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Contents

I HIV CURE RESEARCH

A. The search for a cure

For the past several years, researchers in Canada, the U.S., Western Europe and Australia have intensified efforts to understand how HIV might be cured. Some of these efforts have gone toward lab studies with cells and HIV, while other studies have been done in HIV-positive people. The movement toward a cure has been encouraged by the successful experiment with a patient in Berlin, Timothy Brown (sometimes called "the Berlin patient"). His HIV infection was cured after two stem cell transplants of cells naturally resistant to HIV infection and intensive and sometimes dangerous rounds of chemotherapy and radiation.

Repeated attempts to cure people using similar regimens have not worked. However, scientists are planning many other different experimental approaches with monkeys infected with SIV (simian immunodeficiency virus; a close relative of HIV that causes an AIDS-like disease in susceptible monkeys) and in some people with HIV. The vast majority of these experiments with people are being conducted in the U.S.

In the quest for a cure for HIV, many different approaches are being tested, such as combinations of drugs that attempt to flush HIV out of hiding, antibodies that help capture HIV, and drugs and vaccines that enhance the ability of the immune system to detect and destroy HIV-infected cells. There are also attempts to cure HIV with gene therapy, with many clinical trials underway in the U.S.

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555 Richmond Street West, Suite 505
Box 1104
Toronto, Ontario M5V 3B1 Canada
phone: 416.203.7122
toll-free: 1.800.263.1638
fax: 416.203.8284
www.catie.ca
charitable registration number: 13225 8740 RR

From press release to news

It is important to note that in recent years the funding environment for all biomedical researchers has become much more competitive. At large agencies that provide research funds, only about 20%, often less, of research grant applications get highly reviewed *and* receive funding. This means that many good ideas do not get funded. In this highly competitive environment, teams of scientists increasingly have their university media relations offices issue press releases about their work. This helps the scientists get noticed by media and, in a few lucky cases, results in an interview. They likely hope that such publicity incites interest in their work that perhaps helps them get additional funding in the future. These press releases simplify the scientific advances made and are sometimes republished on media websites as "news" and often changed in the process by people who do not fully understand the subject matter. In some cases over the years, some media outlets have misunderstood press releases or what was said in an interview and have claimed that HIV has been cured or that a cure is very close, when that is not the case.

The hidden virus

In the past, media outlets have arrived at the erroneous conclusion that HIV has been cured after scientists involved in cure experiments have revealed that they are unable to find HIV in the blood of participants in clinical trials. However, this finding is not novel: Only about 2% of CD4+ cells are in the blood; the vast majority of these cells are in lymphatic tissue and lymph nodes scattered around the body, particularly around the gastrointestinal tract. Most HIV is also in the cells of the immune system within these tissues and lymph nodes. The inability to find HIV in the blood, therefore, does not mean that the virus has been purged from the body or that people were cured.

The tests and techniques used to try to find residual HIV in clinical trials of potential cures are imperfect. In nearly all cases in which scientists initially said that they were unable to find HIV, the virus subsequently became detectable after participants had stopped using potent combination anti-HIV therapy (ART) for several months or years. Researchers do not know all the tissues and types of cells where HIV might remain after intensive rounds of experimental cure therapy. They cannot sample every bit of lymphatic tissue, lymph node and delicate and important tissues such as the brain, ovaries or testicles where HIV might be lurking at low levels. This is why in cure research supervised treatment interruptions are necessary. The only way that researchers can be certain about the effectiveness of a potential cure is to take the risky step of withholding ART from participants to see if HIV once again becomes detectable in blood samples. Therefore, participants in cure research experiments need to be monitored, sometimes intensively, for months and years.

In published results so far, HIV has almost always eventually been detected after ART has been withdrawn—the exception being the Berlin patient. These findings suggest that based on currently available technology, scientists are not certain where HIV lurks in the body despite attempts at purging the virus. As a result, in the absence of a breakthrough, it is unlikely that scientists will be able to produce a cure safely, cheaply and effectively in vast numbers of people within the next 10 years.

Changing the goals

However, what may be possible is that with a future experimental therapy, scientists could significantly reduce the amount of HIV in ART users to a level so low that for a time—perhaps weeks, months or hopefully years—participants may not subsequently need to use ART and their immune systems would remain healthy with no chance of transmitting HIV. Researchers refer to such a goal as a "functional cure."

Bear in mind

Many of the drugs and/or therapies that have been and will be used in clinical trials attempting to cure HIV are experimental; they may not have been approved for routine use and/or they likely have toxicities. Drugs and techniques that have potential for cure research today may not appear that way a few years from now and might be quickly discarded from a clinical trial program as scientists search for a drug or combination of drugs that is likely to be more effective.

