

HATiP

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Cotrimoxazole prophylaxis

By Julian Meldrum, with contributions from Dr Vijay Anthony Prabhu (India), Dr Adama Ndir (Senegal), Dr Leon Regensberg, Dr Douglas Wilson (South Africa), Molly Tumusiime (Uganda) and Prof Brian Gazzard (UK).

This article reviews the place of co-trimoxazole prophylaxis (CTX) in expanding treatment for people with HIV. It asks who could benefit from CTX prophylaxis. It sets out some issues for individuals and communities in supporting CTX use. It looks at issues raised where CTX is promoted in the absence of access to antiretrovirals for HIV treatment (ARVs) and finally at how it might be used to support the introduction of ARVs when these become available.

Who could benefit from CTX prophylaxis

Many treatment guidelines support the use of co-trimoxazole prophylaxis (CTX, Septrin, trimethoprim/sulfamethoxazole) in people with HIV, to prevent or control a wide range of infections including bacterial pneumonias and gastrointestinal diseases, Pneumocystis pneumonia (PCP), Toxoplasma gondii, and malaria. However, it is important that international guidelines are reviewed nationally. Where there is clear evidence of widespread bacterial resistance to CTX or where malaria treatment is heavily reliant on Fansidar (sulfadoxine/pyrimethamine) - as in Malawi, for example - CTX may be restricted in its use. (Co-trimoxazole and Fansidar are closely related drugs, so exposure to CTX can select malaria parasites that are resistant to Fansidar.)

Where CD4 counts are available, and where co-trimoxazole preventable diseases are a significant cause of morbidity, it has been recommended by WHO that adults with CD4 counts below 500 should be offered CTX.

More conservative guidelines follow US/European practice (based on PCP prevention in adults) adopting a CD4 count of 200 as the threshold below which CTX is offered.

However, in most places, CD4 counts are not yet affordable for most people with HIV. Even people on ARVs may rarely receive CD4 counts.

One benefit of CD4 monitoring is that it provides a basis for stopping CTX: when the CD4 count is rising, and is above 200, then it is probably safe to discontinue CTX provided that clinical monitoring is frequent and thorough enough to pick up and treat any infections. The real benefit of monitoring is that it provides a framework for supporting adherence to ARVs and other treatment, and here it may be that clinical monitoring - checking body weight, discussing symptoms - will be as valuable as any clinical tests.

People with HIV who are coinfecting with TB are highly vulnerable to bacterial respiratory infections and South African guidelines advise that they are offered CTX regardless of CD4 count.

Babies born with HIV (confirmed using PCR or p24 antigen tests, or with symptomatic HIV disease) may also benefit from CTX, since PCP is a major cause of illness in children with HIV worldwide, especially under the age of 15 months.

TUMUSIIME:

The following strategies have been adopted in my place of work (an exclusively HIV/AIDS care organisation in Uganda). All children known to be HIV positive (confirmed HIV positive) are on daily co-trimoxazole, and all adults whose CD4 counts are known to be below 200 are also on daily co-trimoxazole prophylaxis (for adults it

is on clinical presentation and where possible confirmed in the laboratory).

Talking of CD4 counts as determinants for starting on co-trimoxazole prophylaxis is ideal but a luxury in a resource constrained setting like ours and more so in children who are orphaned with no one to meet the costs!

WILSON:

It is possible to identify patients with significant immune suppression using the WHO staging system, which does not rely on CD4 counts - the presence of oral thrush and oral hairy leukoplakia are exceptionally quick and useful ways to identify patients who would benefit from co-trimoxazole. In addition all HIV-infected patients diagnosed with tuberculosis should be started on long-term co-trimoxazole.

REGENSBERG:

On our programme [Aid for AIDS; South Africa's largest private-sector AIDS treatment programme], all patients with CD4 counts of less than 200, as well as patients with co-existent TB, an AIDS-defining illness, unexplained significant weight loss, chronic diarrhoea, oral hairy leukoplakia or thrush, are encouraged to take co-trimoxazole 480-960mg daily. The lower dose has fewer side-effects, but most studies have been with the higher dose.

