TreatmentUpdate 210

Vol. 27, No. 5
August/
September 2015

Available online at
www.catie.ca/en/treatmentupdate

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I ANTI-HIV THERAPY

A. An outbreak evolves—changes to an epidemic and to treatment

An important note

In this issue of *TreatmentUpdate* we describe and detail important changes that have shifted scientific understanding about the effect of HIV on the immune system, and the need for early treatment of HIV. We also explore some issues related to undiagnosed HIV infection and why some people may be reluctant to initiate therapy for HIV.

To help readers better understand the origin of the emotional legacy that can stick to HIV to this day, it is necessary to revisit the early years of the HIV pandemic. Some of the issues that we mention may be disturbing for some readers, particularly for those who have lived through those early years. However, by unpacking the issues of that era, we show later how these issues can continue to affect decisions about testing and initiation of treatment for some people in the current era.

Looking back in time

In the 1960s and mid-to-late 1970s, doctors in North America, Western Europe and Central Africa began to see rare cases of severe and worsening immune deficiency in previously healthy, generally young adults. As such cases were rare in that era and did not seem to be connected, doctors were deeply puzzled and made no progress in finding the cause of the unexplained syndrome that bedeviled their patients.

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Searching backwards

Commenting on the probable origins of HIV in the early 1980s, Professor Ib Bygbjerg, MD, of the University of Copenhagen, who documented a case of AIDS that occurred in the late 1970s, stated: "Three acutely deadly viruses of central African origin have been discovered in recent years (Lassa, Marburg and Ebola)." Therefore, it is not surprising that another virus that caused serious illness would have originated there.

Over the next 35 years, by closely reexamining medical records on early cases and, when possible, testing stored blood and tissue samples for HIV antibodies and HIV itself, and analysing the genes carried by different strains of HIV, researchers were partially able to trace the early trajectory of this virus out of Africa.

But interest in finding the origins of AIDS likely would have been delayed had cases of AIDS and its precursor conditions not so suddenly and spectacularly begun to appear in simultaneous clusters among largely middle-class gay and bisexual young men in New York, Los Angeles, San Francisco and the cities of Western Europe in the early 1980s. At the same time, cases among heterosexual people were also occurring in Central Africa, though initially this was hardly noticed in the West

Researchers were subsequently able to find a virus that was closely related to HIV, called simian immunodeficiency virus (SIV) in many species of monkeys and apes in parts of sub-Saharan Africa. Exactly how and when people became infected with SIV and when this virus mutated into HIV remains unclear.

Such spillover of a virus from one species to another likely happened many times over thousands of years. So why didn't an AIDS epidemic occur in the past? Perhaps something was different in the early and mid-20th century. Some evidence suggests the possibility that large-scale reuse of syringes and needles as part of public health programs in the early and mid-20th century in colonial parts of central Africa may have played a role in igniting the AIDS epidemic. Add urbanization, social changes and faster transportation routes (including air travel)—HIV would have begun to spread outside of central Africa by the 1960s.

Studies into the origins of HIV, particularly the closely related virus SIV found in monkeys, are important. Understanding how some monkeys have developed the ability to resist SIV infection may one day yield clues for creating an effective HIV vaccine or assist efforts to find a cure for HIV.

The shock of the new

When the syndrome that would later be called AIDS first appeared in high-income countries in the early 1980s, news of its arrival was greeted with surprise, shock and fear.

Now, in the fourth decade of the HIV pandemic, it may be hard for some people to understand the emotions that arose very early in its history.

However, at the dawn of the pandemic there were many mysteries. The chief one being, why were apparently healthy young men suddenly succumbing to unusual life-threatening infections and rare cancers? Scientists did not know which germ caused the new syndrome, exactly how it spread or why it wreaked such havoc with the immune system. News media of the day carried stories not always based on firm evidence, fueling fear, panic and hysteria. The syndrome was also associated with generally despised and persecuted minorities—men who had sex with men and people with addictions who injected street drugs. Observers of the early years of AIDS noted that the news about the new syndrome was associated with two powerful emotional issues—sex and death. This affected how some people viewed the syndrome and the larger society's response to it.

