PROJECT inform

PERSPECTIVE

Information, Inspiration and Advocacy for People Living with HIV/AIDS

39

The World's Most Important AIDS Research?

Despite the effectiveness of anti-HIV therapy and considerable success in reducing the price of the drugs in resource poor settings, the relentless spread of HIV continues to overwhelm all efforts to contain it. AIDS cannot be stopped without an effective means of preventing future infections. Unfortunately, the quest for a vaccine continues to elude our best scientific efforts. The new vaccines that looked so promising a few short years ago have produced disappointing results in early human studies. What happened in the animal models does not seem to happen in humans.

Some scientists argue that there is no guarantee we will ever have a vaccine, while others are more optimistic but recognize that HIV presents a uniquely difficult challenge. Yet even if a perfect vaccine were created today, it would take roughly ten years to prove its effectiveness. It is difficult to overstate the damage that another ten years without a vaccine will do.

Given the high stakes, some researchers and public health specialists are increasingly asking whether there might be other ways of preventing the spread of HIV. Certainly, everyone recognizes the role of behavioral prevention campaigns, but these approaches are today often bogged down by political and religious debate. Condom distribution and needle exchange must be considered the first line defense, as these are best supported by scientific evidence. Over the last four years, however, other voices have come into positions of power, insisting that sexual abstinence must instead be emphasized, particularly among the young. They argue, unsupported by evidence, that condoms and needle exchange encourage risky behavior and that only abstinence can prevent or reduce HIV transmission. While no one opposes the concept of sexual abstinence among the young, it is a misrepresentation of the evidence to suggest that abstinence campaigns have been shown to be an effective alternative to condom and needle distribution. While the debate continues, pitting the scientifically proven tools of prevention against religious and politically inspired beliefs, the band plays on—as was so aptly said back in 1987.

AIDS is a disease whose spread is facilitated by human behavior. Thus, stopping it is almost certain to require behavioral change. A growing majority of new infections occur among women, particularly women who have minimal control over the factors that result in HIV transmission. For these women, there is often little or no choice involved, no opportunity to choose either condoms or abstinence. Even where condoms are universally available, they are only effective when both parties agree to their use. Condom distribution, needle exchange and abstinence education all have a role to play in combating HIV, but for an increasing majority of people at risk of HIV infection, they are not sufficient.

prevention tools are needed that are under the control of the individual, require little or no support from sexual partners and are largely invisible to other parties, just as a vaccine is. Surprisingly, there are at least two types of tools that could be made readily available in the near future, long before any possible vaccine, and which are far more practical in the long-term than relying on behavior change alone to contain the spread of HIV. One is topical prevention with HIV microbicides. These are substances which either destroy or block the replication of HIV and which can be applied to the body at the various possible points where contact might occur between bodily fluids. Making an effective microbicide will require selection of the most effective products as well as their testing in humans. The other type of tool involves the use of certain oral

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anti-HIV medications taken either before a potential HIV exposure or on a steady state basis. This approach is sometimes called pre-exposure prevention or PREP. It relies on certain types of already available anti-HIV medication and requires only an accelerated testing in volunteers. Developing these two technologies may well be the world's most important AIDS research and may offer the only realistic hope of slowing the spread of HIV over the next decade or longer.

Option One: Microbicides

A microbicide is a chemical that directly or indirectly destroys a microbe (in this case, HIV). An effective microbicide would give people an HIV prevention tool that is more in their own control. Such a product would likely be a gel, liquid, suppository or perhaps a lubricant, which could be self-applied prior to sexual activity. It might be able to be used vaginally or rectally, or both. The concept is neither untried nor unproven. Spermicides have been used to prevent pregnancy for decades. The case for accelerated development of HIV microbicides has been endorsed by UNAIDS, the World Health Organization, the International Program for Microbicides, the Population Council and other international agencies.

The importance of microbicide development is hard to overstate, whether looking at national or international expressions of the HIV pandemic. In sub-Saharan Africa, women account for more than 50% of the HIV infections. Among teens in some African countries, the ratio of HIV-infected girls to boys is nearly 6 to 1. These figures reflect the fact that teenage girls are commonly forced into sex and in a male dominated culture with low use of condoms. A prevention method that can be both woman-initiated and woman-controlled is desperately needed. Though the ratios might be different in developed nations, women even in the US sometimes find themselves in similar situations and have a similar need for a prevention method which they can control. Microbicides aren't a perfect answer for women in relationships where there is violence and sexual power imbalances, but they do offer an improvement over current options. When combined with other prevention strategies, they may be enough to significantly turn the tide of the epidemic.

Microbicides may also become an important prevention tool for men. HIV infection rates are on the rise again in many cities with large gay communities. Most observers believe this reflects an increased level of unprotected sexual activity, particularly anal intercourse without condoms. Whatever the rationale for disregarding condom use, it is clear that an effective microbicide/lubricant could play a critical role in slowing the renewed spread of HIV.

Given the obvious need, why isn't microbicide development a front burner issue for AIDS research and AIDS activism? With the exception of the Global Campaign for Microbicides (*www.globalcampaign.org*), few community groups specialize in this area. The effectiveness of condom programs in the developed nations perhaps led to a lack of emphasis on the need for prevention alternatives. But times have changed and the use of condoms seems to have declined. Some speculate that this is simply part of the tendency among younger gay men to feel less threatened by AIDS. Condom use has never been high in resource-poor settings,

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but the needs of such settings have never had much influence on what technologies industry invests in. Resource-poor nations have always presented a dilemma for industry. Companies tend to see them as places where their products, though desperately needed, can't be sold at a sufficient profit to attract much interest in the board room. Perhaps the biggest question then is why government, both the US government and others around the world, have not more heavily invested in microbicide development. For years, government funding has been driven by the assumption that a vaccine was never far off, a view that now seems laughably inaccurate. Yet this view almost certainly contributed to the lack of funding for vaccine alternatives.

