



Lipodystrophy Syndrome(s)

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People living with HIV face numerous challenges when managing their health. One of the distressing observations includes visible changes in body shape and appearance. Although some aspects of this phenomenon were seen in earlier years of the epidemic, reports have increased since 1996 with the widespread use of three-drug anti-HIV therapy.

Although there is no precise, agreed-upon definition of the term, these changes of fat redistribution in the body and related irregularities in certain blood tests are typically called *lipodystrophy*. Only some people with HIV on anti-HIV therapy develop lipodystrophy; its true prevalence is unknown.

This discussion paper describes what's currently known about this condition. You will learn about what may or may not cause lipodystrophy and how it affects men and women. You will also read about a working definition, health risks, and ways to treat its symptoms and associated lab measures. We suggest you read Project Inform's *Mitochondrial Toxicity and Lactic Acidosis* for related information.

Working Definition of Lipodystrophy

A June 1999 meeting held in San Diego led to one working definition of lipodystrophy that includes at least one of the following. This is not a complete list as other changes in fat redistribution may not have yet been reported.

- Sunken cheeks in the face
- Increase of fat in the face
- Prominent veins in the legs (not associated with heavy exercise or muscle building routines)
- Loss of fat in the legs and arms
- Loss of shape in the buttocks
- Increase in fat around the gut (called *truncal* or *central obesity*. This is not the soft fat deposit under the skin that is associated with ageing, but a rapid increase in girth caused by the accumulation of hard fat deposits behind the abdominal muscles)
- Breast enlargement
- Fat pad on back of neck (sometimes called *buffalo hump*)
- Lipomas (fatty growths in different parts of the body)

Some scientific groups have their own definitions that may differ slightly or require multiple symptoms and/or lab abnormalities. Until one common definition is accepted, it will be difficult to calculate the actual incidence level of this problem or what works best in treating it.

Lab Abnormalities and Associated Health Risks

Changes in body shape are sometimes, but not always, accompanied by changes in lab measures of lipid (triglyceride and cholesterol) levels and insulin resistance. In the general population, increases in these measures are associated with a higher risk of heart disease and diabetes. It's unknown if increases in these measures are caused by HIV infection or anti-HIV drugs produce these same effects.

Lab abnormalities sometimes seen in some people with lipodystrophy include:

- increases in triglyceride levels,
- changes in cholesterol levels (increased LDL, or *bad cholesterol*, decreased HDL, or *good cholesterol*),
- start of diabetes or insulin resistance, and
- elevated blood pressure.

One study suggests that women are less likely than men to have changes in triglyceride and cholesterol levels and the reason for this difference is unknown. However, there are many contradictory findings about lipodystrophy in other studies, so it's unclear whether this is a conclusive observation.

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Symptoms and HIV Drugs

At various times, lipodystrophy symptoms have been blamed on individual drugs, on classes of drugs, on therapy overall, or on HIV itself. Although the links between HIV drugs and the problem are not yet well defined, some important observations have been made.

One study compared people using protease inhibitors to those who were not. It showed that people on protease inhibitors were more likely to have much higher cholesterol levels.

66% of people using ritonavir (Norvir) and saquinavir (Invirase) had cholesterol levels high enough to require cholesterol-lowering treatment according to the standards by the US National Cholesterol Intervention Program (NCEP) guidelines. However, only 32% of people taking indinavir (Crixivan) and 39% taking nelfinavir (Viracept) met the NCEP guidelines.

Another recent study showed that people on ritonavir had a 20 times greater risk of high triglyceride levels than those on other protease inhibitors. Some participants used gemfibrozil (Lopid) and/or atorvastatin (Lipitor), the most active drugs used to lower cholesterol and triglyceride levels. They showed only moderate success, suggesting that the problem is more complex than a simple increase in these levels.

These results suggest that protease inhibitors may also interfere with the drugs used to treat high cholesterol levels. Researchers have reported that a small number of people who stopped using protease inhibitors had major improvements toward normal triglyceride and cholesterol levels. This may not always be the case, though, since some nucleoside analogue RT inhibitor drugs (NARTIs) and some non-nucleoside analogue RT inhibitors (NNRTIs) are also capable of increased cholesterol and triglyceride levels.

