

HATiP

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Talking about side-effects

By Julian Meldrum with contributions from Vijay Anthony Prabhu (Chennai, India), Catherine Orrell, Desmond Martin, Douglas Wilson, Leon Regensburg (South Africa), Henry Barigye (Uganda), Miriam Rabkin (MTCT-Plus, USA/international) and Norman Nyazema (Zimbabwe/South Africa).

Most active medicines also have the potential to cause unwanted effects and it is widely accepted that explaining these risks is essential to good medical practice. Communication and patient education about these side effects and more severe adverse events can empower patients, increase their understanding of their treatment, inform them what to do in the event of a problem, and enhance treatment adherence. Talking about side effects is a vital part of HIV and AIDS treatment and may be even more important for HIV and AIDS than for other chronic diseases.

The reality of side-effects

There are at least four reasons why side effects loom large in HIV medicine.

The first is that while most people undergoing treatment for HIV tolerate their medications without difficulty, many of the drugs used do produce side effects in some patients. These are commonly a nuisance, more rarely life threatening (adverse reactions) and sometimes develop slowly, emerging only after extended periods on treatment.

While we all hope for new treatments with fewer side effects most people accept that effective drugs will carry risks to set against their benefits. As Professor Norman Nyazema puts it, it is part and parcel of the drug. Patients who are prepared for side effects may take the experience of them as evidence that the drug is working in their bodies. Some may even need reassurance that the drug can still work, without causing the problems experienced by others to whom they may have spoken.

The second reason why talking about side effects is so critical in HIV care is that these symptoms can lead to non-adherence.

If side effects are intolerable to the individual, or if they are unexpected, then they can undermine peoples faith in treatment, unscheduled breaks in treatment may occur, resistance may develop and treatment may fail. With ARVs, this can end up with the worst of both worlds: lots of side effects combined with ineffective treatment. This is, by any definition, bad medicine. It is important to recognise that a side effect that seems relatively minor to an experienced healthcare worker may still be a very big problem for the person suffering from it. If so, that problem needs to be dealt with.

The third reason is that people with HIV/AIDS are likely to be taking multiple medications, which may interact to produce more severe side effects. These may include over-the-counter and traditional medicines.

A fourth reason is that HIV treatments need to be taken continuously for long periods to keep people well, rather than on a short term basis to deal with illness. As access expands, patients will increasingly be asked to take medications when they are asymptomatic. Instead of taking pills to relieve symptoms, they may find themselves taking pills which introduce symptoms.

It is therefore the responsibility of every treatment provider for people with HIV to find out about the known side effects of the

drugs they use and to find appropriate ways to share that information with patients.

The need for vigilance

Drugs for HIV and AIDS tend to be newer than drugs used in other areas of medicine, especially in settings where resources are limited. This means that new knowledge about problems linked to the drugs is emerging all the time.

Sources of such information include information sheets and dossiers from drug companies, which are generally based on clinical trials and on post-marketing surveillance in countries which have systems to report adverse reactions (known as pharmacovigilance or pharmacosurveillance). This is discussed further towards the end of this article.

Companies have obvious reasons to present their products in the most favourable light, and so their activities are supervised with varying levels of efficiency by drug regulators, which often support independent reporting systems too. Companies also have an interest in safeguarding their own reputations by ensuring that their products are used safely and appropriately.

Independent information resources include fact sheets from organisations such as NAM, and treatment guidelines, which generally outline the most important side effects and adverse reactions in discussing the pros and cons of particular treatments.

Sharing information with patients ? why and how

Patients have the right to know about the risks and benefits of treatment. In addition, informed and empowered patients may be more adherent.

Many practitioners find it helpful to make the distinction between common side effects which may be a nuisance but are mostly transient, and dangerous side effects which should trigger immediate action by the patient. However, there is no point in burdening patients with a list of everything that can possibly go wrong with their treatments. For one thing, there is a very low limit to the amount of information anyone can take in during a medical consultation, especially when they are upset or anxious. For another, it is vital to maintain a proper balance between the actual benefits and risks of life-preserving treatment.

