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I ORGAN TRANSPLANTS

A. Introduction

The widespread availability of potent anti-HIV therapy, commonly called ART or HAART, has led to tremendous increases in life expectancy of HIV-positive people, particularly in high-income countries such as Canada. Despite this good news, some HIV-positive people may face other long-term problems as they age, including liver and kidney damage arising from co-infection with hepatitis B and C viruses, diabetes and higher-than-normal blood pressure.

In the time before HAART, organ transplants were attempted in HIV-positive people. In general, HIV-positive people who received transplants in the pre-HAART era appeared to have shortened survival. In the present era, doctors in the United States and Western Europe have gained experience conducting successful liver and kidney transplants in HIV-positive people.

In Canada, until recently, HIV-positive people were routinely excluded from even the possibility of receiving a transplanted organ. However, in British Columbia, Ontario and Quebec, HIV-positive people will now be considered for the waiting lists for organ transplants. Hopefully in the near future such transplants will become routine when needed.

In this issue of *TreatmentUpdate*, we feature research on several issues related to organ transplantation mostly in the setting of HIV infection.

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B. Before, during and after transplantation: an overview

Vital organs such as the liver and kidneys can become damaged because of the following:

- chronic infections that attack the liver (such as hepatitis B virus and hepatitis C virus)
- inflammation
- exposure to harmful substances (such as in cases of alcohol abuse)
- toxicity of medications
- diabetes
- higher-than-normal blood pressure

As these organs degrade, waste products can build up in the blood and circulate, causing complications and weakening overall health.

The first step in finding out more about transplantation options is a referral from a physician to a transplantation centre. These are usually located in major regional hospitals.

Evaluation

The process of evaluation by the transplant team can take several weeks, as different specialists are seen. For instance, in the case of a liver transplant, the specialists that can be involved include:

- liver transplant surgeons
- liver specialists (hepatologists)
- infectious disease specialists
- nurses
- social workers
- psychologists

In the case of a kidney transplant, a nephrologist (a doctor who specializes in kidney care) and kidney surgeon will be part of the team.

As part of the assessment, overall health and in particular the health of other key organs (heart, lungs and so on) will be checked to confirm not only that a transplant is needed but that a person's health is strong enough to withstand surgery and potential ensuing complications.

A psychological assessment will also take place to ensure that potential transplant recipients are mentally and emotionally ready for living with a transplanted organ. Generally, people who are active substance users are excluded from transplant programs. People who have recovered from addiction are usually required to be off substances for at least six months or longer, depending on the substance use and the transplant program.

Social stability is an important requirement for long-term success after transplantation because an intensive degree of monitoring, medication adherence and self-care is needed.

Each transplant centre may have its own criteria for people who are ideal candidates for transplantation. Usually these criteria are similar within a region. As there is a shortage of organs suitable for transplant, eligible candidates for transplantation are placed on a waiting list.

Where do donated organs come from?

Organs are often removed or harvested from people who have suffered severe and fatal injuries as a result of accidents or trauma to the head. After vital organs are harvested, they are placed in a solution that helps to nourish and maintain them and packed in ice. In this way, harvested organs can be maintained for between 12 and 20 hours and must be transplanted within that time. Sometimes a healthy family member or a friend can donate an organ or part of an organ if he or she is a suitable genetic match.

Balancing needs

People in need of organs who are severely ill are usually prioritized for transplantation. Medical centres also try to balance people's needs and take into account which patients on the waiting list are most likely to have the fewest transplant-related complications so that recipients can provide a hospitable host for the donated organ to survive. To help deal fairly with the needs of many different ill people, transplant centres often use a rating system. In the case of people waiting for liver transplants, this is called MELD—the model for end-stage liver disease. MELD involves an equation that takes into account the following lab values:

- bilirubin
- creatinine
- time for blood to clot

MELD scores are very useful in predicting which patients are likely to survive the transplantation process.

Matching an organ to a person

A person's suitability for a donated organ depends on several factors, such as the following:

- matching the recipient's blood type (A, B, AB and so on) with the donor's blood type
- a similarity of immunologic markers (called HLA factors) on the cells of the recipient's

immune system and on those of the donor's – the more closely the recipient and donor can be immunologically matched, the greater the chances of long-term transplantation success.
- cross-match test – even if there is a match based on blood type and HLA, there is still the possibility that the recipient's blood could have antibodies that can attack the donor's tissue. These antibodies arise most commonly because the recipient has been exposed to another person's tissues through blood transfusion. To rule out the presence of these antibodies, a small sample of blood is drawn from the recipient and white blood cells from a potential donor are exposed to the recipient's blood. If the donor's white blood cells are subsequently injured as a result of exposure to the recipient's blood, this is called a positive cross match and strongly suggests that transplanted tissue from the donor will most likely be severely attacked by the recipient's immune system. If no damage to the donor's white blood cells occurs then the result is called a negative cross match and the recipient's body is less likely to mount a strong attack against the new organ.

Surgery

The surgery involved in an organ transplant is complex and is done under general anesthesia. Removing a damaged liver is complex because the organ is inflamed and there is an increased risk for complications, such as bleeding. Veins and arteries have to be closed off and then reconnected to the new organ. During surgery, levels of many important substances, including glucose and calcium, fall to very low levels and body temperature also falls. These changes cause stress on the body but are successfully managed by the transplant team. Liver transplantation usually takes about three or four hours, while kidney transplantation can take up to 12 hours.