Microbicide research can take multiple forms. Some companies are seeking to develop new compounds that can destroy or disable HIV on contact, without damaging surrounding tissue. Another approach, currently at the proposal stage, is to make use of the new class of anti-HIV drugs called "AFE" inhibitors ("Attachment, Fusion, and Entry" inhibitors). With one very expensive exception though, these are drugs that are at least two years away from approval by the FDA. Still, they could be tested as microbicides at the same time they are being developed as drugs to treat HIV. This could result in their approval as microbicides long before any vaccine makes it to the approval stage. As a general rule, it should take less time to put a microbicide through the development and approval process than a vaccine. If the products were proven safe early on, they could be put into use well in advance of formal approval based on preliminary data.

The one known technical obstacle which has slowed microbicide development is the lack of a suitable placebo to serve as a control in clinical studies. To be useful, a placebo must be visibly and sensually indistinguishable from the real microbicide, and it must not produce any changes of its own in the mucosal area where it will be applied. So far, no one has been able to create a placebo that meets this requirement, and without one, the only way to get a reliable answer from a study is to include a much larger number of volunteers and follow them for a much longer time. This would make the study far more expensive. Still, it would be a mistake to say that this problem explains why microbicide development hasn't been faster. It is primarily a matter of will and a matter of money. Those who truly care about the frightening spread of the disease in Africa, Asia, Eastern Europe and South and Central America, as well as the renewed rise of HIV infection rates in the US, need to raise their voices and demand a higher priority for such research.

Option Two: Pre-Exposure Treatment as Prevention

The second alternative that might be employed while waiting for a vaccine is the use of certain readily available, approved anti-HIV drugs in HIV-negative people. This idea first came to prominence several years ago during the early development of the anti-HIV drug tenofovir (Viread). In 1995, before it was widely tested in humans, scientists reported on the results of an experiment in which monkeys were given a single dose of tenofovir and then deliberately exposed to SIV, a close relative of HIV which infects many primates. A similar group of monkeys was also injected with SIV but not given tenofovir. The results were striking: all the animals that received tenofovir remained uninfected by the SIV challenge. They appeared to be protected for at least several days from a single injection, while all the animals who received the same SIV challenge without first receiving tenofovir were readily infected with SIV. The result appeared to be related both to the drug's mechanism of action and the fact that it remained in the blood for a long period after a single dose.

What is needed are prevention tools that are under the control of the individual, require little or no support from sexual partners and are largely invisible to other parties.

Today, tenofovir is approved for the treatment of HIV. It has quickly become popular due to its once-a-day dosing. It's stable in the body for long periods and it seems to be relatively powerful and generally free of major side effects. It is thus an attractive candidate for testing as a preventive tool.

Researchers are now attempting to conduct studies using tenofovir as a preventive. Given the pressing need for user-controlled HIV prevention tools and the lack of a vaccine that could be ready soon, these studies should rank among the highest priorities of AIDS researchers, public health experts, and activists alike. But such is not the case and several obstacles have slowed the progress of these studies. The sense of urgency that once drove every aspect of AIDS activism seems now seems to be outweighed by other concerns.

One study, with female sex workers in Cambodia, became the subject of protest from activists at the International AIDS Conference in Bangkok this summer.

In memory of . . .

We dedicate this issue of the *PI Perspective* to:

Charles Clifton
Beatrice Frey
Ellen George
Keian Kunkler
Lua Pires

Their memory lives on in the work that lies ahead of us all.

Some advocates argued that the study must guarantee free medical care for any possible drug side effects for 30 years after the start of the study and must provide a free anti-HIV drugs for a lifetime for anyone who becomes infected during the study. While a drug company should certainly take responsibility for damage done by side effects in a study, it is unprecedented to expect a company to provide guaranteed care for possible side effects for 30 years. Any time beyond the first few years after a study ends, it becomes very difficult to determine whether medical events are or are not related to a drug a person took in the past. A guarantee of 30 years support is an open-ended financial commitment that few (if any) companies would ever undertake.

It is an especially difficult thing to ask of a company that wasn't sponsoring the study in the first place (US government agencies were sponsoring the study). It is just as difficult to ask a government to make such a commitment, even with a drug that is so far known to be particularly safe compared to other HIV medications. Similarly, while lifetime treatment for HIV is a benefit that should be due to anyone who is HIV infected, such a request in association with a research study becomes very problematic in a country where guarantees of treatment are not otherwise provided. Some would see offering such a benefit as a form of coercion to get people to participate in the study.

Both demands are no doubt attempts to meet the real needs of people in a resource-poor setting. Nonetheless, there is only so much of the burden of healthcare that can be carried by a single study. These demands have brought the Cambodian study to a halt and since the grant which funds the study expires this year, there seems little chance it can be brought back to life. At the very least, it will require renewal of the grant, which is no simple matter. Additionally, the controversy and anger that have been stirred up have left the Cambodian population and its government angry and divided. While some people believed the study would exploit poor Cambodian women, public health experts and researchers argued that by far the greatest threat to Cambodian sex workers is the unchecked spread of HIV. From their point of view, the study offered the first real hope of breaking the cycle of HIV infection.

The simplest solution is to conclude that if these are the terms demanded by the potential study subjects, their government or their advocates in Cambodia, then perhaps the study should not be run there. The critical scientific questions can be answered by the five other studies of this approach underway in other countries. Still, it will be sad to see two years of work and planning, as well as the contributions of Cambodian study volunteers, come to naught. Researchers need to carefully examine what happened in Cambodia and how it might be avoided in the future. It is unlikely that any research studies are going to provide lifetime treatment guarantees or 30 years of financial responsibility for possible side effects. But it may be possible to find other ways to meet those needs before asking the poorest of people to volunteer for studies in the future.