Other issues can be left to future consultations, or addressed in general terms, by stressing that if people notice unexpected changes or new symptoms or problems, they should get in touch promptly. If they think that a problem is due to the drug, even if they are wrong, you need to know about it.

BARIGYE: Communication of side effects needs to be done in the context of peoples perception of ARVs. This can be a challenge and often requires time. An example is that some patients may not have a clear understanding of risk and so if you suggest a possible side effect they assume that everybody is expected to get it. I emphasize the side effects that are severe and could be life threatening and those that are common and usually minor. I emphasize that not everybody gets the side effects and to consult me if he gets a suspicious complaint. I ask new patients to come back for review within two weeks.

Limits to communicating side effects to patients include:

- Doctors are very busy and have no time to explain every detail to patients. This is true in Uganda where very few centres are currently providing ARVs.
- Doctors prescribing ARVs need refresher courses about side effects as the number of medicines increases. It is quite

common that we doctors actually do not know even the documented side effects.

MARTIN: In the pre-treatment phase counselling is targeted to obtain the commitment from the patient regarding the long-term benefits of treatment and the importance of adherence to life-long ARV treatment. During the pre-treatment session(s) side effects, early toxicities and long-term complications are outlined. Any co-existing morbidities are evaluated as they may impact on the above, e.g. alcoholic liver damage, bone marrow suppression.

The short term side effects related to specific regimens are described to the patient and treatment supporter (buddy). It is stressed that these side effects are usually minor, but must be reported, and will disappear with continued usage of the drugs. Symptomatic treatment can be prescribed, e.g. loperamide for diarrhoea and paracetamol for headache.

Toxicities are outlined along with the monitoring that is needed (liver enzymes, haemoglobin, etc).

Long-term side effects are outlined for individual regimens, and again the necessity for monitoring is described, e.g. lipodystrophy, elevated lipids.

The trick here is to fully inform patients without frightening them off the use of ARVs. This is further compounded by language issues, cultural issues and level of education of patients.

However, our experience has been that patients in resource-poor settings are as adherent as any patients elsewhere. It has always been amazing to me that when healthcare workers taking ARVs for PEP [post-exposure prophylaxis] have suffered side effects, approximately 50% of them discontinue their PEP prematurely.

ORRELL: All education is best done in the patients own language. I find I tell patients about two categories of adverse events severe or common ones I find dire, as a doctor, such as hepatitis or skin rashes and then the ones they may find dire for daily living (and perhaps adherence) such as nausea or peripheral neuropathy.

I tailor what I tell them to their drugs and leave an opening for them to return to the clinic (or call) whenever they have a concern, particularly in the first 2-3 months on therapy. I will usually only outline 3 or 4 key problems, no more, pre-treatment and then add in other issues, like symptoms of lactic acidosis, later. Most of our patients either have access to detailed written information to back up this consultation or are spending time pre-treatment with our counsellors who are supporting them in the education process.

Our take home point is that they must call their counsellor, nurse or doctor if they have any untoward effects, at any time. They should not pick out and stop one drug ever; if they have to stop treatment before getting hold of any of us, then stop it all.

PRABHU: Once we initiate patients on ARV, the key message is to come regularly for follow up. We keep open all channels of communication at all times and tell them they can go ahead and disturb us at any time of day or night, if they so please, and this relaxes and calms them. They feel reassured that they can have somebody to talk to. Patients most of the time find no difficulty in communicating with their doctor!

We talk to them in general terms about side effects and play it down. We understand that the patient has gone through a lot emotionally, mentally, financially and physically. So when they are about to start ARV, we dont want to alarm them that they might develop headaches, vomiting, fever, drug rashes, liver failure, anaemias and what not. At the same time, we dont want to be too complacent and reticent and tell them that nothings going to happen and everything is going to be all right.