After the transplant

Because removing and transplanting vital organs is a major undertaking and because someone who has failing organs will usually be in some degree of ill health and immune-suppressing drugs must be administered, the recipient of a transplant can develop complications after surgery. Some complications are minor, others are major; some are short-term and others are long-term.

Depending on the results of the operation, transplant recipients usually stay in the hospital for about one week after surgery, as the transplant team performs intensive monitoring and tests to ensure that the new organ is working and that there are not any serious complications. Sometimes longer stays in the hospital are necessary.

After surgery the kidneys may temporarily become overwhelmed from the combination of injury caused by surgery and the toxicity of exposure to immunosuppressive medicines, particularly cyclosporine (Neoral, Sandimmune). So mechanical filtration of the blood (dialysis) may be temporarily needed for some recipients of a transplanted kidney.

As with any major surgery, bleeding can occur. Also, the new organ may carry cells of the donor's immune system and once these enter the circulation of the recipient, they can attack his or her red blood cells. This can cause a shortage of red blood cells in the recipient and so blood transfusion(s) may be necessary.

Other non-infection-related complications can include depression and seizures.

Most people who receive a transplanted organ feel better immediately. However, despite an improvement in energy, alertness and possibly mood, it may take several months for a person to regain his or her strength.

Infections

It is common for people to get infections after a transplant. Most of these infections can be treated quickly and suppressed. In the first month after transplantation, infections may appear in the following locations:

- abdomen
- genitals and tubes through which urine flows
- lungs

After the first month, other infections may appear but taking certain drugs called antimicrobials (antibiotics, antifungals and antivirals) can prevent or treat these infections. Commonly used antimicrobial agents include:

- azithromycin (Zithromax) – helps to prevent infection by bacteria called MAC (*Mycobacterium avium* complex)
- Bactrim/Septra (trimethoprim-sulfamethoxazole) – helps to prevent common pneumonias, particularly PCP (Pneumocystis pneumonia), to which HIV-positive people are susceptible

- fluconazole (Diflucan) – helps to prevent some fungal infections
- valganciclovir (Valcyte) – is used to prevent or treat viral infections, particularly those caused by CMV (cytomegalovirus)

Rejection

Despite good pre-transplant tests to ensure a good match between donor and recipient, the host's immune system will attack the new organ unless immunosuppressive medicines are taken. These attacks on the new organ are called rejection. Episodes of rejection can still occur despite the use of immunosuppressive drugs as the transplant team seeks to find a balance between suppressing the immune system so that the new organ can survive but not suppressing it so much that the recipient develops serious infections and other complications.

Signs of rejection can include fever and pain in the area where the new organ has been implanted. However, note that rejection, at least initially, may not result in symptoms. This is another reason why frequent and regular check-ups, including blood tests, are essential after transplantation.

CAT scans or even a biopsy of the liver or kidney may be necessary to be certain that rejection is occurring. When an episode of rejection is suspected, the transplant team may temporarily intensify immunosuppression, often with methylprednisone.

Life after transplant

After transplantation, many people eventually return to the activities that they used to enjoy before they became ill and needed a transplant. The transplant team provides advice to patients about staying healthy when they are ready to leave the hospital. Here are just a few general tips for staying healthy:

- Keep all appointments with your transplant team. Initially it may seem like you have frequent appointments to see different specialists or to have blood drawn, but after the first six months, if you are doing well, you will find that the transplant teams does not need to see you as often.
- If you suspect that an episode of rejection is occurring, contact your transplant team right away.
- Get advice from a registered dietician about eating a nutritious diet and ask your transplant team about what exercises are right for you.
- Avoid tobacco, alcohol and use of other substances.
- Always consult your transplant doctors about the medicines that you are taking, both over the counter and prescription. This is particularly important because many drugs can interfere with your transplant medicines and therefore your health.
- Always discuss the potential use of any supplements (including herbs) with your transplant team. Herbs are particularly troublesome because they can interfere with many medicines, including those used in transplantation and HIV care.
- Take all of your medicines exactly as prescribed. If you have difficult doing this, talk to your nurse or pharmacist as soon as possible.
- Continue to practice safer sex so as to minimize your exposure to germs.

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C. Getting to know your transplant drugs

Different transplant centres use different protocols specifying which combination of immunosuppressive medicines are used after transplantation. Often, one or more of these drugs must be taken, sometimes every day, after transplantation to ensure that the immune system is somewhat weakened, so that its ability to destroy the donated organ is minimized. Immunosuppressive medicines, while necessary for the survival of the transplanted organ, can have side effects. Transplant centres try to balance necessary immunosuppression against possible side effects from these drugs. Note that not everyone will get side effects from these drugs. The dose of each of these immunosuppressive drugs will vary from person to person. The transplant team will take

blood samples to assess the concentration of these drugs in the blood and make adjustments as necessary. This type of intensive medical surveillance is necessary particularly for HIV-positive people because many medicines used to treat HIV infection also affect transplant drugs and vice versa.

We now report on some commonly used immunosuppressive drugs and summarize their possible side effects. For more information about possible side effects and ways to minimize them, speak to your transplant team and pharmacist.

Corticosteroids

These are commonly called steroids. Methylprednisone is most often used in people with transplants, particularly immediately following a transplant and for treating episodes of rejection (where the immune system begins to attack the donated organ). Steroids are given at an initially high dose and this is gradually reduced over weeks or months. Sometimes steroids may be used for longer periods. Some people taking corticosteroids experience increased weight and blood pressure and can develop higher levels of cholesterol in their blood. This drug may also cause mood swings. Over the long-term, steroids can cause bones to become thinner and more fragile.