PRABHU:

We do not advocate any primary prophylaxis, simply because we are unsure if the patients will even return regularly for follow up, since most patients travel long distances to access their primary HIV care providers. It is simpler to treat episodes as they develop. Secondary prophylaxis is advocated, here again only in select motivated patients. In India, the costs of CD4 counts are borne by the patients, unless they are part of certain research studies conducted by a few central government organisations. The vast majority of patients do not get funded. There is nobody to pay for these tests other than the patient - there is no winning argument. Economics and financial viability of the patients is largely the deciding factor.

Managing problems, counselling individuals

The main hazard of co-trimoxazole is a rash, which can occasionally be life-threatening, linked to the sulphonamide component of the drug. While this rash may already be familiar within the community, it is very important that the risk is discussed with the patient before the drug is started. Obviously, if the patient has previously been treated with a sulphonamide drug (such as co-trimoxazole or Fansidar or dapsone) and experienced such a rash, then there is a need for caution in giving co-trimoxazole at all. Other contra-indications include evidence of severe liver or renal damage. (There is further information on side effects on www.aidsmap.com at the URL given at the end of this article.)

REGENSBERG:

The commonest adverse effect and reason for discontinuing the drug we have encountered is rash. Hypersensitivity to the sulphonamide component appears to be more common in advanced HIV infection. Provided the reaction is not life-threatening, co-trimoxazole can be continued with antihistamine cover. Desensitisation is also possible using increasing doses of the drug with antihistamine cover and careful observation. Although dapsone 100mg daily can be used as an alternative, co-trimoxazole remains the drug of choice to prevent several important opportunistic

infections. If the allergic reaction was severe (Stevens-Johnson syndrome) neither dapsone nor co-trimoxazole should be used again.

GAZZARD:

Management of rashes depends very much on the drug being used. With co-trimoxazole I think they can be told to carry on with the medicine and seek help if it gets worse or it does not resolve in a week or so. [If it does not, then] I personally think with cotrimoxazole, probably the best answer is to switch to dapsone rather than try desensitization.

PRABHU: If rashes develop, then a careful history and examination is performed to rule out primary HIV-related pruritic papular dermatitis. They are encouraged to continue with co-trimoxazole if this is the case.

Community involvement

At last year's International Conference on AIDS in Barcelona, community organisations from Uganda and Thailand reported on the success of their efforts to promote the uptake of co-trimoxazole as part of their work to support people living with HIV.

This seems sensible in terms of maximising the involvement of people with HIV in promoting treatment and supporting others who are taking it. It also provides treatment in a way which develops capability to provide additional treatments, as and when they are necessary and resources allow. But how can this be reconciled with very stretched clinical resources?

TUMUSIIME:

Family carers have done a lot in the promotion of adherence to medications. This follows training of family carers in home basic nursing skills with a component of drug management and administration at home. This strategy needs to be multiplied elsewhere as it has shown good results.

GAZZARD:

In terms of mobilising the community, I think this is of the utmost importance. I think TASO [one of the organisations which reported in Barcelona] is an example of good practice in Uganda. I think involving faith communities, particularly, with health groups is vital. I also think that involving traditional healers to work alongside western medicine is an example of good practice.

PRABHU:

Getting the community to be involved in India is very difficult. There are a large number of barriers to be overcome. Why should they help an HIV-positive patient? The moment one comes to know of HIV status, discrimination and stigmatisation results. People lose their jobs, neighbours ask patients to move out, wives desert their husbands and vice versa. Unlike cancer, where support of family and community is given, without even being asked for, in HIV, the very mention of the word draws loud oohs and a total silence thereafter.

