

HATiP

HIV & AIDS Treatment in Practice

Issue 151 | Friday, December 18, 2009



In this issue:

TB & HIV in Practice; by Theo Smart page 2

- Continuous isoniazid preventive therapy (IPT) better at preventing TB than short course – but only in those with a positive tuberculin skin test (TST)
- Interpretation and policy implications of the Botswana IPT trial

Body fat changes in people with HIV: a clinical review; by Carole Leach-Lemens page 6

- Lipodystrophy due to antiretroviral treatment
- What are lipodystrophy and lipoatrophy?
- What causes fat loss?
- Epidemiology
- Methods of diagnosis
- Psychosocial issues
- Treatment
- Conclusion: First, do no harm

TB & HIV in Practice

By Theo Smart

This regular feature on TB/HIV integration is kindly supported by the Stop TB department of the World Health Organization.

Key points

- Isoniazid is an antibiotic used in combination treatment of active TB. It has been shown to reduce the risk of developing TB in people previously exposed to TB who have a latent infection.
- The World Health Organization recommends isoniazid preventive therapy (IPT) in people with HIV who have a positive reaction on a skin test for TB, or who live in settings with a very high burden of latent infection.
- The Botswana Isoniazid Preventive Therapy (IPT) trial has now shown that in people with a positive tuberculin skin test, continuous IPT reduced the rate of TB by 92% compared to a six-month course of IPT during three years of follow-up.
- Continuous IPT in people without a positive tuberculin skin test proved no better at preventing TB than a six-month course of IPT.
- IPT did not lead to an increase in isoniazid resistance due to inadvertent treatment of active TB.
- Antiretroviral therapy resulted in a significant reduction in new TB cases only in the group of patients with a negative tuberculin skin test. In those who were TST-positive and receiving continuous IPT, antiretroviral treatment resulted in only a very small additional reduction in TB risk.
- WHO will consider the results of this study when it hosts an expert consultation on new guidelines for intensified case-finding and IPT in January 2010.

Continuous isoniazid preventive therapy (IPT) better at preventing TB than short course – but only in those with a positive tuberculin skin test (TST)

Taking isoniazid preventive therapy (IPT) for 36 months prevents significantly more cases of tuberculosis (TB) in people living with HIV in a setting with a high burden of TB than simply taking a short course of IPT for six months, according to the preliminary results of the Botswana IPT trial, presented during a special session of the 40 Union World Conference on Lung Health held in Cancún, Mexico from December 4th - 7th.

The study found that the protection provided by the short course of IPT wore off within six months of completing treatment, probably, researchers theorised, because people were at a high risk of re-exposure to, and reinfection with, TB.

In fact, preliminary observations (not presented) suggest that TB rates also go up after the completion of 36 months of IPT, “so it really looks like continuous IPT may be needed,” said Dr Taraz

Samandari of the US Centers for Disease Control (CDC) in Botswana.

Overall, 36 months of IPT reduced the risk of TB by 56% in the cohort that began the randomised portion of the study, which included 1655 people, but almost all of the benefit was experienced by the 400 people with a positive tuberculin skin test (TST+) at study entry – these had a 92% reduction in risk of TB (a profound benefit).

People who have a negative TST – either because they were not infected with MTB or because their immune system was so weak they couldn't mount a reaction on the TST (anergic) didn't seem to be protected by IPT (and over the course of the study, they had a rather high rate of developing TB).

Only antiretroviral therapy (ART) reduced the risk of TB substantially in the TST-negative group, but somewhat paradoxically, ART only added marginally to the benefit experienced by people with positive TSTs taking continuous IPT.

IPT was generally well tolerated by the study participants, but it did cause some serious side effects – mainly liver toxicity and mostly in the first six months. While the benefit of continuous IPT certainly outweighed its risks in people with positive TSTs, “TST-negatives may be unnecessarily exposed to harm from IPT,” said Dr Samandari.

Background

There is no question that something must be done to reduce the burden of TB in people with HIV, who have a 5-10% annual risk of TB disease once infected with TB bacilli compared to a 5% lifetime risk in HIV-negative people with latent TB infection. Moreover, people with HIV have a much higher risk of dying of TB disease.

For instance, in Botswana, TB has spiralled out of control since the emergence of the HIV epidemic (with a TB case notification rate of 620 per 100,000 in 2002 – among the highest in the world). About a quarter of sexually active adults are believed to be HIV-positive but they make up a much greater proportion of the TB cases (80%). At least 40% of hospital deaths in people with HIV are due to TB.

Numerous studies have shown that IPT can reduce the risk of TB by between 30-60% and the World Health Organization recommends it for people with HIV who are TST-positive or who live in settings with a greater than 30% risk of mTB infection. However, as HATIP has described in a number of articles (published in [November 2007](#), in [June 2008](#) and most recently in [July 2009](#)), many clinicians and national programmes have been reluctant to roll out IPT.

The notable exception has been the Botswana National IPT Programme, which offers six months of IPT to anyone who tests HIV positive (not bothering with TSTs as per WHO policy).

However, as the programme was being launched, Botswana and the CDC decided that there were some unresolved questions about IPT that would best be addressed by a double blind randomised clinical study, such as:

- How durable is the effect of IPT, and should it be given continuously in settings with a high risk of reinfection?
- Do TSTs make a difference in a high TB burden setting?
- Does antiretroviral therapy add to TB prevention?
- What is the risk of isoniazid resistance and severe adverse events or death?

The trial design

The study was designed to enrol roughly 2000 subjects who would all start treatment with six months of open-label IPT (the national standard) and then be randomised either to continue IPT

for a further 30 months (referred to as 36-IPT since it involved 36 months of IPT)) or a matched placebo group (referred to as 6-IPT).

The study was conducted at eight sites: five in Gaborone and three in Francistown. These were government clinics where IPT and ART were available. IPT was given as 300 mg isoniazid plus 25 mg vitamin B6 daily (or matching placebo), and patients came back every month for refills from study nurses.

The researchers maintained very high clinical trial standards with ongoing review by an external Data and Safety Monitoring Board, and an external Endpoints Committee (which reviewed and approved TB cases, examined adverse events and deaths (blinded to treatment arm)).

The study included reasonably healthy adults with proof of HIV infection (and whose laboratory tests were within reasonably normal parameters), but excluded anyone with signs or symptoms or a physical exam suggestive of TB, AIDS-defining illness or liver disease. In addition, anyone with a history of IPT, active TB in the past three years or a history of poor adherence to chronic treatment was excluded.

The researchers planned to conduct an intent-to-treat analysis (ITT) on all participants who began the randomised portion of the study, as well as a 'per protocol', analysis including only those who had 80% or better adherence to clinic visits.

Out of 4331 screened, 1995 were ultimately enrolled into the study. Arms were well matched; roughly 72% were women, and the median age was around 32 years old. The median CD4 cell count at study entry was about 300. Approximately 24% were TST-positive. Of note, antiretroviral therapy (ART) was begun by almost half the patients, a median of six months after study entry.

Dr Samandari reported good completeness of follow-up with only eleven participants (0.6%) lost to follow-up after 36 months and 176 voluntary withdrawals. However, this is somewhat misleading because later in the presentation, he mentioned that 340 subjects were excluded before the randomised portion of the study for a variety of reasons (including failure to return to clinic, TB or death in the first six months).

For the remaining subjects who completed the first six months of treatment, adherence remained rather good, falling from a high of 85% to 78% who continued making more than 80% of their clinic visits. Spot urine tests in 200 randomly selected subjects found only slightly lower percentages of isoniazid in the urine (a mean of 74-80% were actually taking the medication).

Results

Because of losses in the first six months, 1655 people were included in the final ITT analysis, 1318 in the per protocol analysis. Overall, 36 month (continuous) IPT reduced the risk of TB by 56% compared to six months of IPT followed by placebo. See details in table.

One of the key questions that the study was intended to answer was: how long people remain protected from TB after finishing a six-month course of isoniazid? The answer, unfortunately, is not very long. After about 200 days (six months), people who were randomised to placebo began developing active TB at a rate that was significantly higher than seen in the 36-IPT arm.

Another key study objective was to determine whether treatment TST status affected outcomes in this setting. To the consternation of many policy makers in the room, it did.

Of the 1594 subjects for whom TST results and data were available, 400 were TST-positive. In the 6-IPT arm, there was a TB rate of 2.53 cases per 100 person years (12 cases of TB) vs 0.19 (or one case) in the continuous IPT arm. This yielded a hazard ratio of 0.08 ($p = 0.015$). In other words, there was a 92% reduction in TB on continuous IPT.