The second alternative that might be employed while waiting for a vaccine is the use of certain readily available, approved anti-HIV drugs in HIV-negative people.

The five other studies which should soon be underway include one in Atlanta and another in San Francisco, both seeking sexually active volunteers from the gay community. These studies have also been under development and discussion for nearly two years and neither study has yet put its first volunteers on treatment (though this may change by publication date). If there is a positive finding in such studies, it holds the promise of changing the direction of the epidemic. Word of the study alone has already led to many people, sometimes with the support of their doctors, to make tenofovir a part of their "weekend" cocktails out on the party circuit. Though this is clearly premature, who can blame them? It would be far better though, if we could provide people with reliable, proven information, and for that, the studies must move forward.

While tenofovir may make the most sense for this application today, this could well change when the the new class of entry inhibitor drugs reaches approval. For the same reason such drugs are attractive as the building blocks of microbicides, so too are they attractive as potential oral infection-blockers. The combination of a mechanism of action that targets early steps in the virus' life cycle, low toxicity, and slow clearance from the blood contribute to make a drug a good candidate for treatment-as-prevention.

Commentary

Most public health experts would prefer to address the problem of HIV transmission with the tried and true approach of a vaccine. At 20 plus years into the AIDS pandemic though, it is no longer enough to hope and wait for such a vaccine. There are alternatives, some of them behavioral and some of them chemical. We must exploit every possible means to slow the spread of HIV.

In debates over behavioral approaches, there are too many lives at stake to simply argue about condoms vs. abstinence. There is room, and need, for both, and there are people of goodwill on all sides of the debate. They go wrong only when they promote their own preferred approach to the exclusion of all others.

When it comes to microbicides and the use of treatment-as-prevention, we need only apply the same rules and values we

Facial Wasting

This article will briefly cover the ongoing research into the causes and possible treatments for lipoatrophy in general. It will also focus on newly approved and experimental facial fillers and implants.

What is facial wasting?

Facial wasting is one symptom of a syndrome called *lipoatrophy*, which describes the loss of the soft layer of fat that sits just beneath the skin (*subcutaneous* fat). When a person has lipoatrophy, it is most noticeable in the legs, butt, arms and face. There is no single identified cause for lipoatrophy. The evidence collected so far shows that both HIV itself and the drugs used to treat it can lead to this kind of fat loss.

There are currently no proven treatments or strategies that consistently lead to restoration of fat, but there are a growing number of facial fillers and implants that can improve a person's appearance and quality of life. Sometimes people see improvements in symptoms of lipoatrophy upon changing anti-HIV regimens and reducing use of specific drugs most associated with the syndrome (e.g., stavudine). Doctors have also reported on rare cases where symptoms of lipoatrophy improved without explanation.

What causes lipoatrophy?

While many in the U.S. consider *fat* a dirty word, it actually plays a role in the function of many of our bodies' systems. It produces chemicals that talk to the immune and digestive systems and can cause the body to release or stop making certain hormones. Like every other cell in the body, fat cells require their own type of fuel to live and function. This fuel is produced and turned into energy by tiny structures inside of cells called *mitochondria*. When mitochondria become damaged or can't reproduce, a cell will cease working properly and eventually die.

Shortly after protease inhibitors were introduced in 1996 and 1997, doctors began to see a growing number of people on treatment who were losing fat in their arms, legs and faces, while simultaneously gaining a hard, dense kind of fat in the belly and behind the neck. This redistribution of fat became known as *lipodystrophy*, and protease inhibitors were blamed.

Since that time, it has been shown that nearly all anti-HIV drugs can contribute at least somewhat to many of the factors associated with changes in fat, including elevated cholesterol and reduced insulin sensitivity, though not all drugs contribute equally. A few studies have also found increased levels of fat cell death specifically among people on protease inhibitor combinations.

However, most scientists now believe that *lipoatrophy* occurs primarily because the fuel source (*mitochondria*) in fat cells becomes damaged and stops reproducing. It is likely that mitochondrial damage to other kinds of cells, notably liver cells, contributes to lipoatrophy as well. A number of studies have identified three factors associated with both mitochondrial damage and lipoatrophy:

- long-term use of nucleoside analog anti-HIV drugs—particularly stavudine and to a lesser degree zidovudine;
- being over 40 years of age; and
- having elevated triglycerides

Studies show that a person possessing all three risk factors has a higher risk for lipoatrophy than a person with only one or two. However, the studies have varied so much in their methods for measuring fat losses or gains that they cannot easily be compared. It is therefore very difficult to predict risks for developing lipoatrophy.

When it does occur, and particularly when facial wasting is more extreme, lipoatrophy can negatively affect a number of different areas of a person's life,

Anti-HIV Drug ID Chart

GENERIC NAME	TRADE NAME
Protease inhibitors	
amprenavir	Agenerase
atazanavir	Reyataz
fosamprenavir	Lexiva
indinavir	Crixivan
lopinavir + ritonavir	Kaletra
nelfinavir	Viracept
ritonavir	Norvir
saquinavir hard gel	Invirase
saquinavir soft gel	Fortovase
NRTI (nucleoside) and NtRTI (nucleotide) analogue reverse transcriptase inhibitor	
abacavir	Ziagen
didanosine (ddI)	Videx
didanosine enteric-coated (ddI EC)	Videx EC
emtricitabine (FTC)	Emtriva
emtricitabine + tenofovir	Truvada
lamivudine (3TC)	Epivir
stavudine (d4T)	Zerit
stavudine extended release (d4T XR)	Zerit XR
tenofovir	Viread
zalcitabine (ddC)	Hivid
zidovudine (AZT)	Retrovir
3TC + AZT	Combivir
3TC + AZT + abacavir	Trizivir
3TC + abacavir	Epzicom
NNRTI (non-nucleoside reverse transcriptase inhibitor)	
delavirdine	Rescriptor
efavirenz	Sustiva
nevirapine	Viramune
Fusion inhibitor	
enfuvirtide (T20)	Fuzeon

including: self confidence; the desire to participate in social activities; sex drive; emotional well-being; the willingness or ability to adhere to treatment, and a commitment to staying on treatment. All of these are symptoms of depression, which itself is more common in people living with HIV. Some of the symptoms listed above can also be a sign of depleted testosterone levels. Anyone experiencing these symptoms consistently for more than several days in a row should be assessed and treated, if indicated, for both depression and low testosterone.