Learning from advances in cancer research

Advances in immunology were once led by scientists working in the field of HIV research

in the 1980s to mid-1990s. Now the excitement in immunological discovery has moved to the field of cancer research. In this field, scientists have uncovered some of the ways that tumours can subvert the immune system. To counteract this, scientists have deployed a growing number of proteins, often specially designed antibodies, which block key molecules (called checkpoints) on cells of the immune system. These antibodies, called checkpoint inhibitors, unleash the immune system so that it can attack tumours. In some clinical trials, checkpoint inhibitors have greatly helped prolong survival in some HIV-negative people with cancer.

Enthused by the discoveries in the immunology of cancer, scientists working in the field of HIV plan to conduct experiments in their labs with HIV-infected cells, in SIV-infected monkeys and, in some cases, in HIV-positive people to assess the effect of intermittent use of checkpoint inhibitors. Note that checkpoint inhibitors have been priced incredibly high by pharmaceutical companies (around $15,000 CAN per person per month for cancer therapy) and can cause intense and complex side effects, so these experiments in HIV-positive people will likely proceed slowly and involve small numbers of people.

Another development from the cancer field is to create T cells that are trained to attack tumours. How this works is, scientists filter the blood of a person with cancer to extract T cells. Through genetic engineering these cells are made to produce a receptor that helps them focus only on attacking the specific tumour. These receptors are called chimeric antigen receptors (CARs). Scientists working in the field of HIV cure research plan to design experiments so that T cells from HIV-positive people can be genetically engineered to produce a receptor that helps them zero in on and attack HIV-infected cells.

Back to finance

Since the onset of the financial-economic crisis in 2008-09, economic growth in many Western countries has been diminished. This has led in some cases to a reduction or just small increases in general research funds in comparison to the era prior to the onset of the Great Recession. Scientists working hard in laboratories to try to find a cure for HIV must now also compete for research funds against proposals that seek to increase research on other infectious diseases, including newly (re) emerging viruses such as Ebola, Chikungunya and Zika and drug-resistant germs. All of these factors suggest that overall funding for HIV research will not significantly increase. This means that progress toward a cure for HIV will require a combination of hard work and more time. As a result of the long-term timeline that is likely needed for cure research, funding agencies must be patient with scientists and continue to support them for the many years it will take to create a safe, effective, affordable and widely available cure.

In this issue

Many of the potential therapies being tested in the hope of finding a functional cure for HIV are experimental. However, some experiments for a cure are repurposing drugs approved for another use. For instance, one cure study underway in the U.S. is testing a drug approved for the treatment of inflammatory intestinal conditions—Crohn's disease and ulcerative colitis—in HIV-positive people. The clinical trial of this drug may or may not result in a cure, but because the drug is already approved for use in people with a different condition, clinical trials with it in the context of curing HIV will likely move faster than studies with experimental drugs. We report on this exciting possibility later in this issue of *TreatmentUpdate*.

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B. Exciting results in monkeys lead to a clinical trial in humans

A close relative of HIV called SIV (simian immunodeficiency virus) causes an AIDS-like disease in susceptible monkeys. SIV-infected monkeys are often used to assess potential medicines and vaccines prior to testing in HIV-positive people.

For at least the past six years a team of researchers in the U.S. has been conducting experiments with SIV-infected monkeys, giving them intravenous infusions of an antibody designed to reduce the spread of virus-infected cells within their immune system. The team's most recent experiment has found that SIV-infected monkeys that were given a combination of SIV treatment and the specialized antibody several weeks after the onset of SIV infection subsequently developed very low levels of SIV in their blood and very few SIV-infected cells. Furthermore, this outcome continued after scientists withdrew SIV treatment from the monkeys. Also, once treatment was completed, the monkeys' immune systems appeared to be largely undamaged by this infection, as they had normal levels of CD4+ cells.

This result was unusual and unexpected. To be clear, the monkeys were not cured of SIV. However, taken as a whole, this experiment raises the possibility that a clinical trial in HIV-positive people might have a similar result. Using an antibody—vedolizumab (Entyvio)—that is approved for use in people with inflammatory intestinal conditions, researchers in

the U.S. have launched such a trial in HIV-positive people. Before we discuss the details about the experiment with monkeys mentioned above, we first provide some information about the immune system and its interaction with HIV.