Cyclosporine (Neoral, Sandimmune)

This drug belongs to the class of drugs called calcineurin inhibitors. Cyclosporine is very good at suppressing the immune system and is sometimes used together with methylprednisone and another drug called CellCept (mycophenolate mofetil). However, cyclosporine can cause certain side effects, such as the following:

- flushing in the face – this resolves a few hours after you have taken your dose
- increased growth of hair on the face, arms and body (if you are bald, cyclosporine will not reverse this)
- slight tremors of the hands – this is common in the first few months of use but tends to clear over time or if the dose is reduced
- swollen gums and sensitivity of the mouth to heat and cold – keeping your mouth and teeth clean with daily brushing and flossing as well as regular visits to the dentist is important to maintain your oral health
- higher-than-normal blood pressure (hypertension) – your transplant team will prescribe medication to help lower your blood pressure. Advice from a registered dietician is also important. Talk to your dietician about how to reduce excessive intake of salt, which also can raise your blood pressure and affect the health of your kidneys.
- pre-diabetes and diabetes – cyclosporine can increase your risk for developing diabetes. Regular blood tests to assess your blood sugar will be done while you are taking this drug. If you have a parent, brother or sister who has diabetes, let your transplant team know. Signs/symptoms of diabetes can include unexpected and excessive feelings of thirst and/or hunger, frequent urination and blurred vision. If you experience any of these, contact your transplant team right away.
- changes in kidney health – regular blood and urine tests are important for monitoring your overall health and the health of your kidneys. Some cyclosporine users can develop kidney dysfunction (nephrotoxicity). If this happens, your transplant team can reduce your dose of cyclosporine or replace it with a different drug.

Tacrolimus (Prograf)

This drug is also a member of the calcineurin class of transplant medicines. It can cause headache and similar side effects as cyclosporine. However, tacrolimus does not cause swollen gums or extra growth of hair.

Mycophenolate (CellCept, Myfortic)

This drug is a powerful immunosuppressive agent and weakens the ability of T-cells to respond to stimulation from transplanted tissues. It can cause headache and gastrointestinal side effects—including diarrhea and nausea—which are usually mild. Fatigue can also occur in people taking mycophenolate.

Sirolimus (rapamycin, Rapamune)

This drug works by interfering with mTOR (mammalian target of rapamycin). mTOR inhibitors are of particular interest in transplant centres that treat HIV-positive people because these drugs may also have modest anti-HIV activity. Other mTOR inhibitors include everolimus (Certican, Zortress). mTOR inhibitors are as effective as cyclosporine but can have different side effects, such as delayed wound healing and increased cholesterol and triglyceride levels in the blood. Further information about sirolimus appears later in this issue of *TreatmentUpdate*.

Antibody therapy

Some antibodies (proteins) infused into transplant recipients can help suppress the immune system. Some antibody therapies such as thymoglobulin

attack the body's T-cells. Other antibody therapies are more specific and attack particular receptors or molecules on the surface of a cell. Examples of these specific antibodies (called monoclonal antibodies) include basiliximab (Simulect) and daclizumab (Zenapax). These two antibodies are not usually associated with side effects in large numbers of people, perhaps because they are only used for brief periods.

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D. Selected complications that can occur after transplantation

Over the long-term, if immunosuppressive drugs are successful in helping to minimize the immune system's attack on transplanted tissue, there are several health issues that can occur. It is difficult to untangle the specific cause(s) of some of these long-term issues for several reasons.

Preexisting issues

People who receive transplanted livers and kidneys often have traditional risk factors for cardiovascular disease prior to transplantation. These risk factors include poor dietary habits, smoking tobacco or engaging in substance use, being overweight, not getting sufficient exercise and so on. Not all of these bad habits are eliminated after transplantation.

Immunosuppressive drugs may amplify some of the effects of preexisting cardiovascular disease risk factors. Because transplant recipients are often given combinations of immunosuppressive drugs, it is sometimes difficult to link every adverse effect to a specific drug.

Cardiovascular complications

Bearing in mind some of these points, note that premature cardiovascular disease—including the development of higher-than-normal blood pressure and abnormal levels of lipids in the blood—is a common complication after transplantation.

Diabetes

Within a year after transplantation, and depending on the study, between 5% and 20% of transplant recipients develop type 2 diabetes. Tacrolimus (Prograf) decreases the body's production of insulin (a hormone needed to help control blood sugar levels) and this drug appears to have greater potential to cause diabetes than cyclosporine (Neoral, Sandimmune). The use of sirolimus (rapamycin, Rapamune) also appears to be linked to an increased risk for developing this complication.

Cancer

In general, as HIV-negative people live longer, their immune system gradually weakens and therefore their risk for cancer increases. As people who have transplanted organs live longer, their risk for developing cancer also increases because of the immunosuppressive therapies that they must continuously take. Researchers in Australia and New Zealand who have been monitoring HIV-negative transplant recipients have found that while deaths from heart attack and stroke have decreased—likely because these are preventable—deaths from infections and cancers have increased. Indeed, overall, compared to the average HIV-negative person without a transplant, HIV-negative people who do get transplants are between three and five times more likely to develop cancer.