TB incidence by treatment arm

	Intent to treat		Per protocol	
	6-IPT	36-IPT	6-IPT	36-IPT
Number analysed	821	834	665	653
TB				
Definite TB	16	9	12	6
Probable TB	2	1	2	0
Possible TB	7	2	5	5
All incident TB	25	12	19	8
TB rate per 100py	1.39	0.61	1.1	0.51
Hazard ratio	0.44		0.43	
P value	0.029*		0.039*	
	56% reduction		57% reduction	

The 1194 people with negative TST results had a TB case rate of 0.92 (13 cases) in the 6-IPT arm versus 0.78 (11 cases) in the 36-IPT arm — for a hazard ratio of 0.86, (p -value non-significant). In other words, treating almost 1200 TST-negative people with IPT for an additional 30 months reduced TB cases by only 14%, resulting in two fewer cases and even this apparent reduction may have been a chance result.

Many of the TST-negatives probably had relatively high CD4 cell counts and had probably never been infected by mTB and/or may have had relatively low risks of mTB infection. IPT would be expected to have less of an impact in that population.

More worrisome are the TB cases that occurred despite treatment. Most of these cases in TST negatives were probably in people who were anergic, in other words, exposed to mTB but unable to mount an adequate immune defence to it. However, no data on median CD4 counts in TST-positive and negative groups were presented, nor the median CD4 count in TB cases in the TST-negative group).

In a conversation after his presentation, Dr Samandari posited that without support from the immune system, IPT may not be up to the task of fighting off TB on its own. However, there may be other mechanisms as well, due to differences in isoniazid metabolism and bioavailability in people with very advanced immune suppression. Also, a subset of people with very low CD4 cells may have established TB infections somewhere in their body without clinically apparent symptoms — meaning that IPT in these people was simply suboptimal treatment.

ART (which was initiated at different times but evenly distributed in the two arms of the study) however had an impact on risk in people who were TST-negative. A Cox regression model, including the interaction of IPT, baseline CD4 and TST, looked at the affect of ART over time and how it interacted with TST and IPT.

The model found that for each extra day on ART, the risk of TB decreased by 0.23 percent ($p=0.04$). When provided for 360 days, the risk of TB was reduced by 50% when IPT was not included. However, the addition of ART to IPT didn't seem to add much benefit - around 4% in TST-positives taking IPT.

More importantly, the addition of IPT to ART in TST-negative participants only seemed reduce the risk of TB by an additional 4% (54%) — so ART did not seem to restore their ability to respond to IPT.

Adverse events, resistance and mortality

The study found a relatively low rate of severe adverse events after the first six months of IPT that were at least possibly

associated with study medication, with seven (0.9%) events in the 6-IPT arm (placebo) and eleven (1.3%) in the 36-IPT arm.

However, one was a case of hepatic encephalopathy leading to death in month 9 (another case occurred during month six).

In addition, it should be noted that there were 20 severe cases of hepatitis (grade 3 or above) in the first six months of open-label IPT — though most had no clinically recognised symptoms.

Coadministration with ART may have increased the risk of liver toxicity somewhat (relative risk 1.59 [0.63-4.0]). The risk was greater on nevirapine (RR 2.09 [0.74 - 5.87]) as opposed to efavirenz (RR 0.96 [0.21 - 4.31]).

IPT did not lead to a substantial increase in isoniazid resistance in this study. The background prevalence of isoniazid resistance among new TB patients in Botswana was 9%. In the IPT study 17% of incident TB cases had mono or MDR resistance in the 6-IPT arm and 14% in the 36-IPT arm.

The data on mortality were less clear-cut. Overall there was a death rate of 1.4% per annum (2% in the first year). "This is comparable to mortality in rich nations," said Dr Samandari.

However, in this clinical trial setting (where TB cases were probably detected and treated earlier than would happen in the field), 36-IPT did not reduce mortality compared to 6-IPT — in fact, there was a slightly higher risk of mortality (25 deaths versus 16 deaths) but this difference was not statistically significant ($p = 0.17$).

References

Samandari T et al. *Preliminary results of the Botswana Isoniazid Preventive Therapy (IPT) Clinical Trial (6 months vs 36 months)*. 40th Union World Lung Conference, Cancun, 2009.

Interpretation and policy implications of the Botswana IPT trial

Although there is no question that the use of IPT could reduce the burden of TB in people with HIV overall, the results from the Botswana IPT trial pose almost as many questions as they answered. So after the findings were presented, researchers, policy makers and patient advocates debated how the results should be interpreted, and expressed somewhat diverging views how they should affect policy.

WHO currently recommends that isoniazid should be provided to people with HIV when active TB is excluded, and IPT is one of the three I's at the heart of its TB/HIV strategy, along with intensified case finding and infection control.

However the results of the Botswana study are likely to influence WHO recommendations very swiftly.

Policy in the works

"The results of the Botswana IPT trial are very timely because we are currently revising the policy of intensified case finding (ICF) and isoniazid preventive therapy (IPT) to re-conceptualise the implementation of IPT — not as a stand-alone intervention but intimately linked to ICF," said Dr Haileyesus Getahun of WHO's STOP TB Department.

WHO is holding a meeting in the last week of January 2009 to reformulate the ICF/IPT policy. As one of the most rigorous trials on IPT to date, the Botswana IPT study will have a significant impact on the new recommendations.

"Clearly the Botswana study, a randomised controlled trial, definitely falls into the strongest area," said Dr Getahun, describing how the WHO currently weighs evidence in its guideline development process. "Once we've graded this evidence, we will consider the strength of the recommendation. But it's not only the evidence but also the operability, the implementation and other issues that will be considered."

Numerous studies have shown that six to nine months of IPT can lower the risk of active TB — but IPT has been a hard sell to national TB programmes, despite the existing WHO recommendation. In fact, even some of the thought leaders in HIV have been questioning IPT.

"I'm not sure IPT is worth the trouble to be quite honest," said Dr Francois Venter of Johannesburg Hospital at the HIV Implementers' Meeting in Windhoek Namibia this year. "We really need to critically re-evaluate IPT. It has distracted national governments and TB programmes like nothing I've seen before — I believe it is a long time coming that people start questioning whether this is how we should be spending our resources."

"IPT has not been a very popular intervention," said Dr Helen Ayles of ZAMSTAR during a session at this year's Union World Conference on Lung Health.

The short duration of IPT's benefit: will IPT have to be given continuously?

Previous studies in Africa have reported that IPT's benefit lasted at least a year and up to two and a half years.^{1, 2}

"Why is the durability so much shorter in the Botswana trial compared to these other two trials?" asked Professor Gavin Churchyard. He pointed out that the two other trials were in the pre-ART era and that after treatment completion, patients were followed only periodically every three to six months (so to some extent the Botswana study may simply have detected cases earlier). But the more frequent clinic visits in the Botswana study might also put people at risk of exposure to TB.

"It makes one wonder whether transmission within the health services is contributing to more rapid loss of durability in the Botswana trial," Prof Churchyard said, "which underscores the need for having infection control in our health services."

The smaller study by Martinson et al found no difference between continuous IPT and short course preventive therapy in the intent-to-treat analysis. However, adherence was an issue in that study and the per-protocol analysis suggested that continuous IPT was more effective than any of the other preventive therapy arms.

Another study that could have a bearing on how this finding is interpreted has just been completed by the Tuberculosis Research Centre in India. The study compared a six-month course of isoniazid/ethambutol to continuous IPT — but the results will only be presented at the Conference on Retroviruses and Opportunistic Infections next February.

One downside of continuous IPT could be an ongoing risk of toxicity. While the Botswana IPT study suggested IPT was fairly well tolerated, and that most severe adverse events were seen in the first several months of IPT, Dr Getahun noted that Martinson et al reported a higher rate of severe toxicity in the continuous IPT arm.

Does the study provide reassurance to national programmes that have been reluctant to roll out IPT?

"Five years ago, I got tuberculosis... I had to suffer from TB disease when this might have been prevented," said Carol Nyirenda, a patient advocate living with HIV and working with the Community Initiative for Tuberculosis, HIV/AIDS and Malaria plus other related diseases (CITAM+) in Zambia. But she said that national programmes are even refusing to provide IPT on an opt-out basis (when people with HIV request it). "I strongly believe this withholding of life-saving drugs is not ethical — we need to move from discussion to implementation urgently. Our lives are at stake."

