

Level of understanding of co-trimoxazole use among HIV infected, recurrent pulmonary tuberculosis suspects at a national referral tuberculosis clinic in Kampala, Uganda: a qualitative analysis.

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Abstract

Background: Co-trimoxazole use is the standard of care for preventing *Pneumocystis jirovecii* pneumonia in sub-Saharan Africa but implementation remains slow. Co-trimoxazole is self-administered with uncertain adherence. Knowledge of co-trimoxazole use among HIV infected persons is unknown.

Objectives: To assess knowledge, attitudes and practices of co-trimoxazole use among HIV infected adults evaluated for recurrent PTB in Kampala, Uganda.

Methods: A qualitative study utilizing 5 focus group discussions among 30 HIV infected PTB suspects at the national referral tuberculosis treatment centre in Kampala.

Results: Males and females had similar median ages. 80% were currently on co-trimoxazole and 50% of participants were on HAART. Majority of participants defined co-trimoxazole as an analgesic. Few noted co-trimoxazole was a drug to treat cough and chest pain. However, few responses revealed that co-trimoxazole prevents opportunistic diseases among PLHIV. Most of participants believed HAART and anti-TB drugs work as co-trimoxazole thus it should not be taken together with them. This belief may lead to increased risk of opportunistic infections, morbidity and mortality.

Conclusions: We revealed gaps in understanding of co-trimoxazole use among study participants. We therefore recommend that more facts about co-trimoxazole as prophylaxis against *P. jirovecii*, bacterial and diarrheal pathogens should be incorporated in VCT fact sheets.

Key words: Recurrent tuberculosis; HIV; Co-trimoxazole use; Chemoprophylaxis; Adherence

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Introduction

Co-trimoxazole prophylaxis among children, adults and adolescents living with HIV has been the standard of care for many years in high income countries as compared to resource-limited settings¹. Co-trimoxazole, a fixed dose combination of sulfamethoxazole

and trimethoprim, is a broad spectrum antimicrobial agent that targets a range of aerobic gram-positive and gram-negative organisms, fungi and protozoa. Providing co-trimoxazole has been part of the standard of care for preventing *Pneumocystis jirovecii* pneumonia and toxoplasmosis in the sub-Saharan Africa since 2000 but the implementation has been slow^{2,3}. Co-trimoxazole prophylaxis has also been found to reduce mortality among patients on HAART⁴.

Studies in Mulago Hospital revealed that the prevalence of HIV-infection among new tuberculosis cases decreased from 67% in 1989⁵ to 19% in 2008⁶. WHO estimates the burden of TB/HIV co-infection at 19,836 Ugandan adults in 2010⁷. Progressive drop of CD4 T cells below 200 cells/ μ L increases the risks for oppor-

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tunistic infections like PCP^{8,9} and bacterial pneumonia^{10,11}.

All HIV infected individuals are offered co-trimoxazole prophylaxis and this is in line with the WHO recommendation^{1,12}. Routine counseling and testing (RCT) is offered to every patient with confirmed tuberculosis¹³. In 2009, 17131 of the 44335 (54%) TB cases in Uganda tested HIV positive of whom 86% were initiated on co-trimoxazole chemoprophylaxis and 22% were started on HAART¹⁴. Co-trimoxazole is self-administered and therefore adherence cannot be ensured. The extent of knowledge, attitudes and practice of HIV infected persons on co-trimoxazole is also unknown. This study was therefore undertaken to investigate co-trimoxazole use among HIV infected adults being evaluated for recurrent PTB in Kampala.

Methods

Study design

As part of a large study of prevalence of co-morbidity among HIV-infected recurrent PTB suspects¹⁵, we conducted a qualitative cross sectional evaluation of perceptions about co-trimoxazole use.

Study setting

This study was conducted at the national referral tuberculosis treatment centre, Mulago National Referral and Teaching Hospital, Kampala. Between 3500 and 4500 tuberculosis patients (70-75% new cases and 25-30% recurrent cases) are treated annually at this TB treatment centre. Current statistics show that 19% of TB cases treated here are HIV co-infected⁶. New TB cases with HIV co-infection are treated with four anti-tuberculosis drugs: isoniazid, rifampicin, pyrazinamide and ethambutol for two months of intensive phase followed by isoniazid and rifampicin for four months.