Mitochondria and Anti-HIV Therapy

Early results from a small study show that people on NARTIs have fewer mitochondria in cells compared to HIV-positive people not taking NARTIs or HIV-negative people. Fewer mitochondria were only seen among people taking d4T (stavudine, Zerit) and not among people on other NARTIs. The average number of mitochondria decreased by 44%. One interesting but unexplained observation was that people with fat loss in the face, arms or legs (*lipoatrophy*) had fewer mitochondria while people who developed a buffalo hump had an increased number.

Another recent study also looked at the number of mitochondria in cells. Forty people participated, ten with fat wasting (group A), ten without signs of fat redistribution (B), ten never on anti-HIV therapy (C) and ten HIV-negative people (D). The number of mitochondria was looked at from tissue samples from the back of the neck, abdomen and mid-thigh.

The study found that people in group A had fewer mitochondria than those in group B who, in turn, had fewer mitochondria than groups C

or D. No differences in the number of mitochondria were found in cells between groups C or D. This study suggests that fewer mitochondria result from anti-HIV therapy and not HIV disease itself.

Protease Inhibitors and Lipodystrophy

New results suggest that each protease inhibitor may contribute differently to body composition changes. A group in Seattle reported that when ritonavir (Norvir) was given to HIV-negative people for two weeks, they experienced a significant rise in cholesterol and triglyceride levels. Now a group in San Francisco has given indinavir (Crixivan) to HIV-negative individuals for four weeks. There were no significant increases in these levels, but people had a marked decrease in insulin sensitivity (a marker of diabetes), something not studied by the Seattle group. Changes in these markers (the way the body uses fats and sugars) are believed to be part of lipodystrophy syndrome.

Another small study suggests that using human growth hormone (rHGH) may benefit people with fat accumulation. Seven people, four with buffalo humps and three with central obesity, used 3mg/day of rHGH for six months. Five people completed the six months, one stopped due to elevated glucose levels and another moved away. All five who completed the course had decreased fat accumulation with an average reduction of 4.4kg (about 10 pounds) in total fat and 5.4kg increase in muscle mass (*lean body mass*). It is unclear, however, whether this fat loss corrected the lipodystrophy at specific sites or was the normal outcome from using rHGH, which favors the growth of muscle tissue in general.

These early results hinting on the cause of lipodystrophy need to be confirmed. A complicating factor is whether all drugs in the same class will have the same effect and therefore cause the same side effect. It may be necessary to do studies for each drug.

Heart Disease

Much concern has been expressed about higher triglyceride and cholesterol levels and the possible risk they pose for heart disease. Dr. Grunfeld from the San Francisco Veterans Administration Medical Center compared these two levels in people taking protease inhibitors to a large study (Framingham Study) of HIV-negative individuals. Through his comparison, he assessed changes in risk of heart disease for people taking protease inhibitor therapy. However, his analysis could only assume that the increases in triglyceride and cholesterol levels seen in people taking protease inhibitors would have the same impact on heart disease of similar changes in these levels in HIV-negative people. This may or may not be the case.

Based on this comparison, he concluded that the use of protease inhibitors may result in a few more cases of heart disease over ten years, but it does not pose a large increased risk. Other factors like genetics, diet, and exercise will almost certainly contribute to these increased levels and risk for heart disease. Whether or not you use protease inhibitors, you should work with your healthcare provider



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What Are Cholesterol and Triglyceride Levels?

Two lab measures are discussed often in this publication. The first one for *cholesterol* checks how well your body processes fat and measures the amount of certain fats in blood. The second measure for *triglyceride* checks how well your body processes proteins. Both measures are important indicators for lipodystrophy and are becoming more often standard care.

Lipodystrophy appears slightly different between people on a protease inhibitor and those not. People only on NARTIs rarely develop changes in these levels, but they usually have a large weight loss before any change in body shape. In contrast, most on protease inhibitors with lipodystrophy have increased triglyceride and cholesterol levels and little or no change in overall weight. In both cases changes in body appearance occurred. They may well have unique causes in each situation—perhaps requiring different forms of prevention and intervention.

Results from the SALSA Study of 140 men and 30 women suggest that how long someone uses three-drug therapy may contribute to changes in body appearance. In this study only a few people who used three-drug therapy for less than a year developed lipodystrophy. About half of those on therapy for one to three years showed some evidence of changes in body shape.

