be launched. Presumptive and possibly periodic mass therapy of high-risk core groups along with educational efforts to promote safer behaviour should be earnestly considered for rapid GUD contaminent. These proposed measures might sound unrealistic for health professionals struggling with limited resources in Malawi. Immediate massive endeavours needed in Malawi, as in other African countries harshly hit by the HIV pandemic, far exceed national budgets and resources and will require international financial solidarity.

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