Treatment for lipoatrophy

Before considering treatment for lipoatrophy or facial wasting, it is important to distinguish lipoatrophy from *wasting syndrome*. While lipoatrophy describes the loss of subcutaneous fat, wasting syndrome describes the loss of both fat *and* muscle mass. The most general sign of wasting syndrome is an unintended loss of more than 10% of a person's body weight, usually in combination with 30 days or more of either diarrhea or weakness, and fever. While lipoatrophy is not inherently a sign of disease progression, wasting syndrome typically is. Therefore, anyone with a progressive loss of fat in the face and limbs should be screened for wasting syndrome as well as lipoatrophy.

As discussed in the rosiglitazone article on page 9, there are currently no drugs approved to treat the underlying causes of lipoatrophy. However, studies have found that people with lipoatrophy who are taking a regimen with stavudine can often reverse fat loss to some degree by swapping it with abacavir. Studies indicate that switching from stavudine to tenofovir may produce similar results.

Glitazones, a type of drug used to treat type 2 diabetes have also shown some promise. However, none of these approaches has led to dramatic and noticeable cosmetic improvements in facial wasting. There are, however, a number of facial fillers and implants that can be used to improve the appearance of people who have lost facial fat.

Facial fillers and implants

Plastic surgeons and dermatologists have tried a variety of facial fillers and implants to address facial wasting cosmetically. Until August 2004, however, none of these had been extensively studied or approved by the FDA for treating this condition. Rather, they are products and techniques adapted from other uses such as standard cosmetic surgery and facial reconstruction due to injury.

In August 2004, the FDA approved Sculptra (a poly-L lactic acid, formerly known as NewFill) for the restoration and/or correction of the signs of facial fat loss due to HIV-related lipoatrophy. The company, Dermik Aesthetics, filed for approval based on European studies in 278 people with severe lipoatrophy. The majority of the people studied were Caucasian men aged 41–45 years, nearly all of who were on anti-HIV therapy.

People received three to six rounds of Sculptra treatment, consisting of multiple small injections, at two-week intervals. Volunteers were then monitored for two years. Roughly 40% of people studied had a significant lasting increase in the volume of tissue in the cheeks for up to two years following the series of injections. Quality of life measures (i.e., anxiety and depression surveys) also improved significantly.

Sculptra causes scar tissue and fat to collect in the areas where it is injected. The amount of Sculptra injected and method and placement of each injection can strongly impact the results, and requires proper training to achieve the best results. It can cause very small lumps called micronodules to form in up to 44% of people receiving it. The micronodules are not usually visible or the source of ongoing inflammation and infection—as with other types of injectable fillers—but they can often be felt under the skin.

Although most doctors use a numbing agent like lidocaine when injecting Sculptra, there is usually mild to moderate pain during the injections. Sculptra can also cause tenderness, swelling and bruising at the site of injection. This typically goes away within days.

The level of fullness resulting from each round of injections can vary from person to person. As well, people with more extreme facial wasting will sometimes require more than six rounds of injections to achieve lasting results. There are few data on the long-term use of Sculptra, or specifically on its use in women and people with darker skin.

The FDA placed two conditions on Sculptra's approval. First, the company may not encourage its use for cosmetic purposes in people not infected with HIV (e.g., to fill in wrinkles). The company also agreed to conduct an open label study of 100 volunteers for five years to evaluate Sculptra's long-term safety. The study will include at least 30 women and 30 people with dark skin types.

Other products

It is highly encouraging that a product has now received FDA approval specifically for facial wasting in HIV. However, Sculptra, which produces effects lasting on average for 18–24 months, represents only a moderate improvement over other types of biodegradable fillers, whose effects usually disappear in less than six months. Therefore, some plastic surgeons prefer to use permanent fillers like artificial microspheres that are coated in collagen (Artecoll) or silicone microdroplets (various products). However, none of the semi-permanent or permanent fillers are approved by the FDA for HIV-related facial wasting, and data on their use is limited and short-term.

Currently, silicone is only approved to treat retinal detachments and hemorrhages. However, the FDA allows plastic surgeons and dermatologists to use any FDA-approved product or device if the provider believes that it can effectively treat a person's medical complaint. However, a doctor may not market their use of an off-label product, so finding a doctor with enough experience with silicone may be difficult. Artecoll is not currently ap-

proved by the FDA, so treatment requires traveling to Canada or another country.

As with Sculptra, both kinds of treatment require expert application. Most experienced surgeons and dermatologists build up the sunken area with multiple tiny injections over many weeks. This is crucial as too much too soon can result in a lumpy appearance, especially if there is further fat wasting beneath and around the areas of the injections. People considering permanent fillers should consider their risks and limitations carefully and thoroughly confirm the experience of the prospective doctor with the product. Failure to do so can increase risks of serious infection and disfigurement.

All artificial implant products can cause an allergic reaction in a small percent of people. The products can also migrate from the area where they were initially implanted. Serious infection and inflammation can occur at the injection site and chronic long-term inflammation and infection are possible in up to three percent of cases.

The use of silicone for implantation was banned in the U.S. for several years because of research suggesting the development of auto-immune disorders in women whose silicone breast implants had leaked. These data were never confirmed by studies, however, and plastic surgeons have gradually begun using silicone implantation products again.