To add to its mystery, once the arrival of AIDS was officially documented in gay men, additional cases began to appear in heterosexual people, babies and recipients of contaminated blood and blood products (such as hemophiliacs). However, despite this broadening of key populations, the syndrome would remain associated with gay men and drug users.

Views from an epidemic

In the early 1980s, psychologists in Los Angeles and San Francisco described what it was like to be at the centre of the emerging AIDS epidemic:

> "An unidentified disease mysteriously focuses on one group. This group, of which you are a member, is a minority. Your friends are becoming ill and are dying ugly and painful deaths. Even the ringing of the telephone is no longer a friendly sound: It may be bringing yet more painful news. You watch yourself daily for symptoms. People in the general population are becoming frightened of catching the disease from you. The government shows a curious lethargy in response to what has, within two years, become one of medical history's most enigmatic major epidemics. There is talk of quarantine. This disease has an incubation period that can be as long as three years, and large numbers of your group may have already contracted the dread disease without knowing it. Even the most healthy-looking people may be capable of transmitting the mysterious agent. Everyone is terrified."

Several years later, commenting in *The New York Times* on how society had responded to AIDS in 1986, H. Jack Geiger, MD, said:

> "…great and lethal epidemics are never merely biological events and never elicit merely biological or scientific responses. They become social forces in their own right, carving deep new fissures in the political and cultural landscape, thrusting up buried fears and hatreds."

Biomedical progress begins to occur

Due to perseverance and persistence, the cause of AIDS—a virus we now call HIV—was discovered in France in 1983, and the first test to help diagnose HIV infection was made commercially available in 1985. As the numbers of HIV-positive people rose quickly, along with documented deaths, pharmaceutical companies began to develop potential treatments.

Early forms of treatment

By today's standards, anti-HIV drugs that were tested in the mid-to-late 1980s had limited benefit, in some cases initially had to be given intravenously, and often caused serious side effects. However, by 1996, combinations of powerful anti-HIV agents became available in Canada and other high-income countries. At the time, these combinations were dubbed highly active antiretroviral therapy (HAART). They worked much better than the anti-HIV drugs that came before them, causing near-miraculous recoveries for some people with AIDS. Thanks to HAART, for the first time people with AIDS were able to resist and recover from formerly life-threatening infections, the lesions and tumours associated with a common AIDS-related cancer called Kaposi's sarcoma (KS) and even some other AIDS-related cancers.

Pills and side effects

HAART was not without issues. The regimens that became available in 1996 and for many years after were cumbersome. People sometimes had to take a handful of pills at least twice, if not three times daily. Some drugs had food and water requirements. Also, drugs in that era could cause a range of short- and long-term side effects, from regular bouts of nausea, vomiting and/or diarrhea to changes in a person's appearance. This latter issue was distressing for affected patients and caused researchers to engage in more study of side effects and to find safer medicines.

In 2015

Fast-forward to the present. Potent combination anti-HIV therapy is no longer called HAART but simply ART. More importantly, the combinations recommended for the initial treatment of HIV are much safer—and simpler—than many treatments that were used in the past. For example, regimens recommended for the initial therapy of HIV today by the U.S. Department of Health and Human Services have not been found to cause changes in body shape. And entire combinations are available in just one pill that needs only be taken, in many cases, once daily.

The power of ART is so profound that researchers in Canada, Australia, the U.S. and Western Europe predict that the life expectancy of some HIV-positive people will be near normal. They estimate

that a young adult who is infected today and diagnosed shortly thereafter, and who quickly begins ART and is able to take it exactly as directed every day, and who responds well to treatment, and who does not have other pre-existing health-related issues (serious co-infections, addictions and so on) should be able to live into their 70s or even 80s. This optimistic forecast is based on trends seen in tens of thousands of HIV-positive people who are being monitored in many high-income countries. It is a far cry from the fate of HIV-positive people upon diagnosis in the 1980s and early 1990s.