"What does it take to actually change practice on the ground?" asked Mark Harrington of the Treatment Action Campaign. "I think that it is obvious [the WHO guidelines] didn't really have much of an effect on practice, and all the same issues are brought up no matter what the data say."

But this study may change things, according to Dr Jeremiah Chakaya, formerly the national TB programme manager in Kenya and presently co-chair of the STOP TB Partnership.

"In Kenya, even though a lot of study indicated that IPT was useful, a lot of us clinicians did not believe in it, we thought it was too difficult, we thought it was impossible. But like some of the people in this room here, I'm a very recent convert of IPT," said Dr Chakaya. "Many of us were concerned that in routine programme settings it may be difficult to exclude active tuberculosis and that in fact a lot of TB could leak through the TB screening procedures and inadvertently lead to isoniazid monotherapy and increased isoniazid resistance. What this study has shown us, is that in fact isoniazid resistance does not seem to increase in this study."

In addition, he said that the study addressed several other key concerns of programme managers by showing that fairly high adherence was possible, and that IPT appears relatively safe.

But the study wasn't designed to address operational concerns of managing 'well' patients, as noted by Dr Francois Venter at the HIV Implementer's Conference in Windhoek this year.

"Wellness programmes are so shocking, not just in developing countries but in developed countries. We know that we cannot retain people within the system unless we have them on antiretrovirals — study after study tells us that — and yet we take these people, we diagnose them and we try to insert them into a system where all we have to offer them is isoniazid. And outside of very specialised programmes, every programme I see seems to haemorrhage people out of the system unless you put them on antiretrovirals — and we need to engage with that before we start offering IPT in my opinion."

Dr Chakaya suggested that programmes might instead have to think about delivering IPT at another level of the health system — moving IPT out to the community and relying much more heavily on "community health care workers, patient support groups and things like that. But we need to remember that the more complex the intervention the less likely that the intervention will be taken to scale."

The role of tuberculin skin tests

But the Botswana IPT findings showing no significant benefit of IPT in people with negative TSTs could wind up making IPT much more complex.

"I think one of the take-home messages - at least for me is: it would be difficult to justify the continual provision of IPT without a TST or an alternative to identify patients most likely to benefit," said Dr Themba Moeti (the man who launched the Botswana IPT programme).

"I think it is clear that if TST-negatives do not benefit - and study after study shows that TST-negatives do not benefit from IPT - *then TST-negatives should not be given IPT*," said Dr Chakaya. "It doesn't seem right for us to know what science is telling us and do different things just because they are easier to do."

Javid Syed of the Treatment Action Group argued that even a small benefit to TST-negatives could justify the routine prescription of isoniazid to people living with HIV, regardless of TST status.

"In fact, 15% of protection was provided to TST-negatives. And for HIV-positives, 15% is not a figure we can ignore," he said.

However, the study did not demonstrate that degree of benefit with any level of confidence, nor did a Cochrane Group meta-analysis.

"All of us would have wished that the data would have shown incontrovertibly that everyone benefited and we don't have to bother with TST, but the data are what they are... and to disregard this is scientifically and intellectually somewhat dishonest," said Dr Ken Castro of the CDC. "And we've been reminded not to disregard the

14% who may have benefited from IPT if TST-negative but [this ignores] the higher side effects in that group — so where's the balance in terms of risk-benefit?"

The bigger problem is that TSTs do appear to be difficult to implement in many resource-limited settings.

"TST is an obstacle to IPT," said Dr Kerrigan McCarthy of Johannesburg's Reproductive Health and HIV Research Unit earlier this year at the South African AIDS Conference.³

"Firstly there's the hassle of the supply chain management of TST - quality tuberculin, syringes, PPD RT23, cold chain management."

In addition, Dr McCarthy said that Johannesburg clinics reported wide variations in the proportion of TSTs interpreted as positive, indicating lack of consistency in performing and interpreting the test. Health care workers arrived at different conclusions about whether the size of the skin reaction, or induration, indicated a positive result or not.

"Quality control of TST is impossible! If the quality of a test cannot be controlled, that test should not be used."

Indeed, many programmes have had difficulty keeping tuberculin for the tests in stock, nurses have to be trained on how to correctly interpret the result (especially in people with HIV), and people have to return to the clinic within a few days to have it read — which can be a challenge in settings where the clinic is far away, transport is limited, and people have to work to survive and can't spend much time going to, and waiting in, a busy clinic. In fact, data suggest at least a quarter never come back for their readings — which means that many people who could benefit never come back for treatment. This is why WHO currently recommends that IPT be given to everyone with HIV if they live in a setting with a very high burden of TB.

"Tuberculin (for the TSTs) needs a cold chain and refrigeration. With HIV care and treatment being decentralised into the most peripheral facilities, how are we going to reconcile that?" said Dr Getahun.

"TST is a real barrier to the implementation of IPT," agreed Professor Churchyard. "In South Africa, as an example, we had absolutely negligible IPT uptake when we had TST as a criteria for enrolling. A year ago, we took IPT out of the revised guidelines, which have now been rolled out and in the last year the number of people put on IPT has tripled."

Requiring TSTs will mean more expense, training and supervision — and could simply become the new excuse not to offer IPT.

It's a conundrum, especially for treatment advocates, who are put into the awkward situation of having to weigh the risk-benefit for the HIV community overall versus the benefit for the individual. Treating everyone would reduce the risk of TB by around 56% (marginally higher than the benefit offered by ART in the study) — but it would also result in treating three quarters of the population unnecessarily, and placing them at risk of toxicity. Perhaps that choice (preferably informed) ought to be left up to each individual.

References

[1] Quigley MA et al. *Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults*. AIDS 15(2): 215-222, 2001.

[2] Johnson JL et al. *Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults*. AIDS 15: 2137-2147, 2001.

[3] McCarthy K et al. *INH prophylaxis: Lessons learned during implementation in Inner City Johannesburg: 2008*. CREATE Three I's symposium, 4th South African AIDS Conference, Durban, South Africa, 2009.

Body fat changes in people with HIV: a clinical review

By Carole Leach-Lemens

This clinical review is kindly supported by the Diana, Princess of Wales Memorial Fund.

Key points

- **Studies support the direct link between stavudine (d4T) and to a lesser extent zidovudine and lipoatrophy.**
- **While lipoatrophy in itself is not life-threatening the physical changes in appearance are psychologically damaging and stigmatising, leading to fear of disclosure, social isolation, poor adherence, stopping of treatment as well as suicide.**
- **Most first-line regimens in resource-poor settings include either stavudine or zidovudine. In spite of extensive advocacy efforts as well as a recommendation from WHO for the phasing out of stavudine, its use and repercussions continue and are expected to persist for a number of years.**
- **Where phasing out stavudine is not possible WHO recommends a reduced dose of stavudine from 40 mg to 30 mg in adults weighing more than 60 kg. Preliminary findings show that this helps prevent early neuropathy and lipoatrophy.**
- **Lipoatrophy is essentially a clinical diagnosis formed once all other explanations for (under the skin) fat loss have been ruled out making early diagnosis very difficult. Once established, changes in body shape are difficult to reverse. Preventive strategies that include earlier detection need to be explored.**
- **Provider understanding and acknowledgement of the psychological effects are essential to effective treatment and improved quality of life.**
- **Substitution of stavudine with either tenofovir or abacavir has shown improvements in the form of weight gain and lipoatrophy scores. These findings support the urgent need for increased availability as well as early substitution of tenofovir or abacavir as part of antiretroviral therapy in resource-poor settings.**

Lipodystrophy due to antiretroviral treatment

Antiretroviral treatment has a number of well-established side-effects, most of which are associated with specific drugs.

Lipoatrophy (a distinct component of lipodystrophy syndrome) is one of particular significance and is extremely difficult to treat. The resulting physical changes in appearance because of subcutaneous fat loss from the face, legs, arms and buttocks (lipoatrophy) and lipohypertrophy, (accumulation of fat in the stomach, neck or breasts) can be psychologically damaging and stigmatising leading

to fear of disclosure, social isolation, poor adherence, stopping of treatment as well as suicide.

Lipoatrophy is linked to antiretroviral treatment and in particular stavudine (d4T) and to a lesser degree zidovudine (AZT) and didanosine (ddI).¹

Stavudine, didanosine (ddI) as well as zidovudine (AZT) are also linked to other metabolic disorders that include hyperlactatemia and lactic acidosis as well as peripheral neuropathy but are beyond the scope of this article. See [HATIP April 2006](#) for lactic acidosis and [HATIP 133, March 2009](#) for peripheral neuropathy.