There are a small number of confirmed cases where silicone injections caused late-forming granulomas. These granulomas, which can appear many years after the injections, can be disfiguring, cause serious infections and be very difficult to treat. Thus, there remain a number of unknown and long-term risks associated with silicone. Experience with Artecoll in Canada indicates that it may be less likely to cause granulomas than silicone. However, there are no long-term data in people with HIV.

There are other treatments than those mentioned here. These treatments include collagen, fat harvesting, hyaluronic acids, polylactic acids other than Sculptra, and permanent implants of materials like Gore-Tex. However, they are typically used less often, either because they are less effective, not available in the U.S. or are most useful in rarer circumstances.

Tipranavir Expanded Access Program

A long-awaited expanded access program for the new protease inhibitor tipranavir should make it available for 3,000–5,000 people starting in mid-to-late November. The main advantage of tipranavir is that it appears to remain active to some degree even in people whose virus has developed resistance to multiple protease inhibitors. Studies in people with multi-drug resistance have shown considerable success.

When used by itself, tipranavir is poorly retained in the body and must be boosted with 400mg daily of ritonavir. This is two to four times as much ritonavir as other protease inhibitors require. Tipranavir will be free during the expanded access program (through Boeringher-Ingelheim), as well as the requisite ritonavir boost (available from Abbott Labs' Patient Assistance Program at 1-800-222-6885). Tipranavir is made by Boeringher-Ingelheim; ritonavir by Abbott Labs.

Details: The tipranavir program will not require people to have any particular CD4+ cell count level or viral load. To qualify, people must meet the following:

- Previously used three classes of anti-HIV drugs, such as NRTIs, NNRTIs and protease inhibitors
- Failed at least two protease inhibitor-based regimens
- Must have documented resistance to multiple protease inhibitors

While on the tipranavir regimen, people may not use any protease inhibitor other than ritonavir or any other experimental (not yet FDA approved) compound.

When the program is announced, an 800 number will be provided through which any physician can register people for the program. Call Project Inform's Hotline for more information once the program begins.

Access to treatment

Accessing treatment for facial wasting is perhaps the greatest hurdle for people with the condition. Neither insurance companies nor government health programs will typically cover the cost of any cosmetic procedure, regardless of the impact a condition may have on a person's quality of life. Therefore, the only way for most people to access treatment is by out-of-pocket payment or by enrolling in a study.

The least expensive fillers, such as collagen, start at around $200 per vial of the product. Products like Sculptra can cost up to $500 per vial, and the most expensive permanent fillers cost in excess of $100 per vial. The amount needed for a treatment can vary a great deal depending on the degree of wasting that has occurred. One vial is typically the minimum used per round of injections. An additional charge will also be the fees of the doctor administering the injections. These charges can vary, but are typically up to $500 or more per round of injections. Since most treatments for facial wasting require a minimum of four rounds of injections, the total cost of treatment often exceeds $6,000.

Doctors and activists are advocating with the makers of Sculptra to form a patient assistance program (PAP) for people who cannot afford the cost of treatment. Even if a Sculptra PAP is formed, however, this will not cover the cost of the injection procedure. Therefore, AIDS activists are also working with policy experts to determine whether programs like Medicaid or ADAP may be able to cover these costs in some circumstances. However, at a time when the escalating costs of drugs are stretching healthcare systems to the breaking point, this is likely to be a challenge.

Update: Guidelines for Use of Anti-HIV Drugs during Pregnancy

In June 2004, a supplement was added to the Federal Guidelines for the use of anti-HIV drugs during pregnancy. These guidelines focus on mother-to-child transmission of HIV and discuss treatment strategies that can reduce the risk of an HIV-positive woman transmitting HIV to her child. The update included information on the use and potential risks and benefits, to both mother and child, of each of the approved anti-HIV medications. This article will briefly highlight the new recommendations. For more information on pregnancy and HIV, call our hotline at 1-800-822-7422 and ask for Project Inform's publication, *Pregnancy and HIV*. You can also get a copy of the Guidelines from the Project Inform website at *www.projectinform.org*.

Anti-HIV medications

The following chart outlines current recommendations for the use of anti-HIV therapies during pregnancy. (A more detailed table and additional information is available through Project Inform's website and hotline.)

The use of nevirapine (Viramune)

We have known for some time that the serious side effects associated with taking nevirapine, specifically a rash and/or liver toxicity; seem to be experienced more often in women than men. In general, non-pregnant women with pre-treatment CD4+ cell counts above 250 who receive continuous nevirapine are at an increased risk for liver toxicity, including liver failure and death. Men with pre-treatment CD4+ cell counts of above 400 also have higher risk for liver toxicity than men with lower CD4+ counts. This suggests an interaction between sex and immune status, as being risk factors for rash associated liver toxicity. In other words, something about being female or male may put you more at risk for liver toxicity depending on your CD4+ cell count.

Research has shown that ruptured membranes for longer than four hours can pose a significant risk.

The guidelines now include a section on nevirapine and liver and rash side effects. It recommends that pregnant women who start therapy for the first time should take nevirapine with caution, specifically women who have CD4+ cell counts above 250. In addition, pregnancy itself can mimic some of the early symptoms of liver toxicity, for example fatigue or nausea. Doctors should monitor liver enzymes, (i.e., alanine amino transferase), especially in the first 18 weeks of therapy for women who receive nevirapine during pregnancy.

Mode of delivery

Management of labor and delivery should focus on minimizing the risk of transmission to the child and complications to the mother. Up until recently, an *elective Cesarean* section was the recommended mode of delivery for HIV-positive pregnant women. Now, given a greater understanding of the correlation between HIV levels and transmission risks, elective C-sections are only recommended for women with viral load above 1,000 near the time of delivery. Whereas women with HIV levels below 1,000 are counseled on the risks and benefits of elective C-section and encouraged to make a choice about natural childbirth or elective C-section.