A prevention plus

ART's impact on HIV also has tremendous benefits for people who do not have this virus. By reducing the amount of HIV in the blood to very low levels, ART can allow HIV-positive mothers to give birth to healthy, uninfected babies. The effect of ART on HIV also significantly reduces the risk of HIV being spread through sex. This latter effect is encouraging policy planners to increase the availability of ART in some regions so that the spread of HIV can greatly be reduced.

The power of history, emotions and stigma

Despite all the good news summarized here, HIV and its treatment, to varying degrees, are still dogged by complex historical and deep emotional issues for some people. These issues may affect a person's ability to accept that they may be at risk for acquiring HIV and their willingness to get tested and may also underpin a reluctance to initiate ART.

The historical and emotional legacy that often sticks to HIV today can be so powerful and causes such distress that some people, dubbed "denialists" by psychologists, still seek to deny the existence of HIV. It is striking that other viruses and their associated diseases—polio, smallpox, measles, hepatitis B and C, rabies, SARS and the flu—have not drawn such a particularly heated emotional response.

The intersection of biomedical treatment and prevention

In the nearly 35 years since AIDS was first officially noticed, the cause of this syndrome, HIV, has spread around the world. It is not likely that there will be a highly effective vaccine in the next 10 years. So efforts to help slow the spread of HIV at the level of a city, region or country will likely focus on accelerating access to HIV testing to help uncover previously undiagnosed infections, followed by counselling and the swift offer of treatment. Furthermore, health systems will likely pay more attention to ART users to help ensure that they are able to take ART every day and achieve a low viral load. In some cities and regions, HIV pre-exposure prophylaxis (PrEP) may also become more available in the years ahead.

In this issue of *TreatmentUpdate*, we provide details about important changes to treatment arising from recent clinical trials. We also explore some issues related to care and treatment—such as the cascade of care, uncovering undiagnosed HIV and why some people may be reluctant to initiate ART.

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B. Study heralds an important shift in care and treatment

Historically, decisions about when to start potent anti-HIV combination therapy (commonly called ART) have centred on different CD4+ cell count levels (or thresholds) in the blood. These thresholds

were developed as doctors sought to balance the benefit of treatment with the risks of side effects. Finding such a balance was particularly important, as older combinations of anti-HIV drugs tended to have many side effects and involved taking several pills several times daily.

In 2015, the leading treatment guidelines in the U.S. greatly simplified choices for the initial treatment of HIV. These choices are fewer and clearer—the initial combination in a regimen should be based on a backbone of either an integrase inhibitor or the protease inhibitor darunavir (Prezista).

Integrase inhibitors are generally safe and well tolerated and can quickly reduce HIV levels in the blood when used as part of combination therapy. Darunavir-based therapy has been available for nearly 10 years in high-income countries and is potent and generally well tolerated.

About CD4+ cells

A key blood test for monitoring the overall health of the immune system is the CD4+ cell count. This is the number of CD4+ cells in a drop (or cubic mm) of blood. In general, in HIV infection, the greater the number of CD4+ cells, the better. In another report in this issue of *TreatmentUpdate*, we discuss other issues related to the CD4+ count, such as researchers interpreting new data about what the normal range should be.

A shifting threshold

As mentioned earlier, discussions about starting ART have usually centred on the CD4+ count. Historically, treatment was usually deferred until the CD4+ count fell and defects in the immune system caused by HIV infection resulted in a high risk for developing serious infections and cancers—the hallmark of AIDS.

However, over the past 15 years the recommended threshold for initiating ART has been climbing, from a low of 200 cells/mm^3 to 350 cells to 500 cells and, in the latest version of U.S. government guidelines, immediate therapy regardless of CD4+ count.