Initiation of patient self help groups and home visits by people living with HIV is difficult to sustain. In Indian villages, such visits are not encouraged, as the entire village community comes to know of the well guarded secret and they are socially, economically and emotionally ostracised. Nobody wants anyone else to know their status. However, patients do not mind attending HIV clinic camps or out-patient departments, where their status is kept confidential and regular clinical monitoring and counselling is done.

In small Indian villages much of the primary health care is carried out by general medical practitioners, who have been in the village for decades and know all the inhabitants. Educating and training these practitioners would be beneficial to create a continuum of care. Communication channels need to be kept open at all times to clear any doubts these physicians may have about the management of a particular case.

Most NGOs conduct HIV screening camps/awareness programmes in sharply demarcated urban and rural areas. Linkage and networking of these NGOs is lacking. Duplication of effort and wasted resources result.

EDITOR:

In Ndola Diocese, Zambia, agencies concerned with the care of people with AIDS hold monthly meetings, rotated between the different locations where they are based, to ensure efficient referral between them and avoid the kind of waste described. There are many examples of good practice that could be adopted: the challenge is to spread the word and find advocates in the right places, prepared to ensure that they are.

The idea of a 'clinic camp' is an extension to HIV of a well-established model for providing other kinds of specialised medical care across large areas where transport is limited, to take specialists to the people rather than expecting people to travel long distances to see specialists.

Promoting CTX in the absence of ARVs

Should this be done? Can it be done? How can it be done? Is it a step towards, or a step away from effective treatment?

The widespread use of CTX to prevent PCP in North America and Western Europe was associated with a marked decline in mortality among people with HIV, which preceded the introduction of ARVs.

This experience, confirming what had been seen earlier in clinical trials, prompted a range of studies of different antibiotics, antifungals and antivirals to prevent diseases. As ever-lower CD4 thresholds were crossed, the diseases to be prevented would multiply, including candidiasis, atypical mycobacteria, and cytomegalovirus, requiring an increasingly complex and toxic cocktail of treatment.

The limitations to this approach are obvious and no physicians who are now able to prescribe ARVs are prepared to advocate it as a serious alternative to ARV treatment of HIV disease.

Using CTX alone, as an "affordable" public health measure in settings where ARVs are still not accessible to people or for people who cannot afford ARVs, is very difficult to sustain. Some people feel they are being "fobbed off" with something that is cheap and second-rate and can experience this as an insult, no matter how well it is intended. Worse, health-care providers can feel the same way. There is a world of difference, for providers as well as patients, between treatment that is just "delaying the inevitable" and something that is visibly "making people better".

Since CTX does NOT prevent fungal infections, especially candida, which are common and have an immediate impact on people's wellbeing, the perception can easily arise that it "doesn't work". Also the side effects - in particular, sulphonamide skin rash, may be all too familiar and may deter some people from taking them, even if they have never themselves experienced those side effects. The answer to this is (a) education and (b) specific treatment for conditions like oral thrush. Offering CTX to patients who (already) have oral thrush, following successful treatment with

antifungals, could be one way to counter a reputation for CTX as a "failure" in that situation.

Since CTX is familiar as a treatment for infections associated with symptoms, often available cheaply without prescription, there can be an assumption that as soon as any symptoms have gone away, it can be discontinued. Clinics faced with large numbers of patients have limited time to explain that CTX prophylaxis is something different, and unless this message is communicated clearly and through multiple channels, including public education, it will not get across. Unfortunately, if the drug comes to be seen as "something that people with HIV take" this generates its own problems, where HIV status is still highly stigmatised. As with so many other diseases, effective treatment - which currently means ARVs - is likely to be the one truly effective and sustainable way to destigmatise HIV.

While there is not complete agreement on the value of primary prophylaxis, most are convinced that CTX can save lives, even before ARVs arrive. When ARVs do arrive, they too will need to be taken consistently, whether or not people feel unwell. People with HIV and their physicians in some communities are clearly making much more use of CTX than others, and some may be making more effective use of it. But whether it is useful may vary, depending not only on patterns of disease but also on the patterns and structures of clinical services provided for people with HIV.