Scattered

The immune system is largely distributed in cells and small pockets of tissue throughout most of the body. There are major organs that are part of the immune system—including the bone marrow, the spleen and the thymus gland. However, a large part of the immune system is in the many lymph nodes and lymphatic tissues that are around the gastrointestinal tract. As a result, most (98%) of the key cells of the immune system—CD4+ cells—are also found in these lymph nodes and lymphatic tissues. Only about 2% of the body's CD4+ cells are in the blood. Therefore, research that focuses on what is happening in the lymphatic tissues and lymph nodes is important.

The first few weeks of HIV

After entering the body, HIV encounters cells of the immune system. These cells capture HIV and take it to lymph nodes and lymphatic tissues scattered around the gastrointestinal tract. Cells of the immune system are drawn to the lymphatic tissues and lymph nodes in the GI tract because of specialized receptors. Once in these pockets of the immune system, the cells that have captured HIV help educate other cells of the immune system about this invading virus so that they can also attack it. Unfortunately, through mechanisms not fully understood, HIV quickly subverts the immune system's defences and infects many more cells. These infected cells release chemical signals that further weaken the immune system and the virus spreads throughout the body.

Blocking the homing receptors

Some researchers think that by interfering with the receptors used by cells to hone in on the gut lymphoid tissue it may be possible to greatly reduce the spread of HIV within the body and, therefore, reduce the injury to the immune system. Researchers in the U.S., Canada and Western Europe have been studying ways to interfere with a specific receptor found on T-cells and other cells of the immune system. The technical name for this receptor is called $alpha_4beta_7$, but we will shorten it to a4b7.

About a4b7

Cells of the immune system, particularly CD4+ cells, use a4b7 to help them migrate to pockets of the immune system that are distributed around the gut. Some research also suggests that SIV (and HIV) can use this receptor to assist the virus in infecting cells. By interfering with a4b7—using antibodies and small molecules—some researchers think that it may be possible to protect the majority of the body's CD4+ cells from HIV. However, before embarking on clinical trials with this antibody in HIV-positive people, experiments in SIV-infected monkeys were first necessary.

Previous research in the U.S. has led to the development of an antibody that can be safely used in SIV-infected monkeys. This antibody binds to a4b7, blocking access to it by cells and SIV. Recent experiments have found that when given prior to or during SIV infection, antibodies to a4b7 are able to protect some monkeys from developing SIV infection. In those monkeys that did develop SIV infection and also received infusions of the antibody, levels of CD4+ cells were near normal and the number of SIV-infected cells was very low. These results motivated researchers to perform a study in SIV-infected monkeys using SIV treatment combined with the antibody against a4b7.

Study details

Key points from the latest experiment with monkeys are as follows:

- Researchers infected 18 monkeys with SIV.
- Five weeks later all monkeys received anti-SIV treatment for 90 consecutive days, then researchers stopped administering this treatment.
- At the ninth week after infection, 11 monkeys started to receive infusions of antibodies every three weeks that blocked a4b7. There were eight infusions in total.
- Seven other monkeys received infusions of an antibody without any specific activity (it did not bind to SIV or a4b7). These seven monkeys were used as a comparison group.
- The study lasted for 81 weeks.

- As SIV and HIV are closely related, the drugs used to treat SIV infection are the same drugs that are used for the treatment of HIV.
- Three of the 11 monkeys that received the a4b7 antibody developed antibodies of their own that attacked the a4b7 antibody (in other words, an anti-antibody). These three monkeys were withdrawn from the study and subsequent data analysis, leaving eight monkeys who received a4b7 whose data could be analysed.

Results—Treatment cessation and viral load

The viral loads of the eight monkeys were initially high—about 3 million copies/mL. However, after three consecutive weeks of therapy, their viral loads fell below the level of detection.

Researchers were somewhat surprised by the results they obtained after they stopped administering SIV treatment.

Among the eight monkeys that received the a4b7 antibody there were different responses, as follows:

- two of the monkeys were able to maintain a suppressed viral load after researchers stopped giving them SIV treatment
- six of the monkeys had their viral load become detectable, but after four weeks without any further intervention it again became undetectable and stayed that way to the end of the study, even though the last infusion of the a4b7 antibody occurred at the 32nd week.

In contrast, monkeys that were not given the a4b7 antibody had their viral loads surge to about 1 million copies/mL and remain high for the duration of the experiment.

Results—Infected cells

After the cessation of SIV treatment in monkeys that were given a4b7 antibodies, the level of SIV-infected cells became undetectable. This suggests that the antibody had a major impact on SIV's ability to infect cells. In contrast, among monkeys given the non-specific antibody, the level of SIV-infected cells remained high.

Results—Focus on CD4+ cells

During the early stage of untreated SIV infection, levels of CD4+ cells in the blood declined. Subsequently, only monkeys that received the a4b7 antibody had significant increases in their CD4+ cell counts. Furthermore, after cessation of a4b7 antibody infusions, CD4+ cell counts remained elevated, approaching normal levels.