The U.S. guidelines are produced under the aegis of that government's federal health ministry, the Department of Health and Human Services (DHHS). Over the past several years, guidelines from the DHHS have been encouraging earlier initiation of ART. This shift was based on emerging research in two important areas:

- how HIV harms the immune system well before CD4+ counts fall significantly
- how ART can lower viral load in the blood below 50 or 40 copies/ml (depending on the test used) and, as a result, significantly reduce the risk of sexual transmission of HIV

Now, a detailed report from START, a large and well-designed clinical trial that ran for several years, provides robust evidence for starting ART soon after HIV diagnosis.

A summary of START

The results from START show that HIV-positive people who are not taking ART and whose CD4+ cell counts were greater than 500 cells/mm^3 (a threshold sometimes considered the lower end of the normal range) are at significantly increased risk for developing life-threatening infections, cancers and cardiovascular complications compared to other HIV-positive people with similar CD4+ counts who started ART relatively early in the course of HIV disease. Furthermore, serious side effects in START were rare, occurring in less than 1% of participants.

The START results are robust and mark a major achievement in medicine:

- They underscore the dangerous consequences of untreated HIV disease, even in people with relatively high CD4+ cell counts who had only been infected a relatively short time.
- They highlight the need for more research about how HIV harms the immune system.
- They confirm the power, effectiveness and safety of ART.

For the future

If the benefits flowing from START are to be realized, more opportunities for HIV testing need to be made available. Also, the healthcare system will require further integration so that people who test positive for HIV can be swiftly referred for care, counselling and an offer of treatment.

Of course, newly diagnosed patients will need support and education about the benefits of early ART and how HIV disease can be managed. As well, counselling from a nurse or pharmacist about adherence (the ability to take medicines as prescribed every day) as well as practising medication-taking (some doctors, nurses and pharmacists use small candies such as Smarties for this purpose) for a few weeks prior to starting ART may be necessary.

Furthermore, clinics and hospitals need to be vigilant to ensure that HIV-positive patients under their care are able to take ART every day as directed so that their viral load reaches low levels (commonly called "undetectable") as soon as possible and remains there.

The next report deals with detailed results from START.

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Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

C. Detailed results from the START study

Researchers in 35 countries across all continents collaborated to recruit 4,685 HIV-positive adults who were in good health for START. Upon entry to the study, all participants had CD4+ cell counts greater than 500 cells/mm^3. Researchers randomly assigned participants to receive one of the following interventions:

- to start potent combination anti-HIV therapy (ART) immediately
- to defer initiation of ART until the CD4+ count fell to 350 cells/mm^3 or until a serious illness developed

In this report we will refer to people in the first intervention as the immediate ART group and to people in the second intervention as the deferred ART group.

After an average time of three years in the study, researchers found that the following occurred among participants:

- immediate ART – 42 participants developed serious illness or died
- deferred ART – 96 participants developed serious illness or died

Clearly, the use of ART early in the course of HIV disease cuts the risk for developing serious AIDS-related illness by more than 50%.

Unexpectedly, nearly 70% of cases of AIDS and other serious outcomes that occurred in START participants did so in those who had more than 500 CD4+ cells/mm^3. In high-income countries most of these unfavourable outcomes were related to cancer or cardiovascular disease. These and other results from the study appear below.

Study details

The average profile of participants at the start of the study was as follows:

- age – 36 years
- 73% men, 27% women
- length of time HIV-positive – one year
- CD4+ count – 651 cells/mm^3
- viral load – 13,000 copies/ml
- current smoker – 32%
- major ethno-racial groups: white – 45%, black – 30%, Latino – 14%, Asian – 8%

Common routes of HIV infection were as follows:

- men who had sex with men – 55%
- heterosexual sex – 38%
- contaminated blood products – 5%
- injecting street drugs – 1%

Researchers assigned 2,326 participants to receive immediate ART and 2,359 to deferred ART.

Results—Serious illness

Later in this report we provide details about the major clinical events (main illnesses) that occurred during START, but for now we summarize the results.