Nonetheless, we do monitor for these things, including laboratory tests.

It is difficult balancing what the patients need to know against adding to their anxieties. Striking a proper balance and keeping a level head, not blowing things out of proportion, with an objective of treating and not mistreating, is important. We feel that a bit of functional overlay [psychosomatic illness] may develop especially in the case of AZT where myalgia and headaches appear after we start the drugs and just do not go away, no matter what we do.

The key message we try and instil in patients minds is communication: to tell us if anything out of the ordinary is happening to them and to let us decide together what to do next. To make them feel part of the decision making process.

We would tell them that ARV drugs may cause side effects just like any other drug and not to be alarmed. If they panic and stop their drugs then they must stop all their drugs together at one time and not to experiment one drug at a time! We stress this a number of times, since [even with fixed dose combinations] some patients may take only a single dose instead of BID dosing. We try to tell them the value of drug adherence. Patients are motivated enough to continue taking drugs.

RABKIN: I find that the most important thing is to convey a message of support, openness to hear about problems, and availability. Information about access how to reach me or my coverage is key. I also prefer very close follow-up (once or twice weekly) during ARV initiation, either in person or on the phone, where possible. This is the period when patients are learning how to take the medicines and setting habits for the future. The first one or two months are also when many side effects present, and having consistent access to care providers can be very reassuring.

Patients need to understand that I think the benefits of treatment outweigh the risks and different patients need this information in different ways. Some want numbers and percentages, but most dont. The other helpful thing, I find, is to make sure they understand the distinction between immediate and chronic risks. Of course, patients need to know about the most common risks (e.g. rash with nevirapine) and the most dangerous risks (e.g. hypersensitivity with abacavir) and I find this distinction most common versus most dangerous to be helpful.

Metaphors and using examples from the patients own life are useful. (We hope for the best but plan for the worst, Buying flood insurance doesnt mean the waters will rise, Trust in Allah but tie your camel, etc.) Also, I never have these conversations once. ARV initiation is almost never an emergency and I like to do my preparatory ARV counselling over several visits and, if possible, with several different people. Peer educators can be enormously helpful. And for literate patients, written information can provide them with a way to review the topic at home, once they have left the clinic.

WILSON: Essentially, any medication can cause adverse effects, but in HIV medicine the worrisome ones are co-trimoxazole, isoniazid and some of the antiretrovirals. To me the side effects associated with ARVs are by far the most important, as stopping and starting therapy can rapidly cause viral resistance. Starting ARVs is an anxious time for many patients, and I dont like to overload patients with too much information about possible adverse events.

Before starting ARVs I need two things from my patients: a commitment to long-term therapy and monitoring and acceptance, in principle, that ARVs can make people feel sick but that the benefits can far outweigh the problems. Patients must be able to access care within 8 hours of beginning to feel unwell. They need to know about nevirapine allergy and that especially within the first six

weeks any rash, fever, right upper quadrant pain or jaundice must be reported immediately to a doctor who knows about ARVs.

In South Africa an ongoing issue is trying to ensure that patients taking ARVs in under-served areas do have rapid access to informed medical care.

Written information resources

BARIGYE: A number of patients read the manufacturers insert but they tend to be complicated and I would suggest a modified patient friendly leaflet for each medicine.

MARTIN: I think information gained from drug companies, including booklets, is useful to inform practitioners of side effects and their monitoring. The discussion of side effects in treatment guidelines is an important source of information. Patient leaflets are also an important tool to demystify side effect and their management.

ORRELL: I never give patients information from drug companies (other than informed consent forms when they enter clinical trials). My clinical pharmacology training makes me anxious about biased reporting. I tend to create information sheets myself with simple diagrams to show how many tablets or capsules must be taken, and when, and listing the top two or three side effects for each.

RABKIN: Written and visual patient education materials are always helpful. In my setting, these need to be written at a low-literacy level and in multiple languages. I particularly like the ones at the New Mexico AIDS infonet website (www.aidsinonet.org) which are available in English and Spanish.