The rate of cancers that are relatively common in non-transplanted HIV-negative people—colon, breast, lung and prostate tumours—is only slightly increased in people who receive a transplant. Other cancers, particularly those affecting the skin and immune system, are ones that tend to occur in transplant recipients. Studies of immunosuppressive drugs in HIV-positive people have not lasted long enough for researchers to be certain about their effects.

In HIV-negative people, exposure to cyclosporine has been associated with an increased risk for cancer, while exposure to mycophenolate (CellCept) has not. Studies that have assessed exposure to the mTOR inhibitors sirolimus or everolimus (Certican, Zortress) suggest that, at least for now, these drugs appear to be associated with a reduced risk for cancer.

Transplant teams are conducting clinical trials using different doses and combinations of immunosuppressive medicines to try to find the most effective and safest ones over the long term.

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E. Kidney transplants and HIV—the American experience

Researchers at transplant centres across the United States performed kidney transplants in HIV-positive people and subsequently monitored them for three years. At the end of this time, survival rates were about 88%. This rate is relatively high and there were no increased reports of AIDS-related illnesses. However, there were greater-than-expected cases of the immune systems of the transplant recipients attacking or "rejecting" the donated organ.

Study details

Between 2003 and 2009, researchers at 19 clinics enrolled 150 HIV-positive people for kidney transplantation. Prior to transplantation, participants were required to have the following:

- need for a kidney transplant
- at least 200 CD4+ cells
- an HIV viral load of 75 copies/ml or less while on HAART 16 weeks before transplantation

Different transplant centres had additional criteria for participants who wished to receive a transplant. Participants who had the following specific life-threatening infections in the past were excluded from the study:

- PML (progressive multifocal leukoencephalopathy)
- Crypto (Cryptosporidiosis)
- Lymphoma in the brain or spinal cord
- Kaposi's sarcoma that affected internal organs

At the start of the study, the basic profile of participants was as follows:

- 78% men, 22% women
- common causes of kidney damage – higher-than-normal blood pressure, HIV-related kidney damage, diabetes
- CD4+ count – 524 cells
- HCV co-infection – 19%
- HBV co-infection – 3%

Results

During the first week after transplantation participants received intense immunosuppression with a combination of two or more of the following drugs:

- mycophenolate (CellCept) – 87% of participants
- tacrolimus (Prograf) – 66% of participants

- basiliximab (Simulect) or daclizumab (Zenapax) – 51%
- anti-T-cell antibodies – 32%
- cyclosporine (Neoral, Sandimmune) – 22%

Survival

Transplantation is a major procedure and is often done in patients who are very ill, so there is always a risk of serious complications and not every person is guaranteed survival. In the present study, it is not surprising that some HIV-positive organ recipients eventually passed away. Survival rates after transplantation were as follows:

- at one year – 95% were alive
- at three years – 88% were alive

Researchers described these survival rates as being "generally between those for older [HIV-negative] kidney transplant recipients (those who were 65 years or older) and for all kidney transplant recipients during a similar time frame."

Causes of death

In total, 11 people died from the following causes:

- cardiovascular complications – three people
- blood poisoning from severe infections – two people
- lung infections – two people
- kidney cancer (in the recipients' original kidneys) – two people
- unknown cause(s) – two people

The researchers noted that the transplanted organs were still working when eight of these 11 people died.

Grafts

Transplanted organs and tissues are sometimes called grafts. In 13 people the grafts died mostly because the recipients' immune systems kept attacking the new kidneys. Analysis of many factors suggested that the following likely played a role in the demise of the grafts:

- needing to treat the recipient for episodes of graft rejection
- using anti-T-cell antibodies during initial immunosuppression following transplantation

Receiving a graft from a living donor was more likely to result in the graft's survival.

Rejection

Transplant centres do their very best to find immunologically similar donors and recipients. Yet the host's immune system can still attack the new organ, in the case of this study, the kidney. Such attacks are called rejection.

Episodes of rejection that occur during the first three months following a transplant are called acute rejection (though some cases of acute rejection can occur later). Among transplant recipients, 33% had episodes of acute rejection.

A single episode of rejection does not usually lead to the loss of a transplanted organ. However, if not properly controlled by immunosuppressive agents, acute rejection can recur and become chronic rejection.

In total, the proportion of participants who experienced rejection was as follows:

- during the first year after transplant – 31%
- by the third year after transplant – 41%

These rates of rejection puzzled the research team because they are greater than seen in elderly HIV-negative people.

Taking many factors into account, the only statistically significant events associated with an increased risk for rejection were as follows:

- receipt of a kidney from a dead donor
- use of cyclosporine

Delayed graft functioning

Even though a new kidney is transplanted and reconnected to blood vessels, it may not immediately begin working; this is called delayed graft function. This problem occurred during the first week after transplant in 15% of people who received an organ from a living donor and in 46% of people who received an organ from a deceased donor. In cases of delayed graft functioning, temporary use of dialysis was necessary.

HIV-related disease and lab tests

After transplantation, because immunosuppressive drugs are used, a few people developed HIV-related illnesses, as follows:

- Kaposi's sarcoma (KS) tumours on the skin – two people
- yeast infections of the throat – one person
- PCP (Pneumocystis pneumonia) – one person
- Crypto (Cryptosporidiosis) – one person

The researchers found that changes in CD4+ cell counts were "significantly greater in patients who received early therapy with [anti-T-cell antibodies]

compared to people who did not." Overall, three years after transplantation, there were no clinically meaningful differences in CD4+ cell counts between people who had received these particular antibodies and those who had not. And, overall, after three years, CD4+ cell counts had fallen by about 50 cells regardless of exposure to anti-T-cell antibodies.