Analysis of the lymphatic tissue around the gut of the monkeys also showed high levels of CD4+ cells only in those that had received the a4b7 antibodies. The researchers think that the antibody may have protected CD4+ cells in the gut and elsewhere from SIV infection.

The role of natural killer cells

An important group of the immune system's cells is called natural killer (NK) cells. These cells can destroy virus-infected cells and tumours. Researchers found that levels of NK cells were initially similar in both groups of monkeys. However, levels of NK cells increased only in monkeys given a4b7 antibodies. Researchers think that this increased level of NK cells may have helped the monkeys control SIV levels.

Inflammation

Viruses such as HIV and SIV cause a significant increase in the general level of inflammation and injury to many different organ-systems in the body. Elevated inflammation was found in all monkeys in the study, at least initially. However, inflammation decreased only in monkeys given a4b7 antibodies.

Vitamin A

The active form of vitamin A in the body is called retinoic acid. At the start of the study, during early SIV infection, researchers found that all monkeys had lower-than-normal levels of retinoic acid. However, in monkeys subsequently exposed to a4b7 antibodies, levels of retinoic acid rose to near-normal levels. Researchers are not sure exactly what role, if any, retinoic acid might have played in the overall study results because retinoic acid levels went down as a result of SIV infection and only rose because of infusion of the a4b7 antibody. It may be that the elevated levels of vitamin A are a consequence, and not a cause, of the effect of the a4b7 antibodies. Other experiments have found that

different levels of vitamin A are found in different species of monkeys whose cells express a4b7, further confounding any clear conclusions about the role vitamin A might have played in this experiment.

Antibodies to SIV

Analysis of blood samples from the monkeys suggested that only those animals given the a4b7 antibodies subsequently developed antibodies that specifically attacked SIV. It is plausible that these antibodies may have played a role in helping the immune systems of the monkeys control SIV.

Bear in mind

The latest experiment with monkeys treated with a4b7 antibodies yielded unexpected and promising results. They need to be reproduced by at least another team of researchers.

An antibody designed for human use, vedolizumab (Entyvio), also binds to the a4b7 receptor of CD4+ cells in people. This antibody is licensed for the treatment of certain inflammatory conditions of the intestine—Crohn's disease and ulcerative colitis. The monkey researchers think that vedolizumab might have beneficial effects in humans with HIV.

Human study underway

The U.S. National Institutes of Health (NIH) has launched a clinical trial of vedolizumab in HIV-positive people who are taking potent combination anti-HIV therapy (ART), have more than 450 CD4+ cells/mm^3 and are otherwise healthy. As with the monkey study described earlier, eventually participants in the NIH trial will take a supervised treatment interruption to assess the effect of the antibody on the immune system. Researchers are uncertain of the outcome of this study in people for at least the following reasons:

- Though they have theories, they are not sure precisely why the a4b7 antibody had the beneficial effects that it did on monkeys with SIV.
- In the monkey study the animals were treated five weeks *after* they had been infected with SIV. Most people with HIV do not know exactly when they were infected so the NIH has recruited people with chronic HIV infection for the study.
- Most studies of a4b7 antibodies have been in monkeys with SIV. Some laboratory experiments with a4b7 antibodies and cells conducted by other researchers suggest that the antibodies did not protect cells from HIV infection.

Despite these caveats, the NIH trial is very important and exciting, as it holds much potential and is studying a drug that has already been approved for human use (for other conditions).

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C. Safety issues with vedolizumab

As mentioned previously in this issue of *TreatmentUpdate*, an important study in monkeys has inspired an American clinical trial in people with HIV with the drug vedolizumab. This is an antibody designed for use in people. Vedolizumab, sold as Entyvio, is given intravenously for the treatment of inflammatory intestinal conditions (such as Crohn's disease). It is licensed for treating such conditions in Canada, the U.S. and the European Union. As vedolizumab will likely draw much interest for testing with HIV-positive people, it is useful to review the information that has been collected about its safety from well-designed studies.

Vedolizumab

The antibody works by binding, or attaching to, a receptor called a4b7 ($alpha_4beta_7$). This receptor helps CD4+ and other cells of the immune system zero in on the pockets of the immune system that are arrayed around the intestines. By blocking this receptor, vedolizumab stops cells of the immune system from migrating to the intestines and enhancing inflammation in people who have Crohn's (and related) diseases.