The distribution of major clinical events was as follows:

- immediate ART – 42 participants
- deferred ART – 96 participants

These differences between the two groups were statistically significant; that is, not likely due to chance alone.

Researchers found that there were two major benefits for participants who received immediate therapy as follows:

- a 72% reduction in the relative risk of serious AIDS-related events
- a 39% reduction in the relative risk of serious non-AIDS-related events; this was mostly due to a reduction in cancers unrelated to AIDS

The following specific major categories of illness that occurred during the study were more likely to happen to participants who deferred therapy:

Serious AIDS-related events
- Immediate ART group – 14 cases
- Deferred ART group – 50 cases

Serious non-AIDS-related events
- Immediate ART group – 29 cases
- Deferred ART group – 47 cases

Death from any cause
- Immediate ART group – 12 cases
- Deferred ART group – 21 cases

Tuberculosis
- Immediate ART group – six cases
- Deferred ART group – 20 cases

Kaposi's sarcoma
- Immediate ART group – one case
- Deferred ART group – 11 cases

Lymphoma
- Immediate ART group – three cases
- Deferred ART group – 10 cases

Serious bacterial infections
- Immediate ART group – 14 cases
- Deferred ART group – 36 cases

Focus on cardiovascular disease

In this study, researchers defined cardiovascular disease as having one or more of the following:

- heart attack
- stroke
- interventions to widen or bypass clogged arteries; these blood vessels supply the heart with fresh oxygenated blood. These interventions generally take one of two forms: (1) A tiny tube is implanted within a blood vessel to keep it open. (2) Doctors can remove blood vessels from a person's legs and implant them in the chest to bypass clogged arteries and to supply the heart with freshly oxygenated blood. These procedures that require surgery are called coronary revascularization.

In START, cardiovascular disease was relatively common as a major event.

Focus on cancers

Common AIDS-related cancers that occurred in START were as follows:

- Kaposi's sarcoma (KS)
- lymphoma (Hodgkin's and non-Hodgkin's)

Cancers unrelated to AIDS that affected a broad range of organ-systems also occurred. However, none of these specific cancers was common.

AIDS-related events

Common AIDS-related events that occurred were as follows:

- TB
- KS
- lymphoma

Researchers found that there were differences in the distribution of AIDS-related events. For instance, most cases (62%) of TB occurred among people who lived in Africa. TB is relatively common in parts of this continent, so this distribution of TB in START should not be surprising.

In contrast, most cases of cancer (81%) and cardiovascular disease (73%) occurred in participants living in high-income countries.

KS is caused by a member of the herpes virus family called HHV-8 (human herpes virus-8). The growth of lymphomas can be triggered by infection with another member of the herpes virus family called EBV (Epstein-Barr virus). Both of these viruses are sexually transmitted and relatively common among men who have sex with men, particularly those living in high-income countries that participated in START. In general, these viruses do not normally cause serious problems unless a person's immune system is weakened, in this case by HIV.

About adverse events

The term *adverse event* applies to certain poor outcomes that can occur in a clinical trial, including potential side effects and so on. Some of these events may not be related to the medicines or procedures used in a study.

In START, a total of 16 suspected serious adverse events occurred in 16 people. All 16 suspected serious adverse events might have been related to the study medicines. After investigators assessed the 16 cases they found that, in general, the majority of them were not apparently related to the use of anti-HIV drugs.

For the sake of argument, let's say all 16 cases were somehow caused by exposure to anti-HIV medicines (highly unlikely). If we divide these 16 people by 3,421 (the total number of people who were taking ART), the result would be equivalent to less than half of one percent of participants. Therefore, it is safe to say that serious adverse events due to ART were rare in START. This should reassure both doctors and their patients.

There was no increased risk for serious adverse events in either study group (immediate or deferred ART).