However, there was no control group of people who had never taken any anti-HIV therapy. So it's unclear if the increased rate of lipodystrophy is associated more with the longer use of anti-HIV therapy or the longer duration of HIV infection. As noted earlier, changes in body shape were observed in the time before potent therapies were available. They're even seen in some people taking no therapy whatsoever.

to assess your own risk for heart disease and begin reducing this risk as part of your health management plan.

Diabetes

Changes in insulin sensitivity may, in some cases, put people at higher risk for diabetes. Several small studies report some success in combating insulin resistance associated with protease inhibitor use. These include times when people stopped using protease inhibitors and switched to regimens with either abacavir (Ziagen) or nevirapine (Viramune).

Among those who used protease inhibitors, taking troglitazone (Rezulin) seemed to increase insulin sensitivity. Two recently approved drugs, rosiglitazone (Avandia) and pioglitazone (Actos), are likely to have the same effect with perhaps a lower risk of the serious liver side effects associated with troglitazone.

Another drug that restores insulin sensitivity is metformin (Glucophage). However, one possible and potentially fatal side effect of using it is *lactic acidosis*, a build-up of lactate in the body. NARTIs that contribute to mitochondrial toxicity, like AZT, ddI and d4T, etc., can also cause *lactic acidosis*. For more information, read Project Inform's *Mitochondrial Toxicity*.

What Causes Lipodystrophy?

There has been much debate over what causes lipodystrophy in people living with HIV. Some researchers have proposed that it's due to direct effects of the protease inhibitors, and it certainly has become more common since they were made available. Others say that some of the nucleoside analogue drugs may be a contributing factor, and these drugs have indeed been more widely used and used for longer times since the advent of the protease inhibitors.

Some researchers report seeing lipodystrophy when using only two-drug nucleoside analogue combinations. Some speculate that it may be caused by rapid and sustained decreases in viral load (HIV RNA levels). This may not be unique to a particular class of anti-HIV drugs but related only to the potency of the total regimen, with the most potent regimens posing the greatest risk. It may also be caused by HIV itself interfering with how the body processes fats.

Some manifestations, like wasting in the face, arms, and legs, have been common since the earliest days of the epidemic. Or, it may even be due to the immune system becoming more aggressive once the onslaught of HIV is slowed down in response to therapy. Finally, it may be due to a combination, or different combinations, of these factors.

In a study by Dr. Kotler, a specialist in HIV-associated wasting, body shape information was collected from people since 1996 and compared to information gathered before the availability of protease inhibitors. This study confirmed that loss of weight, body cell mass and fat, and changes in body fat are characteristic features of HIV infection, and not strictly related to protease inhibitors. Reports of central obesity preceded the protease inhibitor era. These reports were similar in both men and women and in volunteers both taking and not taking protease inhibitors.

Lipodystrophy in Women

There are claims that women might experience lipodystrophy at a higher rate or in different ways than men. A number of women-specific studies and studies of men and women have investigated this issue.

While non-HIV related lipodystrophies are much more common in women than men, HIV studies have yielded conflicting reports. Some



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suggest that women might experience lipodystrophy slightly more often while others show no difference based on gender.

While debate is ongoing as to whether women are more at risk, what seems clearer is that women and men may experience lipodystrophy differently. For example, women with body changes may be more likely to experience increases in breast size and overall weight gain than men. Certainly some men experience these body changes, but they're more common in women.

On the other hand, men with body shape changes may more likely experience face and limb wasting. Also, men may more likely experience abnormal changes in cholesterol and triglycerides.

What the Studies Tell Us

A study of 306 women showed that enlargement of the breasts and waist and wasting of the butt, thighs, and calves were reported in 32 women (10.5%). All who reported fat changes used a regimen with 3TC. Twelve of the 32 women took double combination therapy (including 3TC) that did not include a protease inhibitor. Also, among women taking 3TC, the risk of developing changes in body shape was significantly lower in those also on AZT and higher in women on d4T.

The study suggests a strong association between body shape changes and using 3TC, whether they had taken a protease inhibitor or not. While far from confirmed, these data suggest that the mechanism causing body shape changes in women may not be related to protease inhibitors. Unlike in men, in women there seems to be a strong connection between 3TC and d4T use and lipodystrophy.