The studies

Researchers in Canada, Belgium, the Netherlands, Italy, UK and U.S. collaborated in a review of six clinical trials of vedolizumab. In some of these studies placebos were used. Their review focused on more than 2,800 participants who received the drug between May 2009 and June 2013. About 50% of participants received the drug for one year. However, a minority of participants took the drug for up to five years.

In general, the researchers found that vedolizumab was safe with a low rate of infections and complications occurring. We now summarize the different complications that occurred in the safety review.

Reactions to infusions

Vedolizumab has to be given intravenously. Less than 6% of participants developed adverse effects related to infusion of vedolizumab. The most common of these adverse effects were nausea (14 people) and headache (10 people). These were generally of mild-to-moderate intensity.

Infections

According to the researchers, "We did not observe an overall increase in the risk of infection or serious infection with vedolizumab exposure...." Risk factors for infections appeared to include the use of other drugs such as corticosteroids (which can weaken the immune system) and prescribed narcotics.

Most infections affected the upper lungs, throat or sinuses. These infections, which were described by the researchers as "mild to moderate in severity," responded to standard therapy. Less than 1% of participants who developed these infections discontinued vedolizumab. Furthermore, these types of infections were more common among people who received placebo. Researchers are not certain why this was the case but they proposed that people who received placebo may have "had more active disease and a greater propensity for intestinal infections, which could confound the reported incidence rates." They noted that vedolizumab users had a relatively low rate of infections, which was also noted by other researchers who have collected data about the safety of this drug.

There were 15 cases of bacterial intestinal infections (caused by Clostridia), all of which occurred in vedolizumab users.

Unlike some other intravenous treatments for inflammatory conditions, none of the following serious infections occurred in participants who received vedolizumab:

- disseminated TB (tuberculosis)
- systemic yeast infections
- disseminated shingles (herpes zoster)
- CMV (cytomegalovirus) infection outside of the digestive tract
- PCP (Pneumocystis pneumonia)
- PML (progressive multifocal leukoencephalopathy)

Cancers

During placebo-controlled studies, the distribution of cancer cases that occurred were as follows:

- vedolizumab – five participants
- placebo – one participant

After the placebo-controlled phase of the studies, all participants were offered vedolizumab (this subsequent phase is called "open-label," where participants are aware of the drug that they are getting). During the open-label phase, an additional 13 participants were diagnosed with cancer.

Thus, a total of 19 people in the studies developed cancer. Since there were 2,830 people whose data were used for the safety analysis, these 19 people who got cancer accounted for 0.67% of participants.

Understanding the risk of cancer

When reading the cancer analysis, it is important to bear in mind that tumours do not suddenly appear overnight but can sometimes take months or years to develop until their presence is detected. All the people who developed cancer in the vedolizumab studies had one or more risk factors for cancer, as follows:

- all but one person who developed cancer had previously been exposed to drugs that weakened their immune system. These drugs are often useful for managing serious inflammatory conditions but also increase a person's risk for cancer.
- nearly half of the people who developed cancer had a history of smoking
- some participants had a history of cancer prior to receiving vedolizumab

There was no link between the use of vedolizumab and the development of cancer or any link between the number of doses of vedolizumab used and cancer risk.

Of the 19 cases of cancer, most (12) were resolved with treatment. However, in four people cancer was not in remission and three people died from complications due to cancer.

Deaths from causes other than cancer

There were 13 deaths due to complications from severe bacterial infections. Concerning these, the researchers stated:

> "All…had worsening of underlying disease, significant co-morbidities and complicated hospital courses that included surgeries in two cases, all of which confounded the assessment of relationship to the study drug."

Two people who were being treated for depression died because of suicide.

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II MENTAL HEALTH, SUBSTANCE USE AND HIV

A. Getting to 90-90-90 requires attention to mental health

The Joint United Nations Programme on HIV and AIDS (UNAIDS) has established goals for countries trying to achieve progress in the prevention, care

and treatment of HIV infection. Countries and regions are encouraged to strive to meet these goals by the year 2020. The goals can be summarized in the phrase *90-90-90*, which stands for the following:

- 90% of all people living with HIV will know their HIV status
- 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy (ART)
- 90% of all people receiving ART will have viral suppression (their viral load will be undetectable)

These are laudable and important goals. To enable them, opportunities for the offer of confidential HIV testing must be made more widely available. In cases of positive test results, after counselling patients, healthcare workers must swiftly refer them to care, where they can receive an offer of treatment. By starting treatment and taking it every day exactly as prescribed and directed—getting viral load to an undetectable level and keeping it there—clinical trials have found that ART users do not transmit HIV to their sexual partners and the overall health of their immune system improves.