Study population and sample size

Five FGDs each consisting 6 participants (N=30) were conducted at the tuberculosis treatment center to determine the knowledge, attitudes and practices towards co-trimoxazole use among people with HIV. HIV infected patients who presented with pulmonary symptoms of cough for two weeks or more being evaluated for recurrent tuberculosis were screened for Pneumocystis jirovecii infection. Other eligibility criteria included: (a)

smear negative sputum for acid fast bacilli (AFB); (b) willingness and consent for participating in the study; (c) 18 years or older; (d) willingness and consent to undergo induced sputum procedure.

Recruitment and data collection procedures

Participants were selected from a list of those enrolled in the study aiming for equal representation by gender. They were contacted by cell phone and the next immediate study participant was chosen if the randomly selected one was unavailable. FGDs were conducted in English or Luganda (local dialect), the two most widely spoken languages in the study area. Two study staff conducted each FGD lasting approximately one hour. FGDs were tape recorded and transcribed into MS Word. The domains covered were: participant's knowledge and awareness of co-trimoxazole use, perceptions about who should be given co-trimoxazole, whether HIV patients with or without TB should take co-trimoxazole, relationship between HIV, TB and co-trimoxazole, duration of use, experiences taking co-trimoxazole and its' side effects.

Ethical considerations

This study was approved by the Makerere University Medical School Ethics and Research Committee and the Uganda National Council for science and Technology. Written informed consent was obtained from all study participants

Results

The majority of participants were males (57%) and their median ages was similar for both males 39 (IQR37-44) and for females 40 (IQR 32-44) years. There were also no significant differences in education, marital status and taking co-trimoxazole. Males (88%) compared to females (62%), reported being employed although this difference was not statistically significant (X2 test = 2.93, p = 0.190). Meanwhile more females (62%) compared to males (42%) were taking ARVs although this was not statistically significant, (X2 test = 1.22, p = 0.462). Of note however, female participants had a statistically significant higher median CD4 T-cell counts of 457 (IQR 319-636)/L than males CD4 count of 207 (IQR 38-451), p= 0.021 (Table 1).

Table 1: Clinical and socio-demographic characteristics of study participants by gender, Mulago Hospital, Kampala Uganda

Characteristics	Gender		X2 Test	P-value
	Male n=17 (%)	Female n=13 (%)		
Employment status employed	15 (88)	8 (62)	2.93	0.190
Education Not beyond primary level	13 (76)	10 (77)	0.01	1.000
Marital status married	14 (82)	10 (77)		1.000
Median CD4 T-cell count/L (IQR)	207 (38-451)	457(319-636)	0.021	7.03
Taking co-trimoxazole On ARV	13 (76)	11 (85)	0.672	0.31
Mean age (years)	7 (41)	8 (62)	1.22	0.462
	39(37-44)	40(32-44)	0.29	0.715

There were no significant statistical differences in clinical and socio-demographic characteristics by gender except the median CD4 T-cell counts (X2 test =7.03, p=0.021).

Participant's knowledge and awareness of co-trimoxazole

All participants had ever heard about co-trimoxazole and reported to have used it to treat symptoms like cough at least once in their life time, as one participant noted:

“co-trimoxazole is everywhere in our hospitals and clinics so I think everyone has heard about co-trimoxazole”. Co-trimoxazole appears to be widely available according to the participants. majority described co-trimoxazole as an analgesic (Table 2).

Table 2: Responses of study participants on their understanding the term co-trimoxazole in Mulago Hospital, Kampala Uganda.

Responses	Number of times	Percentage
It is a pain killer	15	51.7
It is an antibiotic that treats any disease	2	6.9
It is any kind of treatment	1	3.5
A drug for cough and chest pain	1	3.5
A drug that protects us HIV-positive from other diseases	10	34.5
Total	29	100

Some participants reported co-trimoxazole to be medicine given to those with decreased immunity to prevent them from getting opportunistic infections associated with HIV/AIDS. The quotes below further illustrates this observation:

“When they found out that I was HIV positive, health workers started me on co-trimoxazole and what they told me was co-trimoxazole is going to help in protecting me from diseases like malaria, diarrhea and cough. So co-trimoxazole is medicine given to those with low immunity like me.”