HIV viral load was suppressed in most participants; in 48 people it became detectable but mostly just once or twice. Only one person had a detectable viral load three years after transplantation.

Serious infections

Of the 150 transplant recipients, nearly 40% developed 140 episodes of infection that required them to be hospitalized. These infections were classified as follows:

- bacterial – 69% of cases
- fungal – 9% of cases
- viral – 6% of cases
- parasitic – 1% of cases

In the remaining cases, researchers weren't certain about the cause(s) of infection.

Common sites in the body affected by serious infections included the following:

- genitourinary tract
- lungs and throat
- blood

The majority of serious infections occurred within six months of transplantation.

Infections were more common among people co-infected with hepatitis C virus.

Cancers

A total of nine cancers were reported as follows:

- KS – two cases
- kidney cancer – two cases
- oral cancer – two cases
- squamous-cell skin cancer – one case
- basal-cell skin cancer – one case
- thyroid gland cancer – one case

Overall

In this relatively large study, the research team stated that its good results were influenced by the following factors:

- careful selection of participants
- adherence to clinical management protocols
- close coordination among care teams that included surgeons, nephrologists, nurse coordinators, pharmacologists, social workers, HIV experts and primary care doctors

The team found that its greatest challenge was achieving sufficient immunosuppression so that the graft would survive without causing toxicity. This challenge arose because of what the researchers called the "complicated" interaction between immunosuppressive medicines and some anti-HIV drugs, specifically protease inhibitors. In the future, the transplant team may conduct experiments with relatively new anti-HIV drugs such as the integrase inhibitor raltegravir (Isentress), as this drug has a very low potential for drug-drug interactions.

Although tacrolimus-based maintenance immunosuppression may be used in place of cyclosporine to reduce the risk of rejection, the team notes that cyclosporine has modest anti-HIV and anti-HCV activity and may therefore be useful in cases of co-infection.

Rejection

The researchers were concerned by the "unexpectedly higher rejection rates (by a factor of 2 to 3) in the HIV-infected kidney recipients, as compared with recipients who did not have HIV infection."

About 50% of these episodes of rejection occurred despite the use of corticosteroids. This resistance to the immunosuppressive properties of steroids is a feature of aggressive rejection. And aggressive rejection often occurred despite low CD4+ cell counts that commonly occur following transplantation. The researchers are not certain about the precise cause(s) driving aggressive episodes of rejection. Several studies are underway to explore possible causes of this problem.

In the future, it is likely that HIV-positive people who will require organ transplants may be very ill with lower CD4+ cell counts and higher viral loads than seen in the present study. Hopefully, transplant protocols will evolve to encompass such people.

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F. Sirolimus—potential applications in HIV infection

Sirolimus (rapamycin, Rapamune) is currently used as an immunosuppressive medication in transplant patients. However, some research in the past several years suggests that sirolimus has several properties that may make it interesting to further study in HIV-positive people.

About sirolimus

Sirolimus exerts its immunosuppressive effect by interfering with a protein called mTOR (mammalian target of rapamycin). This interference has the effect of disabling immune system cells from fully responding to the chemical signal interleukin-2 (IL-2). T-cells exposed to sirolimus are unable to become activated and further develop their infection-fighting abilities.

Co-receptors

In addition to the CD4 receptor, HIV needs one of two co-receptors to attach itself to and gain entry to infect a cell. These co-receptors are called CCR5 and CXCR4. Some strains of HIV prefer to use CD4 and CCR5; other strains prefer to use CD4 and CXCR4. To make things even more interesting, still other strains of HIV can use CD4 and *either* CCR5 or CXCR4.

In the lab

Laboratory experiments with cells have found that an unexpected consequence of sirolimus's interference with IL-2 signalling is that T-cells and other cells of the immune system are unable to display or express large numbers of CCR5 on their surface. This effect on CCR5 has been found even with very low concentrations of sirolimus, less than those used for immunosuppression in transplantation. Also, sirolimus seems to have a modest impact on protecting cells from strains of HIV that use CXCR4; exactly how sirolimus does this is not clear.

Other laboratory studies have found that sirolimus impairs the ability of HIV-infected cells to replicate (produce copies of HIV).

Monkey studies

Experiments with sirolimus in a few healthy monkeys found that the drug greatly reduced CCR5 expression on cells of the immune system and in the vagina. This latter discovery suggests that sirolimus, if formulated into a cream or gel, could be investigated for its potential to prevent the sexual transmission of SIV (simian immunodeficiency virus) in monkeys.

HIV

Small pilot studies of sirolimus have been conducted in HIV-positive people. In such studies the drug was used to provide immunosuppression for organ transplantation. According to reviewers of such studies, sirolimus appears to enhance the viral effects of HAART on HIV. However, no increase in CD4+ counts was found. Further details about one of these studies appears later in section G of this issue of *TreatmentUpdate*.

Future considerations

In people who have received kidney transplants, sirolimus has been prescribed at doses between 2 and 5 mg daily. At these doses, the concentration of sirolimus in the blood is between 4 and 19 nM. In laboratory experiments with cells and HIV, sirolimus at a concentration of just 1 nM can significantly impair production of HIV from infected cells. Strains of HIV used in these experiments preferred to use the CCR5 co-receptor. So a dose of sirolimus that is less than that used in transplantation may be worth considering for testing in a pilot study of HIV-positive people. Other studies are needed to assess how sirolimus's anti-HIV activity might be enhanced when used with drugs such as maraviroc (Celsentri), which can mask CCR5 and protect cells from HIV infection.