However, to achieve and maintain an undetectable viral load in the blood requires a high degree of adherence—the ability to take ART every day exactly as prescribed and directed.

One barrier to achieving and maintaining an undetectable viral load is the ability to take ART exactly as prescribed and directed every day. For most people starting ART in high-income countries, there are entire treatments available in one or just a few pills taken once daily, which can overcome some barriers to adherence. However, not everyone can easily take ART every day exactly as prescribed and directed.

Mental health issues become important

People living with HIV can undergo stressful periods in their life. Much of this stress has its origins in other people's negative attitudes and behaviour, which can result in stigma and discrimination. This can cause HIV-positive people to become socially isolated and oftentimes fearful of disclosing their health status. Some HIV-positive people who survived the early years of the epidemic have lost many friends and loved ones to AIDS. All of these factors can have an impact on a person's psyche.

Although ART can significantly reduce the amount of HIV in the blood, it cannot penetrate all parts of the body—particularly lymph nodes, lymphatic tissues and the brain—in high concentrations. As a result, even in ART users, HIV continues to infect cells in the body on a small scale. What's more, some of these infected cells travel to and reside in the brain. There, infected cells release chemical signals and HIV proteins that cause inflammation and have an unfavourable effect on brain cells, causing them to malfunction and in some cases die. Prolonged elevated levels of inflammation could, in theory, have a negative effect on brain health by increasing some people's susceptibility to poor mental health.

Once HIV-positive people are in care, unless mental health issues are regularly screened for and detected—and, when present, treatment is offered and taken—such conditions can reduce quality of life and interfere with one's ability to take ART and maintain an undetectable viral load. Ultimately, this can affect a person's survival.

Studies have found that mental health conditions, including depression and problematic substance use, can, in some cases, increase the risk for non-adherence to ART (and other medicines). As more people take ART in an effort to reach the goals of 90-90-90, more effort will need to be paid to factors that interfere with adherence to sustain the third 90.

In this issue of *TreatmentUpdate*, we present information from studies that underscore the importance of screening for mental health and related issues in the lives of HIV-positive people.

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B. Eliciting accurate responses about substance use

Achieving and maintaining an undetectable viral load requires a high degree of adherence to potent combination anti-HIV therapy (ART). For some people this may be relatively easy. However, for other people, for a variety of reasons, adherence to ART and other medicines may be difficult. This problem can arise because of competing priorities, including issues such as undiagnosed depression and problematic substance use. This latter issue carries societal disapproval, so some people may find it difficult to disclose substance use to their doctor, nurse or pharmacist. Substances can directly or indirectly affect a person's mood and emotional state, and problematic substance use can affect adherence and ultimately a person's health. Researchers are finding that problematic substance use is linked to poorer health and reduced survival among HIV-positive people.

Researchers in four U.S. cities—Baltimore, Detroit, New York and Portland—conducted a study to help understand interactions between healthcare providers and their HIV-positive patients. In particular, the researchers sought to assess the types of questions used by healthcare providers. They found that when healthcare providers formulated questions in a manner that did not convey judgment or even subtle bias, accurate disclosure of substance use occurred. We reproduce their categories of questions later in this report.

Study details

Researchers sought and received written consent to record the conversations between healthcare practitioners and their patients. After a patient's appointment with a practitioner, researchers also interviewed the patient and asked them detailed questions about substance use.

Upon entering the study, the average profile of participants (healthcare providers and patients) was as follows:

56 healthcare providers
- age – 44 years
- 46% men, 54% women
- professions: physician – 65%; nurse practitioner – 20%; physician assistant – 15%

162 patients
- age – 47 years
- 58% men, 42% women
- substances used included the following: alcohol only – 33%; cocaine only – 35%; heroin only – 6%; more than one substance – 25%

Results

According to the researchers, healthcare providers were aware of 52% of instances of substance use at the end of their patients' visit. Conversely, the researchers stated that healthcare practitioners "remained apparently unaware of [48%] of instances of substance use."

More than one substance

Although there were 41 patients who disclosed the use of more than one substance to the research team, the researchers found that healthcare providers were able to "fully elicit disclosures of all substance use in only 29% of encounters" with patients who used more than one substance. In these 29% of encounters, the researchers stated that "disclosure of cocaine tended to be higher than that of alcohol or heroin."

Types of questions

Researchers identified four categories of questions, which they described in the following way:

Open-ended
"These were questions that invited the patient to be elaborate in their response and cannot be answered with just one word."

Normalizing
These were questions that asked specifically about the last time a patient used drugs or alcohol.

Closed-ended
These were "positively framed" questions that named a substance of interest or more generally referred to a substance using specific names.