Who should be given co-trimoxazole?

Majority of participants believed that co-trimoxazole was for treatment of HIV positive patients.

“Co-trimoxazole is always given to HIV positive patients to protect them from all illnesses since their bodies are weak.” as one participant noted.

A few thought co-trimoxazole should be taken by anybody regardless of HIV status as one participant noted:

“... everyone should swallow co-trimoxazole whether HIV positive or not because we are told that co-trimoxazole prevents the body from becoming weak...”

Should HIV patients with or without TB take co-trimoxazole?

Majority of patients believed co-trimoxazole use by HIV-infected persons is important since it prevents other opportunistic infections. For those participants who were co-infected with both TB and HIV, majority noted that co-trimoxazole should be taken regardless of the disease they had. Notably, some participants thought there is no need to take co-trimoxazole because they perceived it and the TB drugs to treat the same diseases. Thus taking co-trimoxazole and anti-TB drugs would be wastage and an increase on the pill burden. One participant believed there is no need to take co-trimoxazole with anti-TB drugs since health workers never instructed him to do so during the period he was on TB treatment although he is HIV infected as expressed below:

“No, he/she should not take it because co-trimoxazole has nothing to do with TB. When I was found to have TB, health workers never instructed me to take co-trimoxazole. So I think this person should only take TB drugs and ARVs only.”

Relationship between HIV, TB and co-trimoxazole

Most respondents believed there is a link between HIV and TB, attributing this to the high prevalence of TB among HIV infected patients as expressed below:

“Before I was HIV positive I used to hear about TB but after becoming HIV positive I developed TB and many of my HIV positive colleagues in the clinic I attend developed TB. This therefore means TB is a common disease amongst us (HIV positive persons).”

Some respondents believed there is no relationship between the two diseases suggesting that TB is a disease which can affect both HIV infected and non-infected persons.

“Very many people out there have been diagnosed with TB yet they are not HIV positive so there is no link between TB and HIV because even those who are not HIV positives can also be affected by the disease.”

Should an HIV patient on anti-TB treatment also take co-trimoxazole?

Majority of the participants reported that HIV patients on TB treatment could take co-trimoxazole with anti-TB drugs attributing this to the perceived preventive activity of co-trimoxazole and reducing the incidence of opportunistic infections among PLHIV. However, some respondents believed even though co-trimoxazole is very important, the immune status of the individual is critical in the decision to prescribe co-trimoxazole to someone as quoted below:

“...it depends on the strength of the body because I was stopped from swallowing co-trimoxazole when I was taking TB medicine. The health workers told me my body may not withstand the strength of both TB medicine and co-trimoxazole and I was left on TB medicine until the treatment was over then I resumed my co-trimoxazole.”

Notably, some respondents believed there is no need for HIV-infected patients to continue taking co-trimoxazole along with TB drugs because they perceived both to contain the same active ingredients for treating chest infections.

Should HIV patients on ARVs also take co-trimoxazole?

Majority of the participants thought it was important

for a patient to take co-trimoxazole and ARVs simultaneously. Respondents believed that co-trimoxazole would continue protecting the body from other diseases as reported below:

“It is very important for an HIV patient to continue with co-trimoxazole although he/she is swallowing ARVs. For example; I was put on ARVs but I was encouraged by the health workers to continue with co-trimoxazole because co-trimoxazole was to prevent other diseases like diarrhea which may affect my body and am now fine.”

Some respondents felt it is not necessary for HIV infected persons to continue with co-trimoxazole. They believed that ARVs are as effective as co-trimoxazole. Thus if an HIV infected person were to continue with the two kinds of medicine, this would be increasing their pill burden.

For how long should one take co-trimoxazole?

Majority of the participants never knew for how long one should take co-trimoxazole. Some believed co-trimoxazole should be taken as a lifelong treatment. While others thought that health care workers should determine the duration.

“I know we are supposed to take co-trimoxazole forever. But I think at one moment my health workers may decide to put me off this medicine especially when my CD4 cells have gone high because the same thing was done to my friend and she is now fine,” as explained by one participant.