A major issue that needs to be explored is how sirolimus interacts with drugs used to treat HIV infection. Transplant teams have often found that the dose of immunosuppressants such as cyclosporine, sirolimus and tacrolimus require adjustment when given to HIV-positive people who are taking protease inhibitors.

Sirolimus has potential for being used in further experiments to assess its effect on the prevention and treatment of SIV in monkeys. It also has potential in HIV-positive people, particularly those who receive transplanted organs, to assess its anti-HIV activity. This potential of sirolimus is best explored in carefully designed and closely monitored studies.

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G. Sirolimus monotherapy after liver transplants

Sirolimus (rapamycin, Rapamune) is an immunosuppressive drug with additional but modest activity against some tumours and HIV. Unlike many other drugs used to suppress the immune system, sirolimus does not damage the kidneys or increase the risk of developing diabetes. Researchers in Italy performed a pilot study of sirolimus as the sole immunosuppressive treatment in HIV-positive people who received organ transplants. Their results are promising but require confirmation in a well-designed clinical trial.

Study details

Researchers enrolled 14 participants (12 men, 2 women), 10 of whom were co-infected with hepatitis B or C viruses. On average, their CD4+ count was 275 cells and HIV viral load was less than 50 copies/ml. On average, they had been on the waiting list for a liver transplant for about eight months. Half of the participants had liver cancer. Using the MELD scoring system, these participants had a 20% chance of dying within three months if they did not receive a liver transplant. HAART was discontinued just before the transplant and resumed about two weeks later.

Results

Immediately following transplantation, immunosuppression with cyclosporine or tacrolimus (Prograf) together with prednisone was prescribed.

In six cases, researchers replaced cyclosporine with sirolimus an average of 67 days after transplantation because of kidney dysfunction (five cases) and the emergence of Kaposi's sarcoma (KS) lesions on the skin (one case).

In all cases, participants who were switched to sirolimus improved as kidney function returned to normal and KS skin lesions cleared. Moreover, in the person whose KS lesions faded, technicians could no longer detect the virus that causes KS (HHV8; human herpes virus 8) in his blood.

One case of mild acute rejection occurred in a person who was switched to sirolimus but this resolved when additional immunosuppression with methylprednisone was used for 10 days. In contrast, three cases of acute rejection occurred in people who continued to receive cyclosporine or tacrolimus.

After transplantation, hepatitis C virus (HCV) infection became reactivated in seven people, all of whom were taking cyclosporine or tacrolimus. Two other people who had HCV and were taking sirolimus had this co-infection clear.

Survival

Four people died—two taking cyclosporine or tacrolimus and two taking sirolimus. In the latter cases, death ensued because of complications from severe fungal and bacterial infections. Among people who died while taking cyclosporine or tacrolimus, heart failure and severe bacterial infections were the causes of death. After 50 months of observation, survival rates of participants on sirolimus or tacrolimus/cyclosporine were similar—about 68%.

Side effects

Sirolimus can cause side effects such as elevated levels of cholesterol and triglycerides in the blood. Ultimately these can increase the risk for cardiovascular disease. In all cases, treatment with lipid-lowering medications resolved this issue.

The findings from this study should be treated with caution, as this was not a randomized controlled trial, so inadvertent confounding when interpreting the data is a possibility. As a result, researchers cannot be certain that sirolimus provided additional benefits to people.

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H. Adjusting tacrolimus because of HIV treatment

Several transplant drugs interact with medicines used to treat HIV infection, particularly HIV protease inhibitors. These interactions can lead to dangerous levels of transplant drugs in the body, amplifying their immunosuppressive effects and increasing their potential for side effects such as kidney damage and diabetes. As researchers gain

more experience with transplants in HIV-positive people, better regimens for transplantation are likely.

Doctors in Bonn and Frankfurt, Germany, recently reviewed several cases of drug-drug interactions in HIV-positive people who received transplanted organs or who needed immunosuppressive therapy for other reasons over the past decade. Their limited experience with the integrase inhibitor raltegravir (Isentress) suggests that this drug has little potential for interaction with transplant medicines. We now present some of their case reports as well as one from New York City.

Case 1

In 2008, a 45-year-old man co-infected with HIV and hepatitis B virus (HBV) received a liver transplant because his liver was failing. Before transplantation his CD4+ count was 175 cells and HIV viral load was less than 50 copies/ml.

After transplantation he was given a complex anti-HIV drug regimen consisting of the following:

- saquinavir (Invirase) – 1,000 mg twice daily
- lopinavir-ritonavir (Kaletra) – 400-100 mg twice daily
- additional ritonavir (Norvir) – 100 mg twice daily
- 3TC (lamivudine) – 150 mg twice daily
- tenofovir (Viread) – 245 mg once daily

To protect the new liver from his immune system, immunosuppressive medications were prescribed as follows:

- mycophenolate (CellCept) – 500 mg twice daily
- corticosteroids – 4 mg once daily
- tacrolimus (Prograf) – 0.5 mg once every 9 to 21 days, depending on its concentration in the blood

Doctors conducted intensive monitoring of the concentration of drugs in the man's blood. They found abnormally high levels of tacrolimus and lopinavir and unexpectedly low levels of saquinavir.