Leading toward non-use
These questions were "negatively framed" with phrases such as "not using" or "staying clean."

Eliciting accurate disclosure

The researchers found that open-ended and normalizing questions resulted in accurate disclosure of substance use in *all* cases.

Furthermore, the researchers stated that "problematic substance use is a sensitive topic with significant surrounding stigma. Open-ended questions may create a sense of less judgment and greater comfort for the patient, reducing response bias."

The researchers said that asking about the "last time" a patient used a substance "normalizes substance use and thus may lower the barrier for disclosure." They added that framing a question in this way "may prompt more accurate recall by giving a specific reference point, increasing disclosure rates."

Not getting the right information

In contrast to the previous types of questioning, the researchers found that asking "leading questions," such as those that enquire whether the patient is "staying clean" or "not using," makes the questions acquire a subtle but threatening nature and makes substance use "seem less acceptable." Such questions only serve to underscore the stigma attached to substance use and may undermine disclosure "for fear of blame or judgment."

More than one substance

Based on their findings, the researchers encouraged healthcare practitioners to "ask about other substances when one is disclosed."

Getting to ask

The researchers found that nearly half of healthcare providers did not ask their patients about substance use. To remedy this situation, they encouraged the following course of action:

> "It may be worth considering implementation of a universal screening program to increase patient disclosure rates. For example, using [written or tablet-enabled] surveys in the waiting room may lead to greater disclosure without relying on providers to ask about substance use during the clinical encounter."

Bear in mind

Note that the present study was observational in nature. Therefore, there may be factors that were not measured or accounted for by the researchers that could have inadvertently biased their conclusions. For instance, according to the researchers, some patients and care providers have a "more functional" relationship that affected the

type of question used. Also, the researchers stated that their study was too small to draw meaningful (that is, statistical) relationships around questions asked and about the race, gender or other attributes of the healthcare providers and their patients.

Resources

Substance use, mental health and survival
Addiction and survival with HIV – *CATIE News*

Swiss researchers investigate drug use and its impact on health and survival – *CATIE News*

Canadian study links cocaine to kidney injury and dysfunction in some users – *CATIE News*

Study finds sustained-release dexamfetamine is promising for reducing cocaine use – *CATIE News*

What reduces survival 10 years after starting ART in North America and Europe? – *TreatmentUpdate* 217

Pre-fix: A guide for people with Hep C or HIV who inject drugs

Profile: Back from the Brink – *The Positive Side* (Fall 2016)

Ask the Experts: Addictions – *The Positive Side* (Fall 2016)

HIV and emotional wellness

Hepatitis C
CATIE's hepatitis C information

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C. Large study finds mental health issues common among HIV-positive people

Researchers in Sweden accessed a database containing medical information collected from about 3,500 HIV-positive people and, for comparison, medical information from about 2.1 million HIV-negative people, all living in the greater Stockholm region. The researchers sought to compare rates of mental health issues in both populations. For their analysis, the researchers focused on diagnoses that had been made and placed in participants' medical records between 2007 and 2014.

The researchers found that HIV-positive people were significantly more likely to be diagnosed with one of several mental health conditions. The Swedish study's findings are similar to studies done in other countries. In high-income countries in the current era, poor mental health is linked to reduced quality of life and survival among HIV-positive people. The Swedish study underscores the need to screen HIV-positive people for mental health issues and offer treatment.

A shifting focus

Today, the widespread availability of potent combination anti-HIV therapy (ART) in high-income countries has meant that compared to the 1980s or early 1990s AIDS-related infections and deaths are generally much less common.

Furthermore, a young adult who is infected today, and who is diagnosed and initiates ART shortly thereafter, and who takes ART every day exactly as prescribed and directed, and who achieves and maintains an undetectable viral load, and who does not have other pre-existing health issues is expected to live into his or her senior years. As a result, researchers are paying more attention to the factors that impede a person's ability to live longer despite the use of ART.

Study details

Researchers compared mental health diagnoses between 3,582 HIV-positive people (2,448 men and 1,134 women) and approximately 2.1 million HIV-negative people living in the greater Stockholm region.

The specific mental health conditions reviewed were as follows:

- anxiety and related conditions
- bipolar illness
- depression
- post-traumatic stress disorder and related conditions
- psychosis
- substance dependency

The research team also acquired socio-economic data on participants and did analyses by neighbourhood.

Results

In general, the researchers found that mental health conditions "were more common among individuals with [HIV]" compared to people without HIV. However, an exception was anxiety (and related conditions), which were not more common among HIV-positive women compared to HIV-negative women.