An unexpected finding

Study researchers kept close track of participants' CD4+ cell counts, particularly when serious illness developed. An unexpected finding from START was that the majority of serious illness (both AIDS-related and not) occurred when CD4+ counts were relatively high—500 cells/mm^3 or greater.

With START, for the first time, high-quality data from a clinical trial have shown that HIV-positive people who have what was previously considered a relatively high CD4+ count (more than 500 cells) can and do develop serious illness.

Hospitalization and death

According to the START researchers, 12 people in the immediate ART group and 21 people in the deferred ART group died. This difference was not statistically significant.

The causes of death as supplied by the researchers are as follows:

Immediate ART – 12 deaths
- AIDS, ongoing active disease – one person
- cardiovascular disease – one person
- sudden death, cause unknown – two people
- cancer unrelated to AIDS – one person
- accident/violence – four people
- unknown – three people

Deferred ART – 21 deaths
- AIDS, ongoing active disease – four people
- cardiovascular disease – one person
- cancer unrelated to AIDS – one person
- chronic viral hepatitis – one person
- kidney failure – one person
- infection – one person
- type 2 diabetes – one person
- accident/violence – three people
- suicide – three people
- substance abuse – two people
- unknown – three people

A hole in the immune system

The findings from START reinforce the urgency of calls to begin ART shortly after HIV has been diagnosed. These findings also underscore the problem of using CD4+ count as a measure of overall health. For many years prior to START, researchers and doctors discouraged the initiation of ART when CD4+ counts were at or above the 500-cell mark. This practice arose because of at least two reasons, as follows:

1. Fifteen years ago, doctors lowered the CD4+ count threshold at which ART should be started to 200 cells/mm^3 because the anti-HIV treatments then in use could cause serious side effects.

2. The possibility that AIDS-related life-threatening infections and cancers could occur in people with CD4+ counts of 500 cells/mm^3 or greater seemed very unlikely.

That such complications can and did occur in START raises the following issue:

- CD4+ cell counts do not provide a highly accurate measure of the immune system's strength. Indeed, the START results underscore the serious injury sustained by the immune system early in the course of HIV disease. START co-chair Jens Lundgren, MD, of the University of Copenhagen, summed up the immunological injury caused by HIV by stating that the results of START underscore the fact that "there is a hole in the immune system" that occurs early in the course of HIV disease and is not readily apparent when CD4+ counts are used to assess health.

Points to consider

1. Study researchers stated that the results of START "provide policy makers, clinicians and HIV-positive patients with the data to inform policies regarding the initiation of [ART]."

2. A growing international scientific and medical consensus suggests that doctors, nurses and important agencies are going to recommend that immediate treatment be offered to people who test positive for HIV. The U.S. Department of Health and Human Services (DHHS) has treatment guidelines that recommend the initiation of therapy regardless of CD4+ count. The World Health Organization (WHO) will release guidelines that make a similar recommendation. Updated treatment guidelines in the U.K. will also feature similar advice, having taken into account the results of START.

3. Many clinical trials in HIV medicine have a relatively small proportion of women. START pushed back against this trend by having a significant proportion of women enrolled—nearly 27%. Therefore, the findings from START also apply to women.

4. The benefit of starting ART early in the course of HIV disease is clear: a large and significant reduction in the risk of serious infections and cancers. For instance, among people who initiated immediate ART, there was a 72% reduction in their risk for developing serious AIDS-related infections and cancers. Immediate initiation of ART also led to a reduced relative risk of 39% for developing cancers unrelated to AIDS. This led START researchers to state that immediate initiation of ART has "broad positive effects" on health.

5. According to the START team, "most of the AIDS-related and non-AIDS-related infections occurred when patients had a high CD4+ cell count." Furthermore, the researchers noted that "a substantial part of the beneficial effect of immediate treatment is due to changes induced by [ART] in [cells and/or proteins in the blood] other than CD4+ cells." This underscores that there is still much to learn about the immune system and that even people with more than 500 CD4+ cells/mm^3 are at risk for serious illness if they have not started ART.