Since 2004, because of the frequency and seriousness of the side-effects, use of stavudine has been phased out in first-line regimens in high-income countries. World Health Organization (WHO) revised guidelines published this month now recommend for the same reasons that stavudine be phased out in first-line regimens in resource-poor settings too.²

WHO 2006 guidelines based on studies in high-income countries recommend replacing stavudine (d4T) with tenofovir (TDF) or abacavir (ABV) when lipoatrophy occurs.³ Better still, lipoatrophy can be almost entirely avoided if tenofovir is used from the outset.

However, the reality is that in most resource-poor settings choice is severely limited. Most first-line regimens include either stavudine or zidovudine plus lamivudine with nevirapine or efavirenz. Choice of antiretroviral regimen is determined by cost and availability in spite of known toxicities. Cost considerations often mean quality of life issues are not a priority in policy decision-making.

In South Africa, for example, despite longstanding and extensive demands for the phasing out of stavudine, its use continues in public health settings and is expected to continue for a number of years.⁴ So in spite of recent recommendations the practicalities of an immediate change of regimen mean that d4T and, importantly, its side effects will persist for some time in resource-poor settings.

Where replacement of, or the phasing out of d4T is not feasible WHO has recommended a reduced dose of stavudine (from 40 mg to 30 mg for adults weighing 60 kg or more) with the expectation of countering long term side effects while not compromising treatment efficacy. [Preliminary findings](#) support this,⁵ notably in the prevention of early neuropathy and lipoatrophy,⁶ but there is still a need for the further evaluation of long-term side effects.

Working with these restrictions makes long-term adherence difficult for patients and is especially challenging for providers.⁷

A recent literature review of HIV-related lipodystrophy in Africa and Asia revealed a total of 21 abstracts and articles on the subject (excluding those related to children).⁸ The paucity of research underscores the difficulties and dilemmas both patient and provider face and include:

- Absence of a uniform definition. Studies included the following variations: lipoatrophy alone, lipohypertrophy alone, and a combination of both; both lipoatrophy and lipohypertrophy; lipoatrophy; and lipohypertrophy; gynaecomastia as well as the presence of lipomas have been included. Other studies have limited the definition to facial lipoatrophy and others simply referred to "body shape change" or the amount of peripheral and central fat at each body part.⁹
- Lack of commonly agreed standards of measurement; wide variety of assessment methods
- Difficulties of (early) diagnosis
- Lack or absence of treatment
- Change of antiretroviral regimen is not an option

While continuing advocacy efforts to ensure that stavudine is phased out are crucial, appropriate management of its damaging and disfiguring side effects is urgently needed.

Providers need to be very familiar with the evolution of these side effects and know how to manage them with what is available in their settings.¹⁰

Up to now very little guidance has been provided for clinicians for diagnosis and management of lipoatrophy in WHO and national guidelines, in contrast with most other side-effects where clear management guidelines exist, based on the grading/severity of the toxicity.¹¹

Although these changes in body fat distribution are not life-threatening, they are a major cause of suffering for people living with HIV because they can have a hugely stigmatising effect, and may increase a person's sense of discomfort in their own body to such an extent that they become suicidal. A survey among HIV-positive patients in the United States found that "HIV patients with body fat redistribution would trade off length of life or accepted greater risks of mortality in order to maintain a life free of body fat alterations."¹²

Although less is known about the psychological experience of living with lipoatrophy or lipodystrophy in resource-limited settings, there is little reason to believe that these body fat changes will be any less difficult to live with among people in less wealthy regions of the world. Indeed, given the intense stigma that surrounds HIV infection, and the association between stigma and loss to follow-up, there is every reason to believe that lipoatrophy will have a profound effect on the quality of life and the long-term health of any individual who develops it while receiving antiretroviral treatment in low and middle-income countries.

This clinical review looks at what is known about the incidence and presentation of body fat redistribution in resource-limited settings, how it is diagnosed, and what can be done to prevent or alleviate the problems, in particular lipoatrophy, the most frequent and stigmatising problem.

What are lipodystrophy and lipoatrophy?

Lipodystrophy is a syndrome characterised by abnormal fat distribution and metabolic disturbances in the way the body processes fats (lipids) and sugar (glucose). Depending on its severity lipodystrophy can increase someone's risk of diabetes and heart disease.

HIV-related lipodystrophy includes two distinct phenomena: lipoatrophy (subcutaneous fat loss) and lipohypertrophy (fat accumulation). They may be present in a patient at the same time but the two conditions are not part of a single syndrome (in other words, fat from the periphery is not moving to the central fat stores). Although central fat accumulation is not specific to HIV disease, and was not found to be more common among HIV-positive than HIV-negative men in the FRAM case-control study of lipodystrophy,^{13, 14} its rapid emergence in a sizeable minority of patients soon after starting antiretroviral therapy has led many experts in the field to maintain the view that fat accumulation in people on ART is an adverse effect of treatment, not lifestyle.

Lipoatrophy involves loss of fat in the face, extremities (especially the legs, with leg veins becoming more prominent), buttocks, and subcutaneous tissue of the abdominal area. It can lead to a wasted appearance and must be differentiated from wasting resulting from HIV disease progression and/or opportunistic infections that involve loss of muscle mass as well as fat.

Fat accumulation, lipohypertrophy, can present in the neck and back area, abdomen and breasts as well as other areas.^{15, 16} The fat which accumulates is not subcutaneous fat, but visceral, or central fat, which accumulates around the organs in HIV-negative people with metabolic syndrome. Fat accumulation must be differentiated from obesity, which can occur when patients with HIV

infection are started on antiretroviral therapy and become healthier or regain appetite.

What causes fat loss?

At first people with HIV and their health care providers thought changes in body shape were caused by protease inhibitors. Since most patients take a regimen of combined antiretroviral medications it was difficult to identify a specific class of antiretrovirals associated with lipodystrophy. Many different patterns of body fat changes are seen so it is possible that different combinations of drugs cause different patterns of changes. Generally the protease inhibitors have been linked to fat accumulation while the thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs) stavudine (d4T), and to a lesser extent zidovudine (AZT), have been linked to fat loss.

Most studies agree that d4T (stavudine) is a major cause of lipoatrophy. At least three major studies, ACTG 384, Gilead 903 and ACTG 5142 – have indicated that d4T is more strongly associated with body fat changes, specifically fat loss (lipoatrophy) than other NRTIs.^{17, 18}

The precise mechanism by which nucleoside analogues might cause fat loss is unclear. One suggestion is that nucleoside analogues may damage the DNA of mitochondria in fat cells (adipocytes) that store fat in the limbs. NRTI-related fat loss has been linked to alterations in mitochondrial DNA, high levels of lactate in the blood and liver dysfunction.^{19, 20, 21}

There is also evidence from retrospective analyses of clinical cohorts that a low nadir CD4 count, body composition prior to treatment, gender, age and ethnicity all affect the risk of developing lipoatrophy. This evidence is discussed in more detail in [Risk factors for fat changes](#) in the [aidsmap.com](#) guide to lipodystrophy.

Epidemiology

Estimates of the incidence and prevalence of lipodystrophy in people on antiretroviral therapy in resource-poor settings in Africa and Asia vary considerably due to the lack of a standard definition, difficulties in measurement and wide variations in assessment and the paucity of published studies. Definitions have been investigator-driven and vary widely as noted above. Incidence and prevalence is thought to be comparable to resource-rich settings, and notably the United States, with an estimated prevalence rate of 28-38%.²²

Dr. Johan van Griensven of the Institute of Tropical Medicine, Antwerp, who has been involved in the development of HIV treatment services in Rwanda, told HATIP that there could be a number of explanations for the different prevalences observed in different settings and programmes. Besides true differences, and differences in diagnostic method, the following factors could contribute:

- 'Age' of the ART programme: percentage of patients on ART for more than 1-2 years.
- Clinical focus of the clinicians: in a program with diagnostic tools and a high index of suspicion for lactic acidosis, some cases of lipoatrophy might be labelled as symptomatic hyperlactatemia since lipoatrophy can be associated with nausea; on the other hand, some cases might be labelled as neuropathy, since some patients present with neuropathy and lipoatrophy at the same time. Consequently, the same patient might receive two different diagnoses depending on the attending physician.
- In settings where there is no routine screening for lipoatrophy, especially no clinical assessment, cases might be missed easily,

since in Dr van Griensven's experience patients tend not to report body fat changes spontaneously.