Solutions

The Swedish team reminds doctors and nurses of the need to screen their patients for mental health issues, including problematic substance use, and, if a mental health issue is diagnosed, to offer treatment. They also stated that it might be necessary for some physicians to collaborate with other healthcare providers—counsellors, psychologists, psychiatrists, pharmacists—when looking after patients with mental health conditions and HIV.

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D. Detectable viral loads linked to smoking and mental health issues

Surveys have found that rates of tobacco smoking among HIV-positive people are generally greater than among HIV-negative people. So it is important to understand smoking and related behaviours in order to design successful smoking-cessation programs for HIV-positive people.

Researchers at several clinics in the U.S. collaborated in a study to investigate smoking and its possible relation to other health issues among nearly 3,000 HIV-positive people. Participants completed surveys on computers or electronic tablets. Researchers found that some smokers were more likely to have a "moderate-to-severe" degree of depression and engage in the use of street drugs and were less likely to have an undetectable viral load.

Study details

Researchers recruited 2,952 HIV-positive people from clinics in the following cities:

- Birmingham, Alabama
- Boston, Massachusetts
- San Diego, California
- Seattle, Washington

Participants completed surveys about tobacco use and other behaviours between 2005 and 2009. Furthermore, researchers asked participants about anxiety, depression, substance use and their ability to take ART every day exactly as prescribed and directed. Researchers also accessed data from the medical records of participants.

The average profile of participants upon entering the study was as follows:

- age – 43 years
- 84% men, 16% women

- main ethno-racial groups: white – 64%; black – 32%
- 77% of participants were taking ART
- CD4+ count – 472 cells/mm^3
- 44% of ART users disclosed problems with adherence
- 51% of ART users had a viral load less than 50 copies/mL
- 41% of participants currently smoked tobacco
- 42% of smokers had been smoking for more than 20 years

Results—Viral load

As a group, smokers who used ART were less likely (60%) to have a suppressed viral load compared with former smokers (69%) and people who never smoked (65%).

Smoking and its association with mental health

Researchers found the following associations:

Depression
Smokers were more likely to have intense symptoms of depression compared to former smokers and people who never smoked but who also had depression.

Anxiety
Smokers were more likely to have symptoms of anxiety compared to former smokers and people who never smoked.

Substance use
Smokers were more likely to disclose that they were currently using street drugs compared to former smokers and people who never smoked.

Bear in mind

The present study found a high rate of smoking among HIV-positive people, which is similar to other studies of smoking in HIV-positive people.

Researchers found that in their study smoking is associated with "other addictive and psychological symptoms, and demonstrates the negative impact that smoking has on HIV-infected individuals, particularly the influence on detectable viral load."

Many other studies have found associations between smoking and reduced adherence to ART. This does not mean that smoking itself causes non-adherence. Rather, smoking can be thought of as a red flag indicating underlying and likely unaddressed or poorly managed mental health issues that can destabilize a person's ability to adhere to ART and achieve and maintain an undetectable viral load. Studies of smoking in HIV-negative people have found that smoking is relatively common among people with mental health issues, so it should come as no surprise that smoking is also associated with similar issues among some HIV-positive people.

For the future

The findings from the present study underscore the need to design and conduct more studies that address mental health issues as part of smoking cessation programs for HIV-positive people. Treating the underlying drivers of substance use can help people experience better quality of life and put them on the path to better health and adherence, therefore maximizing the benefits of ART. Helping HIV-positive people break free from tobacco can improve their quality of life and reduce their risk for cancers, heart attack, stroke, lung problems and other conditions, and therefore likely prolong their lifespan.

Resources

Smoking, addiction and breaking free

- How to Say "I Quit"—and Mean It – *The Positive Side*
- Smoking and tobacco – Canadian Cancer Society
- How to Quit Smoking – The Lung Association
- Understanding tobacco addiction – *CATIE News*
- Varenicline—An Ontario study assesses safety in HIV-positive people – *CATIE News*
- Smoking cessation: Innovative group therapy–centered support found to double quit rate – *CATIE News*
- Danish study underscores link between heart attacks and smoking – *CATIE News*

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Disclaimer

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

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Writer **Sean Hosein**
Editor **RonniLyn Pustil**

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For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

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A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

The Positive Side **magazine**
Holistic health information and views written by and for people living with HIV.

Fact Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

Contact CATIE

By e-mail:	info@catie.ca
On the Web:	www.catie.ca
By telephone:	416.203.7122 1.800.263.1638 (toll-free)
By fax:	416.203.8284
By social media:	www.facebook.com/CATIEInfo; www.twitter.com/CATIEInfo
By post:	505-555 Richmond Street W Box 1104 Toronto, Ontario M5V 3B1 Canada