PRABHU: Information about drug side effects from companies is not very useful from the patients point of view. They provide fact sheets about their drugs and dosing and pricing to doctors, but regarding side effect profiles they are found wanting. The very least the pharma companies could do would be to provide to the patients, in local languages, some facts about HIV, the life cycle and how the drug works, what precautions they should take, what important side effects to look out for and what to do should these occur, by way of a pamphlet. So far that remains to be achieved. The most important advance would be to improve the quality of the packaging of the drugs to ensure uniform quality in their product. ARV drugs which come in strips do not come with any drug sheet, which I thought was mandatory, but in India, I guess, anything goes which sells!

Picking up unexpected problems

Clinical trials, carried out before a drug is licensed, collect and report information on common side effects, in ways that can help give an idea of what patients can expect. However, this does not always work.

The populations in which clinical trials are carried out for drug licensing often differ from those in which drugs are later used, limiting the usefulness of this information.

Also, unexpected and hard-to-classify side effects like the psychological effects of efavirenz may take longer to describe than simpler side effects such as diarrhoea or skin-rashes or hepatotoxicity (liver damage).

Rarer side effects and adverse reactions are most likely to emerge in the later stages of clinical trials and post-marketing surveillance, including long-term natural history studies of cohorts of patients on treatment. This is why they are often the subject of alerts and warnings from drug regulators and companies, and are reported as news on *aidsmap*. In extreme cases, these lead to the withdrawal of drugs from the market or their abandonment as experimental treatments.

Even in the western countries with the best reporting systems, such as France, many adverse reactions to drugs are not reported. It is a matter of concern that many countries in Africa and Asia which have large numbers of people with HIV appear to have weak or non-existent systems for reporting adverse reactions. It is to be hoped that HIV medicine, with its push towards introducing new treatments simultaneously, north and south, will lead to an early review of this situation.

A major potential source of problems is drug interactions, which may include interactions with non-medical treatments such as herbal remedies. Some interactions can be predicted, to some extent, from research on how the drug is processed by animals and in the human body, but others only emerge when treatments are widely used.

Many traditional remedies contain complex mixtures of active substances in variable amounts and their effects have not been fully studied. Liver toxicity is a major concern and is a reason why several members of our advisory panel recommend that people with HIV discontinue traditional remedies when they begin HIV treatment.

For side effects and adverse reactions to be identified, patients must be empowered to report problems with medications.

ORRELL: I ask at every meeting whether an adverse effect has been experienced. I find that patients tell us readily in fact they probably blame their ARVs for more adverse effects than is actually warranted!

RABKIN: I cant overemphasize the utility of having a multidisciplinary team including peer educators. It is a constant in my practice that patients will tell others nurses, peers, counsellors things they wont tell doctors.

BARIGYE: Patients are willing to communicate information about side effects but are reluctant to talk about complementary medicine if a trusting relationship has not been attained.

MARTIN: The concomitant use of over the counter (OTC) medicines or traditional remedies among our patients is a very real problem. Traditional remedies in our setting [in Southern Africa] are usually very hepatotoxic and can impact on the toxicity profile in the early phases of treatment.

PRABHU: We always probe into traditional remedies that the patient might be taking and ask them details of what is in the formulation. We point out to them that in the modern system of medicine, we have very clear ideas of what we are giving them, how it is going to work, what are the side effects and the definite and visible benefits that in a few months they will go back to work!

Most of them have consumed traditional remedies for months with no benefit. They still have persistent diarrhoea or fevers and they realize it is not cost-effective and are ready to give ARV drugs a shot and stop traditional remedies.

Here again, we stress that should side effects develop, we would not know if they are due to the disease process per se, or the ARV drugs, or the traditional remedies. We urge them to simplify matters and fortunately most patients stop their traditional remedies while on ARV. Those patients who refuse to stop are counselled and started on ARV if their clinical condition or CD4 cell counts warrant therapy. Those who continue to have side effects would then stop traditional remedies, or for those who feel they cant do without, well we have no choice but to continue!