- On the other hand, in programmes with routine screening, a high prevalence might be found, but mostly consisting of mild cases.

Some examples of studies which have reported prevalence, in ascending order of prevalence are:

- In a regional multicentre observational cohort of patients starting ART in 1996 in the Asia-Pacific region: lipodystrophy was diagnosed in 10% (217) of patients. Median duration on ART was 3.8 years, on stavudine 2 years, on zidovudine 1.8 years and on protease inhibitors (PI) 2.6 years. Lipodystrophy was strongly associated with stavudine but PI use was protective in comparison to NNRTI use.²³
- At an HIV clinic in Pune, India lipodystrophy was seen in 26% out of a total of 150 patients taking d4T, 3TC and nevirapine, and 10% of those taking AZT, 3TC and nevirapine after a median of 18 months. Fat accumulation was found in 10% of the d4T-treated patients and 6% of the AZT-treated patients.²⁴
- In Rwanda among 114 patients, of which 112 were getting stavudine, 3TC and nevirapine 24% were diagnosed with body fat changes (of which those with lipodystrophy 12%, lipohypertrophy 4% and mixed patterns 8%)²⁵. This is part of the data from a study with over 400 patients.²⁶
- [Another study in Rwanda](#) involving 571 patients from the Centre Hospitalier Universitaire de Kigali, Treatment and Research AIDS Center, Hospitalier Universitaire de Butare and HIV/AIDS clinics of Kimironko, Bilyogo-Nyiaranuma, Kinyinya and Kacyiru on ART of which 82% received stavudine, lamivudine and nevirapine. While lipodystrophy was diagnosed (patient self report + clinician confirmation) in 34%. Prevalence reached 70% after 72 weeks on antiretroviral therapy of which 72% had peripheral lipodystrophy combined with abdominal lipohypertrophy.²⁷
- An example of how difference in definition and measurement give widely varying results is illustrated [within a single case-controlled study in Senegal](#) in which 83 patients were on antiretroviral treatment regimens that included stavudine and 63 on regimens containing zidovudine. Moderate to severe lipodystrophy was diagnosed in 31% of patients: 13% had fat loss, 15% fat gain and 35 with a combination of both after a mean duration of five and half a years. The use of d4T was the sole risk factor. When the investigators used a broader definition, they found that almost two-thirds of patients (65%) had developed body fat changes to some extent, ranging from mild to severe: 18% with fat loss, 31% with fat gain and 12% with both. When lipodystrophy was assessed using body measurements 50% of patients were found to have developed body fat changes.²⁸

Because of the almost complete lack of published evidence, prevalence of lipodystrophy among children in resource-poor settings is difficult to ascertain. In Thailand a retrospective study of 90 children who started antiretroviral treatment with either nevirapine or efavirenz with stavudine and lamivudine revealed that prevalence was over 50% after 144 weeks on antiretroviral therapy. Outcome was the same for both treatment regimens. Mean age at entry was 7.6 years. Higher prevalence was seen in females and those with more advanced disease.²⁹

In children with HIV one study from Romania showed that both stavudine and protease inhibitors were linked to the development of lipodystrophy in 42% of children aged 3-19 after five years on antiretroviral treatment.³⁰

In multivariate analyses variables associated with lipodystrophy in adults in resource-poor settings include:

- Older age ^{31, 32, 33}

- Being female ^{34, 35, 36}

- Length of time on treatment ; lipodystrophy usually appears within 2-4 years ^{37, 38, 39}

Another multivariate analysis in Thailand found that co-infection with hepatitis C put patients at increased risk for lipodystrophy.⁴⁰

In addition evidence from resource-rich settings suggests the risk of lipodystrophy is increased in whites (5.4 odds ratio) when compared to blacks.⁴¹ The possibility of ethnic differences in vulnerability to the development of lipodystrophy and lipohypertrophy is not well explored, but given ethnic differences in the tendency to store fat – and variations in the sites of fat deposition between races – it would be very surprising if ethnic differences did not exist.

Methods of diagnosis

With no standard case definition nor evidence of the condition within the general population, diagnosis of HIV-related lipodystrophy is difficult. Diagnosis is clinical and is based on a combination of patient (subjective) self-report and provider experience, assessment and measurement of body changes.⁴² Studies in resource-poor settings indicate methods of assessment fall somewhere within these boundaries and are as varied as the definitions.⁴³

Lipodystrophy is not considered significant until it is clinically apparent. This complicates a provider's ability to make a timely (early) diagnosis. Lipodystrophy in particular is progressive, and studies of drug-switching show that any subsequent fat gain is slow. Thus the best hope of effective action is early intervention, making regular monitoring imperative. As noted earlier clear national and WHO guidelines for diagnosis and management of lipodystrophy are urgently needed.

Recent large clinical trials (in resource-rich settings), for example ACTG 5142,⁴⁴ have used a subjective fat loss of 20 percent as the criterion for lipodystrophy. However, subcutaneous fat loss of 20% is rarely clinically apparent. Other clinical trials indicate that 40-50% fat loss is necessary for lipodystrophy to be clinically apparent.^{45, 46}

As lipodystrophy is a clinical diagnosis it is important to consider other causes of fat loss from the extremities, buttocks, abdomen and face. These may include HIV-associated wasting, diarrhoea syndromes (including cryptosporidiosis and microsporidiosis), tuberculosis/mycobacterial disease or reduction in calorie intake/malnutrition.⁴⁷ The latter causes will include loss of lean body mass (muscle) as well as fat. Some studies have suggested that lipodystrophy is associated with recent weight loss.⁴⁸ Treatment failure which typically occurs after a long period on ART and could involve weight loss is also a possibility.

In resource-poor settings lipodystrophy is essentially a diagnosis of exclusion once all other explanations for subcutaneous fat loss have been ruled out. In clinical practice assessment of body changes might include both subjective and objective tools:

- Patient history
- Patient self-report
- Physical examination of extremities, buttocks and subcutaneous tissue of the abdomen, (old photographs may be helpful) and anthropometric measurements (for example weight, waist to hip ratio)
- Questionnaires
- Classification systems

The availability of baseline measurements will help in making diagnosis easier. When no alternative to stavudine as part of a first-line regimen is available then routine examination and questioning patients regularly about body changes is important.

Change to zidovudine, while somewhat less toxic, is preferable to continuing on stavudine.⁴⁹

Questionnaires and classification systems, in a two-step process, are used primarily in clinical practice. They are simple and cost-effective but are subject to observer bias.

Lipoatrophy is assessed using the HIV lipodystrophy case definition (LDCD) questionnaire, developed by Carr and colleagues. Fat loss in any of seven body regions (face, neck, arms, breasts, abdomen, buttocks and legs) is systematically assessed. This is followed by determining the degree of severity of lipoatrophy at each body region using the HIV Outpatient Study (HOPS) scale as follows: absent (score of 0), mild (noticeable on close inspection, score of 1), moderate (readily noticeable by patient or physician, score of 2), and severe (readily noticeable to a casual observer, score of 3).⁵⁰

Objective assessments used mostly in clinical trials can be costly and are of questionable utility and include:

Anthropometric measurements. These assessments are easy, fast and inexpensive and may compare well with results from expensive imaging techniques and include skin fold and waist measurements as well as waist to hip ratio (WHR). The latter is convenient but of variable accuracy.⁵¹

- Skin fold tests: this test uses calipers to measure the quantity of subcutaneous fat. It needs to be done by a dietician or doctor experienced in use of the test, and can be used to monitor changes in the amount of subcutaneous fat on the arms or legs. However, these changes are not representative of total body fat changes.

- Bioelectrical impedance analysis (BIA): this test passes a small electric current through the body. Since fat is a poor electrical conductor compared to muscle, the body presents an impedance (a more complex measure of electrical resistance) to the current which can be measured and used to determine overall proportions of overall lean body mass, fat, and other body composition compartments. BIA cannot detect regional changes in body fat, only total body fat changes.

Dual-energy X-ray absorptiometry: DEXA scan is a method which can show the distribution of fat, muscle and bone in the body, and can detect changes in different parts of the body. It is likely to produce more accurate measurements of fat loss from the limbs, because it cannot distinguish between subcutaneous (under the skin) and visceral or abdominal (organ) fat. However, this test is expensive, requires elaborate equipment which is largely unavailable in resource-poor settings, and is less accurate in very thin or very fat people.