   What's more, the researchers pointed out that even among people who took ART and whose viral load subsequently fell to less than 50 copies/ml, "the risk of AIDS was not zero." They also stated that this finding means that "damage to the immune system may occur early in the course of HIV infection." This provides a strong reason for starting ART as soon as possible after HIV infection has been diagnosed. It also underscores the need for scientists to study the immune system and find more accurate ways to assess its health.

6. In other studies, ART has been shown to reduce the amount of HIV in the blood and tremendously decrease the risk of transmitting HIV via sex. This finding from other studies is yet another compelling reason for HIV-positive people to consider starting ART as soon as possible after their diagnosis.

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D. Important steps between testing and treatment

As opportunities for HIV testing and access to treatment continue to become more available, it is important that all people involved in these efforts remember the following:

- HIV testing should always be *offered* and the many benefits of testing explained

Counselling is an important aspect of testing—it is a chance to reinforce safer-sex behaviours and to help newly diagnosed people deal with the stress of a positive test result. Some newly positive people may not be aware of the massive changes in HIV treatment that have occurred in the past 30 years and the power and safety of potent combination anti-HIV therapy (ART). As a result, they may have concerns and questions that need to be addressed with brief education.

Although the results from START (and other studies) clearly show that immediate treatment of HIV is ideal both for the positive person and for society, some people may need a reasonable period of time after their positive test result to grapple with this development and realize that they generally have a long future ahead of them. However, the final decision to initiate ART should always be left to the person with HIV.

The most comprehensive HIV treatment guidelines are those produced by the U.S. Department of Health and Human Services (DHHS). Taking into account the results of START, the panel that writes the guidelines has made the following statement:

> "The Panel continues to emphasize that patients starting ART should be willing and able to commit to treatment and to understand the benefits and risks of therapy and the importance of adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as is feasible."

Another clinical trial called Temprano, which took place in Côte d'Ivoire, Africa, also compared early versus late HIV treatment. The findings from Temprano support those of START. Readers should note that neither START nor Temprano enrolled adolescents. However, the panel stated, "our recommendations have been extrapolated to adolescents based on the expectation that they will derive benefits from early ART similar to those observed in adults."

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E. New ideas about CD4+ cell counts and when to start ART

The results of the START study have confirmed what some researchers have suspected for some time—the CD4+ cell count is an imperfect measure of the immune system's health. As a result of START, we expect scientists to engage in further work to find out more accurate ways of assessing the health of the immune system. To accompany that work, we present some findings from another study that raised issues about what constitutes a normal or acceptable CD4+ count and some of the immunological injury that can occur early in the course of HIV disease. This information appeared earlier this year in *CATIE News* and we have adapted it for presentation here.

Results from START and other research strongly suggest that starting potent combination anti-HIV therapy (ART) at the threshold of 500 cells/mm^3 is insufficient for normalizing the functioning of the immune system. An American study has shown that starting ART within 12 months of becoming HIV positive results in measureable and significant immunological benefits. This study also provides insight into the normal range for CD4+ cells that has implications for therapeutic goals in HIV treatment.

What is a normal CD4+ cell count?

A team of scientists in California and Texas has reviewed studies from Australia, North America and Western Europe in the current era and sought

to clarify the normal range for CD4+ cell counts among healthy HIV-negative people. To their surprise, researchers found that data from more than 16,000 people suggested that the normal range for CD4+ cells was between 700 and 1,100 cells/mm^3. In this range, 900 CD4+ cells/mm3 would be considered the mid-point or average CD4+ cell count. This figure of 900 cells/mm^3 is much greater than the figure of 500 cells/mm^3, which was the figure used in many treatment guidelines before the results of START were known. Furthermore, it appears that the figure of 500 CD4+ cells/mm^3 significantly underestimates what a normal CD4+ count should be.