An elective C-section is normally scheduled at the 37th–38th week of pregnancy. Unlike an emergency C-section, that happens after a woman's water has broken and is oftentimes performed in high-risk situations, an elective C-section is planned and done *before* a woman's water has broken. The longer an infant is exposed to the torn membranes and blood, the higher the risk of transmission at labor and delivery.

zidovudine (AZT/Retrovir)
lamivudine (3TC/Epivir)
nevirapine (Viramune)
nelfinavir (Viracept)
saquinavir (Fortovase)

didanosine (ddI/Videx)
*do not use with d4T
emtricitabine (FTC/Emtriva)
stavudine (d4T/Zerit)
*do not use with ddI
abacavir (Ziagen)
indinavir (Crixivan)
lopinavir+ritonavir (Kaletra)
ritonavir (Norvir)
*use only as a booster

tenofovir (Viread)
zalcitabine (ddC/Hivid)
efavirenz (Sustiva)
delavirdine (Rescriptor)
amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
enfuvirtide (Fuzeon)

Research shows that babies exposed to ruptured membranes for more than four hours are at significantly higher risk for infection. An elective C-section can minimize the length of time an infant is exposed to the membranes, reducing the risk of HIV transmission. However, like any surgery, an elective C-section comes with potential complications, such as infections. These complications and associated healing time can increase if a woman is HIV-positive.

Recent data underscores the importance of lowering a mother's HIV levels in order to reduce the risk of transmission. A woman with a viral load of 1,000 or below close to the time of delivery has a lower risk of transmitting HIV to her infant.

Recent data underscores the importance of lowering a mother's HIV levels in order to reduce the risk of transmission. A woman with a viral load of 1,000 or below close to the time of delivery has a lower risk of transmitting HIV to her infant. Several studies show that elective C-section offered little additional benefit in lowering HIV transmission risk when a women's viral load is below 1,000. As a result, current guidelines recommend that women with a viral load of less than 1,000 be counseled on the risk and benefits of an elective C-section. This allows a woman more of a choice in how she would like to have her child.

We've come extremely far in terms of preventing mother-to-child transmission. This is a success in the treatment world that is often not discussed or honored. Today many women living with HIV with good medical care and support systems are able to have a healthy child, not infected with HIV.

Can *Glitazones* Reverse Lipoatrophy?

A recently published study found that an anti-diabetes drug, called rosiglitazone (Avandia), is able to reverse the loss of fat under the skin (*lipoatrophy*) that some people with HIV experience. While these results are encouraging, they are just the latest in a series of conflicting study results involving two different *glitazone* drugs.

What are *glitazone* drugs?

Rosiglitazone and pioglitazone (Actos) are both approved to treat insulin resistance and are frequently a part of type 2 diabetes treatment. Both showed promise in small studies initiated in 2001 in people with HIV who had lipoatrophy. Unfortunately, both have side effects and may not be safe for people with active liver disease. They may also be difficult to use in people with heart disease and high cholesterol as they can interact with common cholesterol-lowering drugs, and can cause fluid retention.

Some researchers considered rosiglitazone dead in the water after a large controlled study reported in early 2004 found no improvements in body fat among those using the drug. Though this latest study was much smaller, its results are compelling enough to warrant further research. The only other treatments for lipoatrophy involve avoiding or replacing anti-HIV drugs that contribute to fat loss—a strategy that's not proven wonderfully effective in managing lipoatrophy—or investigating purely cosmetic approaches (such as facial implants).

In the study published earlier in 2004, 108 people with lipodystrophy received 4mg of rosiglitazone *twice* daily or a placebo for 48 weeks. Despite improvements in insulin resistance and another marker connected to fat accumulation, the investigators found no statistically significant increase in limb fat in the group receiving rosiglitazone compared to the group receiving the placebo.

In the more recent study, 28 people with lipodystrophy received either 4mg of rosiglitazone *once* daily or placebo for three months. This study found dramatic increases in overall body fat and limb fat among those receiving rosiglitazone vs. the placebo group.

Which study is true?

Granted, the second study was so small that some percentage of the improvement in the rosiglitazone group could have occurred by chance. There were, however, several important differences between the people who participated in the second study compared to those in the larger study.

First, having a high level of insulin resistance was a requirement to enter the small study. This was not true in the large study. Therefore, it is possible that insulin resistance was more of a factor in the lipodystrophy among those in the smaller study. When insulin resistance improved, so too did the lipodystrophy. Also, the use of stavudine, which is strongly associated with lipoatrophy, was higher among those receiving rosiglitazone compared to those in the placebo arm of the larger study. Lastly, 25% of those in the small study were women, compared to only 2% of those in the larger study. Each of these factors could have played a role in the differing results.

Avoiding the use of anti-HIV drugs associated with lipoatrophy, like stavudine, can help prevent it and lead to at least some improvements in those who've already lost fat. However, anti-HIV drugs are only one factor with lipoatrophy and much is still unknown. Other than the *glitazone* drugs, there are few promising treatments being researched for lipoatrophy. Thus, despite the mixed results of studies so far, and the side effects and drug interactions associated with both rosiglitazone and pioglitazone, further research must continue.

Understanding HIV: GBV-C and HIV—Better Together?

Since the early days of AIDS research, some scientists have wondered if HIV could be slowed or rendered harmless by another virus. A number of studies suggest that hepatitis G (GBV-C) may be just such a virus, reducing disease progression and death in some people who are co-infected with both HIV and GBV-C. The authors of a recent article in *The Lancet*, went so far as to suggest that GBV-C be used as a model for designing new treatments for HIV. Other researchers, however, remain skeptical that GBV-C is responsible for slowing down HIV. Nevertheless, the findings so far demand further research.