Self-report combined with clinical examination by a health provider incorporating the LCDS and HOPS questionnaires described above appear to be the most frequent assessment method used in Africa and Asia according to published studies.⁵²

Van Griensven and colleagues assessed weight change using self-reporting, clinical assessment and in particular “weight evolution” to indicate fat recovery after substitution of stavudine with tenofovir or abacavir, although noting that this is a possible limitation of the study. Yet, they argue that in resource-poor settings high numbers of patients, together with staff limitations in both numbers and skills, and a lack of sophisticated technologies, mean that “measurement of body weight is a relevant and easy-to-use parameter for the follow-up of patients on ART, as it can indicate important clinical events such as treatment failure, malnutrition and infections”.⁵³

Psychosocial issues

Lipoatrophy leads to other psychological, social and physical consequences severely impacting quality of life.

The physical changes often cause the most distress.

“After surviving many years with HIV a patient of mine began to get lipoatrophy of the face and people began to ask him what was wrong. He thought they knew of his diagnosis. I counselled him and suggested he change his treatment regimen. He could not afford the increased cost. Disgusted and disheartened he stopped treatment and died a few months later. Another patient of mine, a lawyer by profession, could not deal with this side effect and committed suicide”.⁵⁴

Changes in body shape are reported to be associated with negative emotional and social consequences,^{55, 56, 57, 58} and include:

- Lowered self-esteem, poor body image, social withdrawal
- Perceived and experienced stigma and discrimination

The repercussions of which may lead to:

- Fear of or forced HIV disclosure due to facial fat loss
- Poor adherence or stopping of treatment
- Mood disorder including severe depression and suicide

Dr. van Griensven commented: “I think these body fat changes have a substantial impact on mental health and stigma. Although most quotes and experiences on that are often anecdotal, they speak for themselves.

“For example, we had female patients that were ‘encouraged’ by their husbands to interrupt ART because they did not like the body changes in their wives. Some patients expressed reluctance to start ART in fear of these body changes.”

“Other non-HIV infected patients mentioned that they could locate the ART clinic in any health centre just by looking for the characteristic body habitus changes in this patient population.”

“As such, besides individual suffering, this side-effect could potentially affect the acceptance of ART within a community, and lead to ongoing stigmatisation. Especially now that we aim to test and treat early (ideally starting ART in asymptomatic patients), acceptability and acceptance of ART are key issues.”

We asked Dr van Griensven how he would rate body fat changes as a cause of suffering in his patients in comparison to other drug side-effects seen commonly in ART patients?

Dr. van Griensven replied: “Here there is high individual variability; although the ‘intensity’ of the suffering is not so high, the chronicity and irreversibility could make it an overall important contributor to patient psychological suffering. These issues might become even more important for patients the longer they are on ART.

“In our experience, early detection and drug substitution (after ruling out alternative diagnosis) improves the chances of reversibility.”

Treatment

Currently there is no treatment available to reverse all body fat changes and people with body fat changes are not in a position to stop taking antiretroviral drugs.

Fat loss from the arms, legs and face may be improved by switching from d4T to abacavir or tenofovir.⁵⁹ However the restoration of fat observed in ‘switch’ studies is very slow, and is often imperceptible to the patient for a long time.

In cases of severe lipoatrophy fat restoration will be particularly difficult because the population of cells that make up the subcutaneous fat layer have been so severely depleted by mitochondrial toxicity.

Waiting until serious fat loss has occurred before switching severely diminishes a patient's chance of experiencing any fat restoration as a result of a therapy switch.

A variety of techniques are being tested to restore the facial appearance of people who have lost fat from the face. Most of these involve injectable substances such as poly(lactic acid) (*New Fill*), polyalkylimide gel (*Bio-Alcamid*) and others. These injectable substances are rarely available in low and middle-income settings, although use has been reported in Latin America, particularly Brazil, where several surgeons have been pioneers in the global field of lipoatrophy repair.

Support and counselling

Given the limited treatment options within resource-poor settings and the limited possibilities for reversing the side effects of lipoatrophy the role of the health provider is especially challenging. There are no easy solutions. Knowing that no other treatment options exist, the provider may understandably be reluctant to talk of the potential side effects. However if antiretroviral treatment contributes to the patients' perception of stigma within the context of a highly stigmatised disease then providers need to be concerned about this. To help patients better prepare for and handle the potential side effects doctors and other health care workers need to be more up-front in providing information in advance.⁶⁰ Studies suggest that psychological support and attention to patients' concerns about the effect of body fat changes may be beneficial.⁶¹

A "patient-centred care approach in which African patients are included in therapeutic decisions and paying attention to patients' perceptions of the effects of HAART, may contribute towards greater adherence to proposed interventions and develop a more stable quality of life continuum over time," write Mutimura and colleagues. "An assessment of quality of life is integral to efficient treatment outcomes to evaluate long-term strategies that optimize the durability of response to antiretroviral therapy in sub-Saharan Africa".⁷⁴

Diets and exercise

Mutumura and colleagues have demonstrated that exercise may have a beneficial effect on mood and well-being among people with lipodystrophy in Rwanda,⁶² while research in the developed world has shown that resistance exercise may reduce central fat accumulation. However for others lipoatrophy may actually prevent people from engaging in exercise as they are self-conscious of the wasting on their limbs and may fear others' comments.⁶³

There is no evidence to suggest that change of diet improves the condition.

Reducing dosage of stavudine

In 2007 the World Health Organization recommended that resource-poor country treatment programmes use a 30 mg dose of d4T if it was not possible to phase out use of the drug. Their recommendation was based on a number of small studies which showed no negative effect of using a lower dose in adults weighing more than 60 kg. While preliminary findings support this recommendation evaluation of long-term side effects according to dose is recognized as essential.⁶⁴

In a three year retrospective observational study in Rwanda use of 40 mg of d4T was associated with increased risk of lipoatrophy and early (less than six months) neuropathy and is in line with findings from another large three-year cohort study in South Africa.^{65, 66}

The Rwanda study looked at the independent effect of d4T dosing to assess whether the association of certain side effects with baseline body weight persisted after adjusting for weight-based dosing. Irrespective of the d4T dose (40 mg or 30 mg) higher baseline body weight increased the risk of symptomatic

hyperlactatemia/lactic acidosis as well as late neuropathy. Dose reduction (30 mg) resulted primarily in a reduction in early neuropathy as well as lipoatrophy. The authors noted that one in four patients placed on a d4T-containing fixed dose combination in their programme ended up with significant long-term toxicity. Relevant strategies they feel need to be urgently considered include d4T dose reduction to 30 mg, increased access to safer antiretroviral drugs in low-income countries and close monitoring for those at risk.

Replacing stavudine with abacavir or tenofovir

Evidence from several small studies in resource-rich settings has suggested some benefit from switching from d4T treatment but the numbers treated in these studies are small, with no matched control groups or randomisation. Current evidence from resource-rich settings suggests that switching from d4T to another nucleoside reverse transcriptase inhibitor seems to produce modest benefits in fat wasting.

Van Griensven and colleagues undertook the first cohort study in Africa to assess weight evolution after substituting stavudine because of lipoatrophy.⁶⁷ Substitution with either tenofovir or abacavir was associated with weight gain, while substitution with zidovudine led to a progressive weight loss over time. Significance in weight change between the two groups developed from six months after stavudine substitution. In addition differences in evolution of lipoatrophy scores were seen between the two groups, adding to the clinical relevance. The authors note that while the two cohorts were not randomly selected those in the tenofovir/abacavir group had more severe lipoatrophy symptoms at baseline making the difference clinically more significant.

The authors note that their findings are consistent with three studies from high-income countries that demonstrate the positive clinical evolution when substituting stavudine with tenofovir or abacavir.^{68, 69, 70}

These findings add to the evidence that tenofovir or abacavir are better than zidovudine as an alternative to stavudine. The authors stress the need for improved access to tenofovir or abacavir and that earlier substitution with either may well be justified.