TUMUSIIME: Patients taking co-trimoxazole as a prophylaxis here in Uganda have not expressed any fatigue in taking this drug so far, but the problem lies with us, the health care providers.

Due to the overwhelming numbers of patients to see, health care providers rarely have time to give information comprehensively on duration, when to replenish the home stock, action and possible side effects. This has some adverse effects, e.g patients relate co-trimoxazole to curative properties especially in the treatment of cough, so when the cough (or any other bacterial infection) resolves the patient stops taking the co-trimoxazole.

Under-staffing in health care settings gives no room for ongoing support counselling that is appropriate for someone with a chronic illness on taking medications for life, so patients on co-trimoxazole give themselves a break without knowing what they are doing!

Strategies to increase uptake and adherence to co-trimoxazole prophylaxis should include information-giving at all points of contact in a health facility. The doctors, nurses, pharmacy staff and counsellors should reinforce adherence messages at all those different levels.

Treatment advisory/counselling services will have a very important role to play especially in the administration of long term medications like ARVs and co-trimoxazole prophylaxis. They should be incorporated in the essential health care package for all PLWAs.

NDIR:

In our Senegalese context, there is high uptake for co-trimoxazole. The reason is simple: before ARVs arrived, cotrimoxazole was widely used to treat bacterial infections. It is familiar to patients and it is not uncommon to see them take it without prescription when they feel sick. However, this has caused bacterial resistance in some cases.

So use of cotrimoxazole as prophylactic drug is not a big problem for our patients but correct use may be one. Indeed, we generally have to face two situations: patients who often need to take cotrimoxazole whether or not they feel unwell, patients who think that if they don't take cotrimoxazole, then they'll feel sick.

Now, [according to WHO guidelines] cotrimoxazole must be taken only when CD4 cell counts are less than 500/mm³.

So better monitoring of this prophylactic drug for a good compliance could be one of the best solutions. The fact remains that co-trimoxazole is not sufficiently available in care services.

I agree that if people can show that they can take co-trimoxazole correctly according to WHO or to their national AIDS control programme guidelines, then they (and their providers) will be able to make a stronger case that they are ready to make good use of ARVs.

WILSON:

My impression is that people with symptomatic HIV infection are often eager to take therapy that is perceived as being helpful - ultimately patients will need to choose to "buy-into" the allopathic medical model - consistent messages from health-care workers, support groups and the media are important. The business sector (for example the insurance industry) have been involved in producing patient information booklets. Co-trimoxazole seems to have widespread acceptance in high HIV prevalence communities and is widely prescribed by the medical community in Cape Town.

PRABHU:

My experience in Chennai, India, with co-trimoxazole prophylaxis is mixed. Certain patients feel that co-trimoxazole is an "HIV" drug because all HIV patients are taking them. Some patients regard their doctors as "gods", who can do no wrong ... others are very circumspect and if all they get is Septrin they would probably throw their medications away the moment they leave the clinic. Those that do take prophylaxis wonder why they still fall sick inspite of regularly taking medicines. When they develop oral thrush and episodes of itching, they are inclined to stop CTX. Another worrying prospect is the development of resistance, which would face us with some very serious decisions. Would it not be simpler to regularly follow up and treat episodes when they do develop, rather than offer prophylactic treatment which inevitably fails, and then be stuck wondering what to do next?

Today, we should be moving towards rational use of drugs. We must rethink this whole strategy of prophylaxis. We cannot afford to lose more drugs to resistance. We will be left with precious little to fight this disease should this happen!

The motivation for uptake of CTX prophylaxis is difficult. Since most often these medications are freely provided or are very cheap, affordability is not an issue. However, tolerability and side effects - rashes - are important issues, deterring uptake of these medicines. They do not drastically alter the quality of life, unlike ARV drugs where the patients feel the difference within a few months and so are motivated to continue ARV! Prophylaxis with CTX only seems to delay the inevitable and, if the broader issue of ARV therapy is neglected, the inexorable decline continues whether prophylaxis is given or not.