On the other hand, some participants believed that someone should stop taking co-trimoxazole if he or she develops side effects particularly when the side effects are severe and can lead to death as expressed below:

“When I was started on co-trimoxazole a few days later I developed a very severe skin rash and burns all over the body and after talking to the health workers, they decided to stop me and instead I was given another medicine (dapson) which I am currently using.”

Notably, some participants believed a patient could stop at any time he/she feels better.

Experiences with co-trimoxazole

All participants reported improvement in their quality of life after taking co-trimoxazole, as shown by significant reduction in pain and incidences of opportunistic infections. However, some respondents expressed the view that despite perceived improvement in their lives, they still face a challenge of taking co-trimoxazole every day as this is cumbersome.

“Co-trimoxazole has improved our lives, for example I used to feel weak, headache and fevers but currently I am fine. However, this does not mean that it is easy to swallow co-trimoxazole regularly. Imagine every day I must swallow two tablets; for sure this makes it very cumbersome.”

Side effects of co-trimoxazole

Majority of the participants had not experienced side-effects of co-trimoxazole although they heard from their friends. The commonest side effects heard included skin rash, itching of the body and burning sensations in the stomach. Many of respondents, who had not experienced side-effects of co-trimoxazole thus far, expressed their fear of risks of adverse events of co-trimoxazole in future they believed as a consequence of its long term use.

What happens if co-trimoxazole is not taken every day?

Most participants believed that it is not good to stop taking co-trimoxazole. They believed that without co-trimoxazole, opportunistic diseases will infect them and this will increase the incidences of morbidity and possibly mortality among them. The quote below illustrates this perception.

“I have seen many of my colleagues, who stopped swallowing co-trimoxazole and developed diseases and later died.”

Discussion

The study established that all participants had ever heard about co-trimoxazole and majority had taken it. Majority demonstrated that co-trimoxazole prevents opportunistic infections among HIV infected individuals with low immunity. They also indicated that HIV and TB were linked, and co-trimoxazole could be used concurrently with anti-tuberculosis medications and HAART. Most respondents were also aware of the need for daily use. Similarly, most had ever heard of side effects of

co-trimoxazole and were aware that treatment had to be discontinued if side effects events were experienced. However there were mixed views about duration of co-trimoxazole use. Some participants believed that co-trimoxazole use was lifelong treatment while others believed health care workers determined the duration. In this study, the significantly low CD4 T-cell counts among males may imply that they present to health care facilities late and therefore more likely to be very sick. Moreover in the main study (15), 8.3% (8/96) of males had *P.jirovecii* as compared to 4.9% (4/82) female although this study was not designed to address this aspect of the finding. Further studies in this setting show that males have generally poorer health seeking behavior compared to females^{24,25}.

Despite overall wide knowledge, few respondents had important knowledge gaps and misconceptions resulting from real life experiences of co-trimoxazole use. For example, some participants perceived co-trimoxazole as an analgesic. Others believed that co-trimoxazole is exclusively for HIV-infected people. The later belief is quite positive for encouraging the use of co-trimoxazole by HIV-infected individuals. The benefit of this is consistent with findings of one study conducted in Uganda and Zimbabwe⁴. There were divided views among participants whether or not to administer co-trimoxazole to HIV infected patients taking both HAART and anti-tuberculosis drugs. Those participants who support concurrent use of co-trimoxazole believe that co-trimoxazole does reduce the incidents of opportunistic infections among PLHIV. This shared view is encouraging and consistent with WHO recommendations on use of co-trimoxazole by PLHIV¹. Similarly, several studies have shown that prophylaxis with co-trimoxazole reduced mortality in HIV positive adults with confirmed tuberculosis¹⁶⁻¹⁹.