An Italian study included 92 men and 96 women, none of whom had used a protease inhibitor or non-nucleoside (NNRTI). In this study 26% of women and about 7% of men experienced changes in body shape, showing that these changes do not strictly relate to using protease inhibitors. Women had a five times higher risk of fat changes, with the largest differences being breast enlargement (14.6% women, 0% men) and loss of weight in legs.

A French study of 624 people (84% men) also showed evidence of gender differences. All participants used three-drug anti-HIV therapy. Breast enlargement was seen in 49% of women and only 15% of men while central obesity was observed in 67% of women and 48% of men.

Another study of 100 people shows that those taking d4T are more likely to have fat loss compared to those taking AZT (zidovudine, Retrovir). All the participants had only ever used AZT, ddI (didanosine, Videx) and/or ddC (zalcitabine, Hivid).

During the study, volunteers took 3TC (lamivudine, Epivir) + indinavir (Crixivan) and either AZT or d4T. There was no difference in anti-HIV response, fat accumulation, cholesterol, glucose or triglyceride levels between the two groups after 30 months. However, people on d4T had more fat loss in the arms, legs and buttocks. Seventy percent of

people taking d4T experienced some fat loss compared to 43% of people on AZT.

This study found that older age, lower CD4+ cell counts and female gender had an increased risk for fat loss. This is the first study to show that women may be more likely to experience fat loss, while several others have shown that women are more likely to experience fat accumulation than men.

Yet another small study showed that gemfibrozil (Lopid) may help lower triglyceride levels. Thirty-two people with elevated triglycerides and on a protease inhibitor-based regimen participated. All were on a low saturated fat diet and used gemfibrozil or placebo. People taking gemfibrozil had a small reduction in triglycerides, but only one had a return to 'normal' levels. There were no changes in cholesterol or glucose for either group.

These results suggest that gemfibrozil alone is insufficient to lower triglycerides, especially in people using protease inhibitors. Gemfibrozil may need to be combined with another lipid-lowering drug for optimal effect.

Other studies, reported in posters at the VII Conference on Retroviruses and Opportunistic Infections, showed similar yet sometimes conflicting results. If fat accumulation proves more common among women, then certain risks like diabetes may also be more common. However, it's important to know that imprecise definitions, inconsistent measurements, and the relatively small number of women who were followed so far, may hamper these studies, like all lipodystrophy studies.

Treating Symptoms

Since its cause is uncertain, treating lipodystrophy is an inexact science and tries to deal mostly with the changes in body appearance and blood work. Some ways to manage it are explained below.

SWITCH THERAPY Switching to a new anti-HIV therapy or stopping therapy altogether might be a useful, although unproven, approach to stop these changes. Studies of this approach have shown conflicting results. Again, it's important to remember that changes in body shape have been seen in people on no therapy and in people on one-, two-, and three-drug regimens. If anti-HIV therapy causes body shape changes in your case, then switching off the offending drug(s) might stop these changes.

However, if lipodystrophy seems associated with a protease inhibitor, try a different one or switch it with a NNRTI. Three separate reports claim some success in switching people to a NNRTI. Doctors report some decrease in central obesity; however, not everyone had a return of fat in the arms and legs. Lower cholesterol and triglyceride levels and a reversal of insulin resistance were also reported.

A Sydney group has conducted a great deal of lipodystrophy research on a study of 80 people who either continued using protease inhibi-



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tors or switched to a regimen of abacavir/adefovir/nevirapine/hydroxyurea. People who switched had decreases in triglyceride and cholesterol levels but no change in HDL or *good cholesterol*. Also, those who switched had some reduction in abdominal fat but continued to lose peripheral fat from their arms and legs. They also lost, on average, about six pounds. It's not clear whether the weight loss is due to switching anti-HIV drugs or other factors. (Several studies report that people on adefovir lose weight.) People who continued using protease inhibitors continued to gain abdominal fat.