I firmly believe that regular clinical monitoring and periodical health visits and counselling are better options than thrusting pills down patients throats as a primary prophylaxis. Though if documented evidence exists for low CD4 counts or previous history of PCP pneumonia, secondary prophylaxis may be offered to selected patients who are motivated. Even here, I would prefer to treat episodes as they develop, rather than see patients irregularly who take prophylaxis since they are falling sick often, whether with vomiting or diarrhoea or skin rashes.

Do these prophylactic treatments really have a public health benefit? Do they really alter the course of infection and decrease the mortality of people living with HIV? I feel that people with HIV are dying at great speed, no matter what prophylaxis we would like to implement.... tons of Septrin, a lot of money and resources and

many years down the line, we are still clutching at strategies which have clearly failed. I cannot but reiterate the difference ARV therapy has made to decrease morbidity, mortality and bring the HIV positives back into the mainstream of life. We need to look ahead at ways to ensure improved access to and proper prescribing of ARV drugs.

When ARVs do become accessible, what then of CTX prophylaxis

Everyone concerned with ARV treatment needs to understand that while it treats the cause of immunodeficiency in HIV disease, it does not directly correct that immunodeficiency. Thus, patients who commence treatment at low CD4 counts will remain extremely vulnerable to opportunistic infections until the virus has been suppressed for long enough to allow their immune systems to recover.

This is why, in Western medical practice, prophylaxis with CTX and maintenance regimes with antifungals, antibiotics or antiherpetic drugs following opportunistic infections are continued during ARV treatment.

The relevance of this to practice in resource-limited settings was brought home for many people by reports at the International Conference on AIDS in Durban, in 2000, of early experience in Uganda, where the use of ARVs that were barely affordable did not have quite the impact on mortality, at least in the early stages of treatment, that clinicians and patients had hoped for. This was seen as being the result of ARV treatment having been purchased at the expense of effective treatment to control opportunistic infections.

Dr Paul Farmer of Harvard University, speaking at the recent Retrovirus Conference in Boston about the introduction of HAART in rural Haiti, said the real criterion for early access to ARVs in the Clinique Bon Sauveur had been CIOs - "carried in on stretcher". However, their remarkable success in keeping patients alive on ARVs and enhancing their health may point to an important practical issue; that commencement of ARVs should only follow effective treatment of any immediate illness.

REGENSBERG:

If the patient is on antiretroviral therapy [in the Aid for AIDS programme, in South Africa] and the CD4 count is rising, we recommend withdrawing the drug [CTX] once the CD4 count is consistently above 200. This also applies to secondary prophylaxis.

GAZZARD:

What works quite well in Botswana [where he has advised Francistown clinicians on the introduction of ARVs] in a supply limited setting is actually to identify people with opportunistic infections as inpatients and to give them an early outpatient appointment. Although this does not meet the criteria of treating the illest patients first, it is extremely important to actually ensure that ARV gets a good reputation rather than a bad one. A bad reputation would certainly be obtained by treating people who are so severely ill that they don't survive to leave hospital.

I personally think that co-trimoxazole prophylaxis should be continued until the CD4 count is above 200 and I would emphasize that there is a survival value in this not just because of PCP but also salmonella and other chest infections.

Further information of aidsmap.com

Co-trimoxazole - main entry

<http://www.aidsmap.com/treatments/ixdata/english/5f044e0b-e353-412f-9708-79920f55184f.htm>

PCP - prevention & prophylaxis Research [includes a discussion of paediatric dosing]

<http://www.aidsmap.com/treatments/ixdata/english/1E521B4C-CD6B-4666-9DBF-8ECEB44A6209.htm>

PCP - treatment research and references [includes references for the previous articles]

<http://www.aidsmap.com/treatments/ixdata/english/5DEC8655-F8AE-49DA-91DF-A9F585B63AA1.htm>

about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

For further information please visit the HATIP section of aidsmap.com