Those who disagree with concurrent use of co-trimoxazole by PLHIV on both HAART and anti-tuberculosis therapy argue that anti-tuberculosis drugs work like co-trimoxazole, hence it is inappropriate to take it. Anti-tuberculosis drugs including rifampicin, isoniazid, ethambutol, streptomycin and pyrazinamide are used to treat active tuberculosis. This means that these drugs are active mainly against *M. tuberculosis* microorganisms that cause tuberculosis disease than other opportunistic diseases. Meanwhile co-trimoxazole is used to prevent and treat other opportunistic diseases such

as bacterial pneumonia, *Pneumocystis jirovecii* pneumonia, toxoplasmosis, *Isospora* berri diarrhea and non-typhoidal salmonellosis among PLHIV²⁰⁻²³. Therefore if these participants stopped taking co-trimoxazole, the risks of infection with opportunistic pathogens, incidence of opportunistic diseases and mortality would increase among them¹⁹. A well designed information, education and communication (IEC) package needs to be put in place by the MoH as an intervention strategy to address this misconception and knowledge gaps.

Although majority of participants thought that co-trimoxazole should be taken by all HIV-infected people on HAART, there was significant misconception that co-trimoxazole should not be taken for long because HAART works like co-trimoxazole. These knowledge gaps would likely contribute to low co-trimoxazole adherence which can lead to increase of opportunistic diseases.

There has been evolving guidelines on when to stop co-trimoxazole prophylaxis. Previous WHO guidelines recommend that co-trimoxazole prophylaxis can be stopped if one is on HAART and CD4 is above 200 cells/ μ L for 6 months¹. Meanwhile the ministry of health (MoH) guideline recommends co-trimoxazole prophylaxis for life in the absence of HAART, but inconclusive for patients on HAART and CD4 count >200 cells/ μ L¹³. Although some study participants expressed the view that co-trimoxazole prophylaxis has improved their health by reducing the incidences of opportunistic infections, many of them face challenges. One of the biggest challenges is adherence to long term medication. In this study, the following factors were identified as contributing to negative influence on adherence: cumbersomeness to take co-trimoxazole daily, side effects of co-trimoxazole and advice from relatives to discontinue administration of co-trimoxazole. Low adherence to co-trimoxazole increases risk of development of resistance by microorganisms. Given the emergence of resistance to trimethoprim-sulfamethoxazole among many bacteria²⁶, and a more recent study that found co-trimoxazole resistance to *Streptococcus pneumoniae* of 91% and to non-typhoidal salmonella of 67%²⁷, concern has focused on the potential development of resistant *Pneumocystis*. In the Uganda context, co-trimoxazole is widely available in the country. Studies on use of medicines especially antibiotics use in Uganda²⁸ show that, drugs including antibiotics,

are widely available over the counter with or without prescriptions in pharmacies and most drug shops. We also have drug hawkers within the public commuter taxi parks and bus stations who likewise advise patients on what medication to take including antibiotics²⁹. These situations may lead to irrational use of antibiotics including co-trimoxazole. The prescription practices by clinicians in Uganda may also encourage irrational antibiotic use despite the existence of national standard treatment guidelines on rational drug use^{30,31}. In terms of administration of co-trimoxazole concurrently with anti-tuberculosis therapy in HIV co-infection with TB, majority of the participants believed that co-trimoxazole should be taken since it prevents other diseases. This particular belief is very positive because it encourages co-trimoxazole use among them.

The study draws strength from use of FGDs because they were helpful in interpreting previously obtained quantitative results and diagnosing the potential problems with a new programme or service: the number of participants on co-trimoxazole and co-trimoxazole role out programme, in this case.

Limitations

Limitations of the study include the following: selection of respondents was not stratified by duration of HIV infection, co-trimoxazole and HAART use. And patients with recurrent PTB are likely to have persistent coughs and coughs due to viral pathogens, making it hard to appreciate the role of co-trimoxazole in improving their quality of life.

Conclusion

There are information gaps in the use of co-trimoxazole among study participants. The belief that HIV infected adults can stop taking co-trimoxazole at any time could lead to low adherence. Females had statistically significantly higher median CD4 T-cell counts than males. For policy and practice, the following recommendations are therefore proposed: as part of a comprehensive HIV Health Care package, all HIV and TB clinics should have IEC materials that address benefits of co-trimoxazole prophylaxis and warning signs of side effects, adherence, concurrent use with other medications like HAART, anti-tuberculosis drugs and drugs that treat other opportunistic infections.

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