A Barcelona study followed 106 people who used therapy that included protease inhibitors or switched to ddI/d4T/nevirapine. Those who switched significantly lowered their cholesterol and triglyceride levels while those who continued on protease inhibitors saw no change in either measurement. Neither group had changes in glucose levels. The loss of peripheral fat seemed to stabilize among

people who switched while those on protease inhibitors continued to lose peripheral fat. There were no significant reductions in abdominal fat in either group. There were also no differences in viral load rebounds (from below to above 50 copies HIV RNA) between the two groups after 36 weeks. Those switching therapy had a small increase in CD4+ cell counts.

These and other results suggest that protease inhibitors are primarily responsible for the reported increases in triglyceride and cholesterol levels. Switching to a regimen without protease inhibitors does appear to lower these levels. However, it's unclear whether this is true for all non-protease inhibitor drugs. For instance, several studies have shown that the non-nucleoside, efavirenz, also increases these levels.

Changing therapy may or may not reverse fat redistribution. It is entirely possible that some side effects are due to specific drugs but not whole drug classes. In other words, one protease inhibitor may increase these levels while another may not. Some newer results support this theory.

For example, based on some relatively short-term studies, amprenavir does not appear to increase triglycerides and cholesterol as much as other currently available protease inhibitors. Other studies suggest that d4T affects peripheral fat loss more than other nucleoside analogue drugs. Two studies show that people who switched from d4T to other nucleoside analogues had increases in peripheral fat but no change in abdominal fat. These observations suggest that some fat redistribution may be reversible.

LIPOSUCTION/PLASTIC SURGERY Liposuction is surgery that is almost literally a vacuuming out of fat. Some people with a buffalo hump have had liposuction to remove it. Likewise, some men and women with breast enlargement have had breast reduction surgery. Treating central obesity with liposuction has generally been discouraged since the fat deposits are hard to reach and not well suited to liposuction.

These surgeries are not without risk and anecdotal reports of success have been varied. Some claim that surgery resulted in a long-lasting resolution while others report that the hump just "grew back" over time.

HUMAN GROWTH HORMONE (Serostim) Unconfirmed reports from a physician in New York claim that treating with human growth hormone (HGH) therapy reduced buffalo humps and central obesity. The physician, Dr. Torres, presented photos of patients with severe body shape changes showing improvement after therapy with HGH. Dr. Torres notes that when HGH therapy was stopped, buffalo humps and central obesity returned. He further noted that HGH therapy had no impact on treating facial or limb wasting. However, the number of treated patients was very small, and the study was not controlled by a comparison group. Studies are now ongoing to formally study HGH for treating these symptoms.

Statin Inhibitors and HIV Drug Interactions

New information on the statin drugs used to lower cholesterol and their interaction with protease inhibitors show that they should be used with caution. Fifty-two volunteers took ritonavir (Norvir) and saquinavir (Fortovase) at the standard 400mg dose each taken twice a day. They also took one of three statins: pravastatin (Pravachol), simvastatin (Zocor) or atorvastatin (Lipitor). The statin dose was 40mg once a day.

The study found that pravastatin levels decreased 47%, atorvastatin levels increased 343% and simvastatin levels increased 2,676%. These results suggest that pravastatin can be used safely with protease inhibitors without need for a dose adjustment. Other statins like fluvastatin (Lescol), cerivastatin (Baycol) and lovastatin (Mevacor) behave similarly to pravastatin, atorvastatin and simvastatin respectively.

The activity of the statins are not directly related to their drug levels found in blood, but statin side effects are directly related. Atorvastatin should be used with great caution. Simvastatin should not be used with ritonavir and saquinavir and likely applies to other protease inhibitors as well.

One serious side effect associated with increased statin levels is a muscle disorder called rhabdomyolysis. People experiencing muscle aches should report this to their healthcare providers. People with mild kidney dysfunction (a creatinine clearance above 1.5mg/dL) are more at risk for developing statin side effects. Gemfibrozil (Lopid), a drug sometimes combined with the statins to lower triglyceride levels, can also result in muscle disorders and kidney failure.



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Treating Lab Abnormalities

Several small studies have looked at using specific drugs to treat some of the lab abnormalities associated mainly with using protease inhibitors. There are mixed reports of using anti-lipid drugs such as clofibrate (Atromid) and gemfibrozil (Lopid) to lower triglyceride levels. Similarly, there are mixed results with using the *statin inhibitors* such as cerivastatin (Baycol), fluvastatin (Lescol), atorvastatin (Lipitor), lovastatin (Mevacor), pravastatin (Pravachol) and simvastatin (Zocor).