Reporting adverse effects

Many countries do not have any systems for gathering information on adverse effects of drugs. Indeed, some do not have functioning

drug regulatory systems at all. Others, notably South Africa, have professional drug regulators who are strongly committed to supporting the development of good practice in the use of medicines.

The idea of a birth registry, raised by Dr Henry Barigye from Uganda, is to enable assessments to be made of side effects that may emerge months or years later, in (mostly) HIV negative children exposed to ARVs owing to their mothers treatment. This is in addition to the need to monitor the effectiveness of programmes to prevent mother-to-child transmission, although the two concepts are linked. For example, information collected through such a registry in Europe and North America was invaluable in providing safety information as a basis for clinical trials in pregnant women, that finally proved that ARVs can prevent mother-to-baby transmission of HIV.

ORRELL: I do report serious adverse events, even well-known ones like Stevens-Johnson syndrome the companies are interested in post-market research. The route to do this can be unwieldy a contact number from each pharmaceutical company for AE reporting would be good. I also report serious adverse events to our National Adverse Events Monitoring Centre (there is a form to complete and fax in the back of our national formulary; the centre, at the University of Cape Town, is staffed by the Medicines Control Council of South Africa).

MARTIN: Regarding reporting of side effects, this is not commonly done outside of the confines of clinical trials.

BARIGYE: In Uganda, there is no organised way to report probable or actual side effects and I think this is an oversight because the long term complications of these medicines are not really known and the possibility that some side effects may differ in different populations and environments is real. In addition, I would like to see a registry of births to women undergoing ARV treatment.

PRABHU: There is definitely room for much improvement in reporting systems in India. It is very difficult first of all to substantiate our claim that this is a drug side effect. [For example,] should hepatitis or nephritis develop, one would [ideally] get tissue evidence, exclude other causes and then on withdrawal of the drug expect cessation of symptoms and resolution of signs. All of this is a tall order and then where is one to take this information to? Taking it to the pharma companies brings guarded replies, Doctor, it has been reported in the literature, please stop the drug, and that's it. Sharing information with colleagues is mostly done through literature by way of journals and case reporting but it is not easy getting acceptance or to be listened to & other channels are clinical symposia and of course the internet ... which seems to make the world a smaller place!

NYAZEMA: The central issue is the rational and safe use of drugs and medicines, and the collection and proper use of information

about adverse events must be seen in that context. In addition to the regulatory authorities, professional bodies have a responsibility to take it up as an issue, to make sure that drugs are being correctly used.

In Zimbabwe, there is an Adverse Drug Reactions and Medicines Review Committee established by the Medicines Control Authority of Zimbabwe. This receives reports of adverse reactions from any healthcare worker, preferably using forms that are distributed with the Essential Drugs List, though in fact any letters received will be logged and assessed in the same way. The Chairperson of the Drugs and Therapeutics Advisory Committee sits on that Committee too, so that information is conveyed to those who look at broader issues of the use of treatments.

There is an African Drug Regulatory Association which is helpful in developing better practice, but there are still countries such as Benin which have no drug regulatory authority at all. In Zambia, there is a beautiful strategy on paper but it is not clear that it is working in practice. In Mozambique, similarly, regulation is very weak. Even in South Africa, there is a long way still to go.

Further information on aidsmap

There is a very large amount of information on side effects within aidsmap. Unfortunately, this makes it difficult to select particular resources to make available by email. However, questions and observations about particular side effects would be very welcome.

[This page](#) provides links to many of the resources on aidsmap concerned with side effects, not only lipodystrophy. It includes factsheets on particular symptoms or problems which may be drug side effects.

[This page](#) links to factsheets on particular drugs, which always include discussion of their side effects and any problems associated with them.

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