When routine replacement of stavudine with tenofovir or abacavir occurs most patients will have been on stavudine for a considerable length of time, also putting them at increased risk for treatment failure. Lipoatrophy typically becomes apparent after 1-2 years of ART, which is the same time that virological failure is increasingly seen. Consequently, there might be a risk that patients change from d4T to tenofovir with a detectable viral load (a single drug substitution with a 'failing regimen'). Substituting tenofovir for stavudine in a person on a failing ART regimen will cause resistance to tenofovir. Van Griensven and colleagues suggest that before substitution an assessment of the efficacy of the ART regimen is carried out, preferably with viral load testing. They suggest to consider switching to tenofovir with a protease inhibitor-containing regimen where treatment failure is suspected.⁷¹

Facial fillers

Current estimates suggest that approximately 30 to 40% of people taking antiretroviral therapy will develop some form of facial wasting, and that facial fat loss tends to occur quite rapidly, often within six months. How to prevent or reverse facial wasting remains unknown. Consequently research has focused on reconstructive or surgical procedures to fill out sunken cheeks.

Several approved and experimental procedures are being used in resource-rich settings and include: poly(lactic acid) (*New Fill*); polymethyl methacrylate (PMMA); poly(vinyl)/polyacrylamide gel (*Evolution*)/polyalkylimide gel safe (*Bio-Alcamid*) and fat transfer injections.

Polylactic acid is already used in cosmetic surgery as treatment for fine lines, wrinkles and furrow. It works by stimulating the growth of collagen, a structural component of the skin and other body tissues, and the development of a thicker layer of skin which fills out the wasted regions of the cheeks. Polyactic acid is not immunologically active, and so cannot cause any allergic or inflammatory response.

Polyalkylimide marketed as *Bio-Alcamid* is injected into the face and forms a soft gel replacement for lost fat. Studies suggest that both polylactic acid and polyalkylimide can be used safely and effectively reduced the visible symptoms of facial lipoatrophy in HIV-positive patients and improved self-reported anxiety, depression and overall quality of life.⁷²

Facial fillers are not available in resource-limited settings because they cost anywhere from \$1000 - \$3000 for a course of treatment. They also require physician or nurse training in how to carry out the injection of the facial filler, and the use of a local anaesthetic. Given these barriers, it is all the more important to look at how lipoatrophy can be avoided in the first place.

Treatment for lipohypertrophy (fat accumulation)

There is very limited evidence concerning the ability of switches in drug treatment to reverse fat accumulation, and the only unequivocal data showing a successful intervention for treating central fat accumulation concerns the human growth hormone-releasing factor tesamorelin, which reduced belly fat by around 15% over 26 weeks in a randomised study, compared to a 5% reduction in the placebo group.⁷³

Patient demand for treatment

The available evidence suggests that facial fillers are successful. Yet in a study of Africans with lipoatrophy in a London clinic, few of the participants had had *New Fill* treatment. The findings reveal some interesting insights into patient perceptions of lipoatrophy, and the extent to which patients complain about a stigmatising side-effect, even when corrective treatment is available.

Based on their clinical observations the authors suggested that this may be because:

- Patients are reluctant to speak to their doctor about this and within the context of depression it may be too difficult for them to raise the issue with their doctor
- Depression may make them feel that they are not entitled to it and that nothing will help them so there is no point in mentioning it
- Where many patients have had close family members die of HIV disease, they may feel they have no right to complain about life-saving medication.

These reasons, the authors stress, place the responsibility on the health provider to raise the issues and be aware of the data which suggest that lipodystrophy syndrome is highly associated with mood disorder, and in the case of this particular study, associated with the perception of HIV stigma.⁷⁴

Pain

In addition to the psychological pain described above pain will be experienced as fat cushioning is lost from bony prominences, for example, from the buttocks, making it difficult for patients to sit even for short periods of time. Measures to relieve pain need to be discussed with patients suffering severe fat loss.

Conclusion: First, do no harm

All the available data suggest that patients receiving stavudine-based ART are at high risk of developing lipoatrophy and other body fat changes, and that risk rises as time on treatment lengthens. As yet it is unclear whether there is a subset of patients who are permanently immune to fat loss, or whether some people

just take longer than others to manifest the condition, due to genetics or baseline fat levels.

While peripheral neuropathy is difficult to ignore when it is causing crippling pain, many people with HIV do seem to live with lipoatrophy without complaint to their health care providers, accepting it as the price that must be paid for life-giving treatment.

Yet there is good evidence that eventually the stigmatising effect of lipoatrophy undermines treatment adherence, and has a profound effect on quality of life.

In Europe, Australia and North America people living with HIV had to protest vocally about this side-effect in order for it to be taken seriously, and had it not been for enlightened clinicians who listened to their complaints and undertook extensive research to understand the condition, stavudine-based treatment might still be the norm for first-line treatment on grounds of cost even in the wealthiest countries in the world.

Recent guidance from WHO suggests that countries should begin planning for the phase-out of stavudine as soon as budgets allow. This could be a recipe for inaction. The history of the HIV epidemic shows that strong advocacy by people with HIV, by civil society and by scientists has been necessary for policy change whenever change has come with a price tag.

In the case of first-line treatment, change will not be cheap, but the long-term cost of doing nothing will be to consign a very large number of people to years of treatment with drugs that are not just sub-optimal, but downright harmful.

References

- [1] van Griensven J et al. *Weight evolution in HIV-1 infected women in Rwanda after stavudine substitution due to lipoatrophy: comparison of zidovudine with tenofovir/abacavir*. *Trans R Soc Trop Med Hyg* doi:10.1016/j.trstmh.2008.08.015, 2008.
- [2] WHO. *Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents* 2009 Revision; World Health Organization, 2009. <http://www.who.int/hiv/pub/arv/advice/en/index.html>
- [3] WHO. *Antiretroviral treatment for HIV infection in adults and adolescents in resource-limited settings: towards universal access. Recommendations for a public health approach*. 2006 Revision: World Health Organization; 2006 <http://www.who.int/hiv/pub/guidelines/adult/en/index.html>
- [4] van Griensven J et al op cit
- [5] Hoffmann, CJ et al. *HIV suppression with stavudine 30 mg versus 40 mg in adults over 60kg on antiretroviral therapy in South Africa*. *AIDS* 23 (13): 1784-1786, 2009
- [6] van Griensven J et al. *Stavudine- and nevirapine-related drug toxicity while on generic fixed-dose antiretroviral treatment: incidence, timing and risk factors in a three-year cohort in Kigali, Rwanda*. *Trans R Soc Trop Med Hyg* (2009), doi:10.1016/j.trstmh.2009.07.009 (in press)
- [7] Murphy RA et al. *Antiretroviral therapy-associated toxicities in resource-poor world: the challenge of a limited formulary*. *The Journal of Infectious Diseases* 196:S449-S456, 2007
- [8] Womack J. *HIV-related lipodystrophy in Africa and Asia*. *AIDS Reader*. 19: 131-139, 148-152, 2009
- [9] Ibid
- [10] Murphy RA et al. op cit
- [11] van Griensven J et al. *Substituting tenofovir for stavudine in resource-limited settings: there are challenges ahead*. *AIDS* 23:1027-1033, 2009 and personal communication.
- [12] Lenert L et al *Adverse effects of medications and trade-offs between length of life and quality of life in human immunodeficiency virus infection*. *Am J Med*, 113: 229-232, 2002
- [13] FRAM (Study of Fat Redistribution and Metabolic Change in HIV Infection). *Fat distribution in men with HIV infection*. *J Acquir Immune Defic Syndr* 40(2):121-131, 2005.
- [14] FRAM (Study of Fat Redistribution and Metabolic Change in HIV Infection). *Fat distribution in women with HIV infection*. *J Acquir Immune Defic Syndr* 42(5):562-571, 2006.