What is GBV-C?

Originally named hepatitis G, the GBV-C virus was discovered fairly recently. Scientists did not uncover its unique genetic structure until the early 1990s, showing that it is closely related to hepatitis C virus (HCV). Unlike HCV, however, GBV-C does not cause illness or liver damage.

GBV-C is highly transmittable through blood-to-blood contact. Therefore, nearly all IV drug users with either HIV or HCV have probably also been infected with GBV-C. It is also transmitted through sexual contact and some studies have found evidence of current or previous infection with GBV-C in up to 55% of people with HIV.

What does the research show?

A number of studies have found that, in general, people who are infected with both HIV and GBV-C have slower disease progression and death rates than people with HIV who are not infected with GBV-C. Several studies presented at the Ninth Conference on Retroviruses and Opportunistic Infections (CROI) in 2002 and subsequently tell a more complex story.

GBV-C infection can be shown in a couple of ways, through an antibody test (anti-E2) or a viral load test (GBV-C RNA). However, only the GBV-C RNA test can confirm that a person is actively infected with GBV-C. This is because it is possible to become infected with GBV-C, develop antibodies, and then clear the infection while still retaining those antibodies for some time after. Therefore, the anti-E2 only provides evidence that an active infection has occurred at some point in time. It may be current or the body may have cleared it long ago.

To add further complexity, it is believed possible to become infected with GBV-C without ever developing antibodies, and still clear the infection. So some people who test negative for GBV-C RNA and the anti-E2 test may have actually been infected at some point. Gaining this knowledge has been key to developing a better understanding for how GBV-C may be protective against HIV disease progression.

The most recent studies have found that only people who have an active GBV-C infection (i.e., a positive GBV-C RNA test) will also have delayed HIV disease progression, and that this protection is lost when and if the body clears GBV-C. It was reported in some studies at the 2002 CROI that people living with HIV who cleared GBV-C infection may actually be worse off than people who never had GBV-C infection. More recent analysis of this same data indicates this may not be true.

Some researchers, however, remain skeptical that GBV-C infection plays any role at all in delayed HIV disease progression. It has been shown that GBV-C uses CD4+ cells to reproduce, thus competing with HIV. In studies documenting a survival benefit it has been shown that active GBV-C reproduction ceases at the same time as CD4+ counts begin to fall.

A number of researchers interpret this to mean that CD4+ counts are falling because the body has cleared GBV-C. Other scientists argue that the truth may actually be the opposite: when CD4+ cell counts drop, GBV-C no longer has a place to reproduce and is thus eliminated. A study appearing in the June 19 edition of *Lancet* may convince at least some skeptics.

The study, out of the Iowa VA Medical Center, tested the degree to which GBV-C was able to reduce HIV replication in cells. In a test tube, HIV-infected cells were infected with different quantities of GBV-C virus. HIV reproduction was significantly decreased in all cell cultures where the strain of HIV in the test-tube was dependent on one of two very common cell receptors (CCR5 or CXCR4). Moreover, the quantity and timing of the dose of GBV-C was strongly linked to the degree by which HIV reproduction decreased.

The researchers were also able to measure the effect of GBV-C and HIV infection on cellular factors that have been identified as protective against HIV. GBV-C-infected cells had fewer receptors like CCR5 on their surface, and they expressed chemical messengers (*chemokines*) known to block HIV entry into cells. (For more information, read Project Inform's publication, *Understanding HIV: Co-Receptors–CCR5*, available at 1-800-822-7422 or *www.projectinform.org*.)

The exact manner by which GBV-C infection accomplishes this is not yet known. These data certainly suggest that examining GBV-C co-infection is a promising avenue for further research. Might it be possible to build drugs based on how GBV-C protects cells? Would it be helpful or possible to infect people with GBV-C as a way to control HIV? Could a strain of GBV-C be used as a vehicle for some kind of gene therapy? The answer to any of these questions may very well lead us toward a cure for AIDS.

HIV Replication Capacity and Treatment Decisions

Researchers have known since the mid-1990s that some versions (strains) of HIV are less potent than others. Yet only recently have a number of studies sought to determine whether reductions or increases in HIV's ability to reproduce (i.e. replication capacity) can be measured accurately and if these measurements could provide a useful tool for HIV research, and monitoring HIV progression and the effectiveness of therapy. While more research is needed, emerging data suggest that developing an effective test of HIV replication capacity is not only possible, but that such tests may become an important new tool in the fight against HIV disease.

What is *replication capacity* and why does it matter?

The term *replication capacity*—often used interchangeably with the term *viral fitness*—refers to how quickly a sample of HIV taken from your blood reproduces (replicates). The HIV taken from one person's blood may reproduce more slowly or quickly than another person's. Scientists have observed that the slower a person's HIV reproduces, the less likely they are to have disease progression.

How to test for replication capacity

Currently, only one company in the U.S., ViroLogic,Inc., has a widely available test of HIV replication capacity (RC). Their RC test is included free of charge, whenever a doctor uses their combined phenotypic/genotypic HIV drug resistance test (PhenoSense GT). The RC test compares the rate at which HIV taken from your blood reproduces and compares this to the median rate at which a number of drug sensitive (wild-type) strains of HIV reproduce. The result is reported as a percentage, compared to the median wild-type at the bottom of the PhenoSense GT report. The makers claim that the results are about 95% accurate, so the actual percentage may be about 5% higher or lower than the number reported.

The company began offering the test in June of 2002, but only recently have data been published determining when and whether the results are at all meaningful.

What does the research show?