They reduced his dose of tacrolimus to 0.02 mg once daily and then gradually increased this to 0.06 mg once daily. This latter dose is about 1% of what is normally prescribed for post-transplant care. This resulted in a level of 6.6 ng/ml of tacrolimus in his blood. Following this large dose reduction in tacrolimus, the concentration of protease inhibitors in his blood normalized.

Case 2

In 2004, a 34-year old man co-infected with HIV and hepatitis C virus (HCV) was deteriorating because of a failing liver and received a transplanted organ. His anti-HIV regimen consisted of standard doses of the following drugs:

- AZT (Retrovir, zidovudine)
- abacavir (Ziagen)
- tenofovir (Viread)

He also received treatment for HCV infection and was subsequently cured. Following transplantation, while taking the immunosuppressant cyclosporine (Neoral, Sandimmune), he experienced two episodes of rejection. So doctors added large doses of prednisone to his regimen and this suppressed his immune system and these reactions. However, after the second episode of rejection, which occurred 17 months after transplantation, his doctors replaced cyclosporine with tacrolimus at a dose of 3 mg per day.

Subsequently the level of liver enzymes in his blood rose, suggesting liver inflammation and damage. Doctors then replaced AZT with the HIV protease inhibitors fosamprenavir (Lexiva, Telzir) 700 mg and ritonavir 100 mg, both drugs twice daily. This caused the man's concentration of tacrolimus to soar. So his doctors reduced the dose of tacrolimus to 0.08 mg once daily. After this change the man's doses remained stable. His liver enzymes are now only somewhat elevated and his CD4+ count is at 319 cells and viral load less than 50 copies/ml.

Case 3

A 44-year-old man co-infected with HIV and HCV had a liver transplant in 2002. At that time his HIV therapy was as follows:

- saquinavir – 1,000 mg twice daily
- lopinavir-ritonavir – 400-100 mg twice daily
- 3TC – 150 mg twice daily

Immunosuppression was given with three drugs as follows:

- cyclosporine
- mycophenolate
- prednisone

Several years later the man developed kidney dysfunction, likely due to cyclosporine toxicity, and so doctors replaced that drug with tacrolimus at a dose of 0.02 mg twice daily. Also, saquinavir and lopinavir were replaced with darunavir (Prezista) at a dose of 600 mg twice daily. His dose of

tacrolimus was adjusted to 0.01 mg in the morning and 0.02 mg in the evening.

Two years later, blood concentrations of his drugs were still within their expected range and his CD4+ count was 739 cells and viral load less than 50 copies/ml.

Case 4

A 60-year-old man co-infected with HIV and HBV developed liver cancer. At the time of this diagnosis in 2007 he was not taking HAART. He received a transplant and was given this combination of anti-HIV drugs at standard doses:

- AZT, 3TC and tenofovir

His dose of tacrolimus was 1 mg twice daily. Additional immunosuppression came from mycophenolate and corticosteroids.

Two and half years later, the man's kidneys began to malfunction and doctors suspected that this was due to tenofovir toxicity. They replaced tenofovir with raltegravir (Isentress) at a dose of 400 mg twice daily. His raltegravir and tacrolimus levels were within their expected ranges.

Case 5

A 45-year-old man was suffering from Crohn's disease (inflammation of the digestive tract) and received long-term treatment with corticosteroids. Subsequently he developed very thin bones (a side effect of corticosteroid therapy). Doctors replaced his steroid with tacrolimus at a dose of 2 mg twice daily. His anti-HIV therapy consisted of standard doses of raltegravir and tenofovir + FTC (Truvada). This combination did not affect the concentration of tacrolimus in his blood and vice versa.

Atazanavir

In a separate report, doctors at New York–Presbyterian Hospital recently published their experience with drug-drug interactions. They had a 53-year-old man who was co-infected with HIV and HBV. His kidneys were severely damaged because of diabetes and higher-than-normal blood pressure. His CD4+ count was 451 cells and HIV viral load less than 50 copies/ml. His treatment consisted of these drugs:

- atazanavir (Reyataz) 400 mg + Kivexa (abacavir + 3TC)

Doctors withheld HAART on the day of transplantation and then resumed it 48 hours later. The immunosuppressive agents he was initially given were as follows:

- anti-T-cell antibodies
- methylprednisone – 500 mg
- mycophenolate – 2 g per day
- tacrolimus – 0.5 mg per day

Using intensive blood monitoring, doctors found unusual changes in his levels of tacrolimus. Initially the concentration of tacrolimus would rise but then six hours after taking a dose his levels fell below their effective concentration. Fortunately, the use of anti-T-cell antibodies caused temporary immune suppression so that the organ was not rejected and this gave the doctors time to conduct brief experiments with different doses of tacrolimus. They subsequently found that a dose of tacrolimus 1.5 mg every 12 hours was best. The transplant team noted that this dose adjustment was unusual because in their experience with other HIV-positive patients taking protease inhibitors, such as darunavir + ritonavir, tacrolimus could be dosed at only 0.5 mg twice weekly to provide sufficient immunosuppression. After their experience with this particular patient, the hospital changed its protocol and now conducts brief experiments *before* transplantation in HIV-positive people, prescribing small doses of tacrolimus and measuring the ensuing concentration in the blood. This has resulted in only minor changes being needed post-transplantation.

Three months after transplantation the man's HIV levels remain below the 50-copy/ml mark, his CD4+ count is at 279 cells and he is otherwise stable.