- [15] Cofrancesco, J *Lipodystrophy*. John Hopkins poc-it center, HIV guide. www.hopkins-hivguide.org/diagnosis/complications_of_therapy/lypoatrophy.html
- [16] NAM, Side effects, December 2008 <http://www.aidsmap.com/cms1314814.aspx>
- [17] Dubé MP et al. *Prospective study of regional body composition in antiretroviral-naïve subjects randomized to receive zidovudine + lamivudine or didanosine + stavudine combined with nelfinavir, efavirenz or both*: A5005s, a substudy of ACTG 384. *Antiviral Therapy* 7:L18 (abstract 27) 2002b.
- [18] Staszewski S et al. *Efficacy and safety of tenofovir DF (TDF) versus stavudine (d4T) when used in combination with lamivudine and efavirenz in antiretroviral naïve patients: 96-week preliminary interim results*. Tenth Conference on Retroviruses and Opportunistic Infections, Boston, abstract 564b, 2003.
- [19] Brinkman K et al. *Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy*. *Lancet* 354: 1112-1115, 1999.
- [20] Carr A et al. *A syndrome of lipodystrophy, lactic acidemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome*. *AIDS* 14: F25-F32, 2000.
- [21] Boyd MA et al. *Changes in body composition and mitochondrial nucleic acid content in patients switched from failed nucleoside analogue therapy to ritonavir-boosted indinavir and efavirenz*. *J Infect Dis* 194 (online edition) 2006
- [22] Womack J, op cit
- [23] Han S et al. *Prevalence and risk factors of lipodystrophy among HIV-infected persons receiving HAART in the Asia Pacific region: results from the TREAT Asia HIV observational database (TAHOD)*, ICAAC, H1576, 2009.
- [24] Pujari SN et al. *Lipodystrophy and dyslipidemia among patients taking first-line World Health Organization-recommended highly active antiretroviral therapy regimens in western India*. *J Acquir Immune Defic Syndr* 39:199-202, 2005.
- [25] van Griensven et al. *Prevalence of lipodystrophy after 1 year of WHO first line ART in Kigali, Rwanda*, 13th Conference on Retroviruses and Opportunistic Infections (CROI), abstract 560a, 2006.
- [26] van Griensven J et al. *High prevalence of lipodystrophy among patients in stavudine-containing first line antiretroviral therapy regimens in Rwanda*. *Trans R Soc Trop Med Hyg*. 101:793-798, 2007.
- [27] Mutimura E et al. *Metabolic function and the prevalence of lipodystrophy in a population of HIV-infected African subjects receiving highly active antiretroviral therapy*. *J Acquir Immune Defic Syndrome* 46: 451-455, 2007.
- [28] Mercier S et al. *Lipodystrophy and metabolic disorders in HIV-1 infected adults 4-to-9-year antiretroviral therapy in Senegal: A case-control study*. *J. Acquir Immune Defic Syndr* (online edition) 2009.
- [29] Aupribul L et al. *Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy*. *Antivir Ther*. 12 (8): 1247-54, 2007
- [30] Ene L et al. *Prevalence of lipodystrophy in HIV-infected children : a cross-sectional study*. *Eur J pediatr* 166:13-21, 2007
- [31] van Griensven J et al. op cit (2007)
- [32] Tin EE et al. *The efficacy and adverse effects of GPO-VIR (stavudine+lamivudine+nevirapine) in treatment-naïve adult HIV patients*. *Southeast Asia J trop Med Public Health* 36:362-369, 2005
- [33] Chariyalertsak S et al. *Prevalence of lipodystrophy after 3 years of WHO first line ART and its impact on quality of life and negative perception of ART in Thailand*. 17th International AIDS Conference, Mexico, Abstract MOPDB101, 2008
- [34] van Griensven J et al. op cit (2007)
- [35] Chariyalertsak S et al. op cit
- [36] van Griensven J et al. *Toxicity of stavudine- and nevirapine-containing antiretroviral treatment regimens : incidence and risk factors after three years in a large cohort in Rwanda*. 17th International AIDS Conference, Mexico. Abstract THPEO 188, 2008
- [37] ibid
- [38] Chariyalertsak S et al. op cit.
- [39] Han S et al. op cit
- [40] Han S et al. ibid
- [41] Lichtenstein K et al *Incidence of and risk factors for lipodystrophy in ambulatory HIV-1 infected patients*. *J Acquir Immune Defic Syndr* : 32 (1) 48-56, 2003.
- [42] Lichtenstein K et al. *Clinical assessment of HIV-associated lipodystrophy in an ambulatory population*. *AIDS* 15:1389-1398, 2001.
- [43] Womack J. op cit.
- [44] Haubrich R et al. *Metabolic outcomes of ACTG 5142; a prospective randomised phase III trial of NRTI, PI-and NNRTI sparing regimens for initial treatment of HIV-1 infection*, Fourteenth Conference on Retroviruses and Opportunistic Infections, Los Angeles, abstract 38, 2007.
- [45] Moyle G et al. *A randomised open-label comparative trial of abacavir or tenofovir DF as a replacement for a thymidine analogue in persons with lipodystrophy and suppressed HIV RNA on HAART: The RAVE study*. Twelfth Conference on Retroviruses and Opportunistic Infections, abstract 44LB, 2005.
- [46] McComsey GA et al. *Improvement in lipodystrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the TARHEEL study*. *Clin Infect Dis* 38:263-70, 2004.
- [47] Murphy RA et al. op cit.
- [48] van Griensven J et al. op cit *Weight evolution...* 2008 (in press)
- [49] Murphy RA et al. op cit
- [50] Carr A et al. *An objective case definition in HIV-infected adults: a case control study*. *Lancet* 361: 726-35, 2003
- [51] Ketel IJ et al. *Superiority of skinfold measurements and waist over waist to hip ratio for determination of body fat distribution in a population-based cohort of Caucasian dutch adults*. *Eur J Endocrinol*. 156 (6): 655-61, 2007.
- [52] Womack J op cit
- [53] Mangili A et al cited in van Griensven J et al op cit (*Weight evolution* 2008).
- [54] Bharti R. *Lipodystrophy (body fat changes) in resource poor settings* AIDS-India eforum October 20, 2009
- [55] Campbell T et al. *Does lipodystrophy syndrome (LDS) have an effect on mood stigma and illness perception in HIV+ African people? A comparative study in a London clinic*. *AIDS Impact*, Botswana, Abstract 288, 2009
- [56] Chariyalertsak S et al. op cit.
- [57] Nachege J et al. *Impact of metabolic complications on antiretroviral treatment adherence: clinical and public health implications*. *Current HIV/AIDS Reports*. 6:121-9, 2009.
- [58] Mutimura E et al. *Assessment of quality of life in HAART-treated HIV-positive subjects with body fat redistribution in Rwanda*. *AIDS Research and Therapy*. 4:19, 2007
- [59] van Griensven J et al op cit *Weight evolution in HIV-1 infected women in Rwanda after stavudine substitution due to lipodystrophy: comparison of zidovudine with tenofovir/abacavir*. *Trans R Soc Trop Med Hyg* doi:10.1016/j.trstmh.2008.08.015, 2008.(in press)
- [60] Campbell. T personal communication
- [61] Mutimura E et al. op cit. 2007
- [62] Mutimura E et al. *The effects of exercise training on quality of life in HAART-treated HIV-positive Rwanda subjects with body fat redistribution*. *Qual life Res*. 17 (3):377-85, 2008
- [63] Campbell T. personal communication
- [64] Hoffmann CJ et al. op cit
- [65] van Griensven J et al. *Stavudine- and nevirapine-related drug toxicity while on generic fixed-dose antiretroviral treatment: incidence, timing and risk factors in a three-year cohort in Kigali, Rwanda*. *Trans R Soc Trop Med Hyg* (2009), doi:10.1016/j.trstmh.2009.07.009 (in press)
- [66] Boulle A et al. *Substitution due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort*. *Antivir Ther* 12:753-60, 2007.
- [67] van Griensven J et al. op cit *Weight evolution in HIV-1 infected women in Rwanda after stavudine substitution due to lipodystrophy: comparison of zidovudine with tenofovir/abacavir*. *Trans R Soc Trop Med Hyg* doi:10.1016/j.trstmh.2008.08.015, 2008.(in press) .
- [68] McComsey GA et al. *Improvement in lipodystrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the TARHEEL study*. *Clin Infect Dis* 38:263-70, 2004.
- [69] Martin A et al. *Reversibility of lipodystrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX extension study*. *AIDS* 18: 1029-36, 2004.

[70] Moyle GA et al. *A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipodatrophy*. AIDS 20: 2043-50, 2006.

[71] van Griensven J et al. *op cit* AIDS 23:1027-1033, 2009.

[72] Loufty M et al. *Immediate versus delayed polyalkylimide gel injections to correct facila lipodatrophy in HIV-positive patients*, AIDS 21: 1147-1155, 2007.

[73] Grinspoon S et al. *Metabolic effects of growth hormone-releasing factor in patients with HIV*. N Engl J Med 357:2359-2370, 2007.

[74] Campbell T et al. *op cit* and personal communication

about HATIP

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

Its publication is supported by the UK government's Department for International Development (DfID), the Diana, Princess of Wales Memorial Fund and the Stop TB Department of the World Health Organization.

Other supporters include Positive Action GlaxoSmithKline (founding sponsor); Abbott Fund; Abbott Molecular; Caviidi; Elton John AIDS Foundation; Merck & Co., Inc.; Pfizer Ltd; F Hoffmann La Roche; Schering Plough; and Tibotec, a division of Janssen Cilag.

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