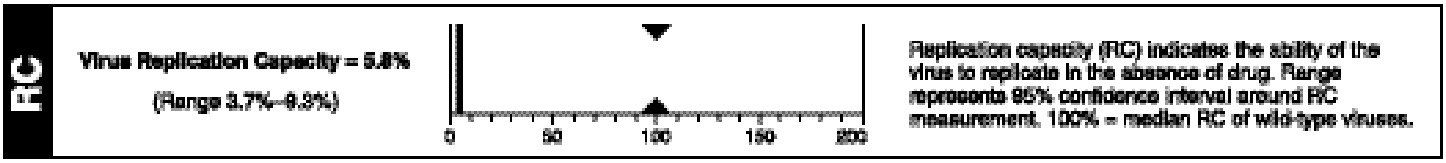
In 2001, researchers in San Francisco began to publish data on a group of people with HIV who maintained improved CD4+ cell counts and continued to do well clinically despite having persistently detectable HIV levels while on treatment. This stands in contrast to most people, whose CD4+ counts tend to fall soon after their viral load increases. Researchers sought to explain this observation, and further research concluded that reduced viral fitness, as measured by RC tests, is responsible.

In Italy, researchers studied a group of 18 people who were about to change anti-HIV therapy. Viral load, CD4+ count and HIV RC were tested at the time of the therapy change and one year later. People in the study fell into one of two groups; those who had a sustained increase in CD4+ counts to greater than 100 (immune responders) and those who did not (non-responders). Twelve of the 18 were immune responders and six were non-responders. Immune responders had a significantly greater reduction in HIV RC, compared to non-responders, regardless of their CD4+ cell count or viral load at study entry. Immune responders were also more likely than non-responders to have a specific mutation (M36I) in their virus.

A larger study of 189 people in San Francisco reported that reduced RC helps explain what is happening in people who have sustained increases in CD4+ cell counts even though HIV remains detectable. The study also showed that viral load was an important factor in predicting who might do well despite an incomplete virologic response to therapy. People who had viral loads below 10,000 were most likely to have continued good health.

A couple of very small studies also indicate that measuring HIV RC right after infection might be meaningful. The studies measured people's HIV RC right after infection. None of the people were on anti-HIV drugs yet. The studies found that people infected with a version of HIV with reduced RC had less disease progression than those whose HIV reproduced more rapidly. Further research is needed to confirm these results in greater numbers of people. But the data so far imply that RC testing may become another useful tool to help people decide when and whether to start anti-HIV therapy.

Example of replication capacity percentage on the PhenoSense GT report.



Commentary

The role and value of RC testing is becoming increasingly clear. The data most strongly suggest that it can be a useful tool for people who have become resistant to most anti-HIV drugs and whose current regimen is no longer keeping HIV undetectable. There may be a number of reasons why a person may wish to stay on such a regimen, including good tolerability as well having too few potent drugs with which to construct a new regimen. The risk of sticking with such a regimen, however, is the potential for worsening CD4+ counts and the development of new drug resistance that could be even more harmful to potential future combinations. The use of RC testing, along with viral load tests, can now offer additional guidance about when and whether to switch regimens.

What remains less clear is the degree to which RC test results will be a useful measure of a person's risk for disease progression when they've never taken anti-HIV drugs at all. The decision about whether to start anti-HIV therapy for the first time can be a difficult one. While there's consensus that people whose CD4+ cell counts drop below 200 should definitely be taking anti-HIV drugs, there is much less agreement for people with CD4+ cell counts of 200–350. The US Guidelines for the Use of Antiretroviral Drugs recommend that 350 should be the starting point for treatment, while others prefer to delay starting therapy until it falls below 200. Of course, there are other factors that must be considered, such as a person's general health, viral load and how rapidly CD4+ counts are falling. However, it could be tremendously helpful if an RC test could more clearly identify those people most at risk of disease progression.

Like any new test, including viral load and resistance tests, the more people who use them and the more they undergo the scrutiny of research, the more useful they become. Replication capacity has promise, and future studies will certainly improve the test and our ability to use it.

New Strategy for Blocking HIV: Trim5-alpha

It's well known that baboons and most monkeys cannot be infected with HIV, but until recently it wasn't known why these animals are protected from HIV infection. While there are related viruses that can infect non-human primates, called simian immune deficiency virus (SIV), those viruses rarely cause disease in the animals. Researchers have recently discovered a protein that these animals produce, called Trim5-alpha. It appears to block HIV infection of cells, though has little to no effect on SIV. Humans produce a form of Trim5-alpha, but the human form does not block HIV as well as the animal form of the protein.

In research conducted at Harvard University/Dana-Farber Cancer Institute, scientists found that when they chemically blocked the animal form of Trim5-alpha, the monkey cells were infectable by HIV in test tubes. Also, adding the animal Trim5-alpha to human cells in test tubes resulted in their protection from HIV infection.

This discovery is potentially important for several reasons:

- It may lead to the development of animal models for HIV/AIDS—by blocking Trim5-alpha in monkeys and infecting the monkeys with HIV it may be possible to better study HIV/AIDS—hopefully leading to increased understanding of the disease and new and better treatments.
- It may be possible to use the discovery in gene therapy for HIV. Human cells might be modified with a gene that will enable them to produce the animal form of Trim5-alpha and thus protect cells against HIV infection.
- Human Trim5-alpha does not prevent HIV infection of cells, though human Trim5-alpha has about 80% similarity to the animal form. It might be possible to modify human Trim5-alpha so that it is more potent against HIV.
- It may represent a therapy of particular interest in vaccine/prevention research, pre- or post-exposure prevention study and for treating very early/acute HIV infection.

Trim stands for T Cell Receptor Interacting Molecule. The Trim family of genes plays a part in regulating interactions between receptors on the outside of cells and signals on the inside of cells. The discovery that this particular Trim gene may have protective effects against HIV will undoubtedly pave the path to more research on this gene family. Also, this discovery likely leads the way to identifying other animal gene/proteins that block HIV.