One study showed that combining gemfibrozil (Lopid) and atorvastatin (Lipitor) lowered lipid levels to the normal range in about half the people. Another study showed that metformin (Glucophage) reduced central obesity and insulin resistance but also led to an average 2kg weight loss. Finally, one other study showed that troglitazone (Rezulin) lowered glucose levels but had no effect on lipid levels.

People on protease inhibitors who consider experimenting with these *statin inhibitors* should talk to their healthcare providers about possible drug interactions and dose adjustments. The same liver enzyme processes both these two classes of drugs, and there's a strong potential for interaction. Read more about these statin inhibitors in the box on this page.

Commentary

Ongoing reports of changes in body shape have raised questions about the long-term benefits of potent anti-HIV therapies vs. quality of life issues. People may also meet others who notice these physical changes and assume they're HIV-positive. These and other issues, like increases in triglyceride and cholesterol levels that theoretically increase the risk for heart disease, have made many people re-evaluate when to start anti-HIV therapy.

Many people who develop these symptoms are considering whether to switch or stop therapy completely. But the benefits of potent anti-HIV therapies are undisputable. Death rates and the numbers of opportunistic infections have decreased dramatically. However, the right time to start anti-HIV therapy is not known. Some researchers and clinicians who earlier advocated for starting therapy as early as possible have changed their views.

What causes lipodystrophy is not known. But one thing is now clear: protease inhibitors are not the sole cause. Controlled studies with adequate numbers of men and women must be conducted under a single definition before hard conclusions can be reached.

There's much frustration among people with HIV-related lipodystrophy because of the uncertainties they face. While a large amount of work is now ongoing, we may not get any information on what causes it or how to treat it for another year or more.

If you truly have lipodystrophy, it's important to consider all the positive results that have been attained with potent anti-HIV therapies while factoring in these and other potential side effects that have

not yet been discovered. Remember, lipodystrophy is not the same thing as the "spread" or "love handles" that people get as they age. It's also important to talk to your healthcare provider—and if at all possible an expert in this field—when coming up with a strategy that's right for you.

Cosmetic Surgery for Facial Wasting: New-Fill Injections

Results from a French study of New-Fill (polylactic acid) shows that it may help increase the thickness of the cheek fat pad and other places where fat loss is sometimes apparent. Some people have experienced *lipoatrophy* (fat loss), which is believed to be associated with anti-HIV therapy and in particular the nucleoside analogue (NRTI) drugs. This study involved four injections of New-Fill (3cc in each cheek) at days 0, 15, 30 and 45. A fifth injection was given at day 60 if there was inadequate response.

Fifty people participated and all began the study with a marked and visible reduction in fat tissue in the cheeks (sunken cheeks) as measured by *ultrasonography* (using ultrasound technology to produce an image). At the time of the report, four people had received three injections, 29 had four injections and 17 had five. All volunteers had a dramatic improvement, with the majority regaining fat tissue in the cheeks. Some participants experienced a slight swelling at the injection site.

The manufacturer claims that New-Fill does not directly fill the spaces left empty by lipoatrophy. Rather, the product is claimed to build or grow a matrix under the skin which is then filled in by the body's own production of collagen.

New-Fill is not currently approved by the FDA and is not commonly available to physicians. For a time, the product was being imported from France for personal use, but in recent months the FDA blocked bulk importation of the product, arguing that the product should be classified as a "device" rather than a drug or natural supplement. The agency feels it is thus not subject to the personal importation rules for drugs. Still some people are successfully bringing back personal supplies of New-Fill from Tijuana, Mexico.

Discussions with the FDA are ongoing, looking for a way to make the product available to people in need while further studies are designed. A major problem is that the supplier is a small company that does not have the resources to conduct clinical trials. Some dermatologists offer products they claim are similar, and a few clinics near the Mexican border treat patients with New-Fill or similar products.

Facial lipoatrophy may not be physically harmful, but it can add a serious psychological burden for people with HIV infection. Although New-Fill has not been proven to be effective, neither has it shown any serious toxicity to date. Project Inform supports the right of people with HIV to have access to this and similar products.