All of these reports over the past 10 years underscore the complexity of drug interactions that can occur when both immunosuppressive medicines and protease inhibitors are used together. The limited experience with raltegravir in this German report suggests that this drug does not interact with commonly used transplant medicines. In a separate report, French researchers also found no interactions between raltegravir and tacrolimus in 13 people given both drugs following organ transplant.

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I. Liver transplants for liver cancer in HIV infection

Co-infection with hepatitis B and C viruses can rapidly degrade the liver in the setting of HIV infection. Furthermore, both of these hepatitis viruses can eventually cause liver failure, liver cancer and death. Several studies have found that about 25% of liver-related deaths in HIV-positive people in high-income countries are due to complications from liver cancer. In selected HIV-negative people with liver cancer, transplant with a new liver can be life saving.

Researchers in France conducted a study to assess the risks and benefits of liver transplantation for HIV-positive people with liver cancer who were also co-infected with hepatitis B (HBV) or C (HCV). Their results found a high rate of successful transplant outcomes.

Study details

Between 2003 and April 2008, 147 patients (124 men and 23 women) were referred for treatment at Hôpital Paul Brousse in Villejuif, France, because of liver cancer. This diagnosis was based on results from CAT scans or biopsy.

Meetings with a large team of the following specialists were convened to review the results of medical assessments and make decisions about which patients would get a liver transplant:

- liver surgeons
- hepatologists
- virologists
- oncologists
- radiologists

People who were not placed on the waiting list for a transplant had these complications:

- spontaneous bleeding in blood vessels near the tumour(s)
- tumours outside the liver
- history of other cancers in the past five years

Of the 147 patients, assessments found that 86 had severely damaged livers. Specifically, these 86 people had cirrhosis, as their healthy liver tissue had been replaced with useless scar tissue, and 21 of these 86 were HIV positive.

Grafts of new livers or parts of livers were transplanted. After transplantation, immunosuppression was provided by cyclosporine- or tacrolimus-based regimens. All patients received corticosteroids; these were gradually withdrawn between three and six months after transplantation. Patients were given comprehensive medical monitoring and also received ultrasound liver scans.

The basic profile of 21 HIV-positive participants who were placed on the waiting list for a liver transplant was as follows:

- 85% men, 15% women
- age – 48 years
- HBV co-infection – 9%
- HCV co-infection – 80%
- HBV and HCV co-infection – 9%

Using a scoring system called MELD (the model for end-stage liver disease) that is useful for predicting survival, overall most HIV-positive patients on the transplant list had a low risk of death in the next three months.

Results—On the waiting list

While on the waiting list for a transplant, 61% of HIV-positive patients received TACE, or transarterial chemoembolization. In this procedure, doctors, guided by X-ray or other scans use a thin flexible tube to penetrate the artery that supplies fresh blood to the liver and any tumours there. Small doses of chemotherapy are then piped through the tube and this bathes the tumour(s), damaging them. After chemotherapy is applied, the smaller blood vessels that supply blood to the tumour(s) are blocked. Both of these actions help to slow down the growth of tumours and can extend the survival time of people on the waiting list.

AFP

Assessment of alpha-fetoprotein (AFP) is an important part of liver cancer care. AFP has no known function in healthy adults. However, in certain conditions, including testicular cancer, liver cancer and tumours from other parts of the body that have spread to the liver, AFP levels rise.

Disappearing from the waiting list

Researchers found this trend: HIV-positive patients were more likely to leave the waiting list without a liver transplant. Usually this departure from the waiting list happened within six months

after being listed. This greater dropout rate was likely due to worsening health because medical records showed that AFP levels rose more quickly among HIV-positive patients, suggesting the spread of cancer within the liver. This likely resulted in the appearance of complications. All of the people, both HIV negative and HIV positive, who prematurely left the waiting list subsequently died. None of the HIV-positive people who prematurely left the waiting list had a CD4+ cell count below 100 cells.

Transplantation

In total, 16 HIV-positive and 58 HIV-negative people who were on the waiting list received a transplant. In the first two months after transplant, three people died as follows:

- one HIV-negative and one HIV-positive person – complications from a burst artery to the liver
- one HIV-negative person – complications from multiple organ failure

Overall survival rates

At one year

- HIV-positive people – 81%
- HIV-negative people – 74%

Recurrence of liver cancer occurred in 31% of HIV-positive people given a transplant and in 15% of HIV-negative people. This difference was not statistically significant, likely because the number of people used for comparison was relatively small. Four of the HIV-positive people whose liver cancer recurred died. Moreover, when liver cancer recurred, HIV-positive people appeared to die twice as fast as HIV-negative people. According to the researchers, increases in AFP of more than 15 g/uL per month while on the waiting list were highly predictive of a recurrence of cancer after transplantation.

The French researchers noted that their study raises several important issues:

- Monitoring AFP levels while patients are on the waiting list is very useful for predicting (1) survival before transplantation and (2) the risk of liver cancer recurring after transplant.
- As none of the HIV-positive patients on the waiting list dropped out because of low CD4+ cell counts, therapy for liver cancer may help HIV-positive people on the waiting list survive until a new liver is ready.

The present study was based on a small number of HIV-positive patients with a relatively short period of monitoring after transplantation. So these findings need to be interpreted with caution. However, the study does provide valuable information that may save the lives of other HIV-positive people on the waiting list for a liver transplant.

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Disclaimer

Decisions about particular medical treatments should *always* be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.

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