Unmeasured immunological injury

Assessing CD4+ cell counts only captures some of the changes brought about by HIV infection. However, there are many complex and sometimes subtle changes to the immune system that historically have not received as much attention as the CD4+ cell count, including the following:

- excessive activation and inflammation of the immune system
- immunological exhaustion

These and other changes begin shortly after HIV infection and ultimately have an adverse effect on a person's health.

Timing

Here is another issue: Relying on CD4+ cell counts alone underestimates the injury caused to the immune system by HIV. New research suggests that delaying the initiation of ART until the CD4+ count falls to a level of 500 cells/mm^3 does not reverse immunological injury caused by HIV. In other words, starting ART shortly after HIV infection may be highly beneficial because waiting for the CD4+ count to fall allows HIV more time to injure the immune system. The U.S. researchers suggest that in part this problem arises because using the CD4+ cell count as an indicator of the overall health of the immune system is not a highly accurate way to assess the subtle injury caused by HIV. What also needs to be taken into account, they say, is the duration of HIV infection. Historically, the duration of HIV infection has not been factored into the decision-making process for deciding when to start ART.

A large study

To gain a better understanding of the impact of HIV infection and early or delayed initiation of ART, the researchers in California and Texas also analysed health-related information from the U.S. Military HIV Natural History Study (NHS). Participants in the NHS are from the U.S. military and include spouses and children. What is important to note about the NHS is that participants received regular and extensive assessments (checkups and blood tests). As a result, the estimated dates when they became HIV positive are relatively accurate.

Researchers used data captured from 1,119 HIV-positive participants in the NHS. Most of them were male (95%) and relatively young (31 years) and came from the major ethno-racial groups in the U.S.

Timing of therapy

In their analysis, researchers found that nearly 40% of NHS participants achieved a CD4+ count of about 900 cells/mm^3 when ART was initiated within 12 months of becoming HIV positive. In contrast, among participants who began ART 12 months or more after becoming HIV positive, only about 30% were able to achieve a CD4+ count within the normal range. This difference was statistically significant; that is, not likely due to chance alone.

Sophisticated tests revealed that the closer participants' counts rose to 900 cells/mm^3, the more their immune systems were like those of HIV-negative people—with very low levels of immune activation, inflammation and immunological dysfunction. Such participants also had improved responses to vaccination against hepatitis B virus compared to HIV-positive people whose CD4+ counts did not approach the 900-cell mark. However, it is important to note that the immune systems of early initiators of ART never became identical to those of HIV-negative people.

The researchers concluded that delaying the initiation of ART beyond 12 months of the estimated date of becoming HIV positive "diminishes the likelihood of restoring immunologic health in HIV-1-infected individuals."

Close but not there

There are likely several reasons that underlie the failure of ART to fully heal the immune system. Here are just a few:

- ART can reduce the production of HIV in the blood, however, sophisticated research has found that ART does not fully penetrate the lymph nodes and lymphatic tissues that are a major part of the immune system. As a result, HIV can infect cells within these tissues throughout the body and continue to produce new viruses and viral proteins that impair the immune system and perhaps other organ-systems.
- Members of the herpes virus family, including CMV (cytomegalovirus) and human herpes virus-8 (HHV-8), are likely sexually transmitted, particularly among men who have sex with men. These viruses can cause low-level infection in some HIV-positive people and scientists suspect that co-infection with CMV and/or HHV-8 may play a role in the excess inflammation seen in ART users.
- Some scientists suspect that HIV causes subtle changes to the immune system that are difficult to fully reverse.

Teams of researchers in North America and Western Europe are busy trying to find ways to safely reduce excess inflammation in ART users. Results of some research on HIV-related inflammation appear in *TreatmentUpdate 205* and additional reports will appear later on the CATIE website.

Implications of the U.S. study

According to the research team, its findings have "broad implications for the management of care for HIV-1-infected patients, as well as public policy," as follows:

Restoring the immune system

If a major goal of treatment is to restore the immune system, the researchers stated: "Our data indicate that normalization of CD4+ counts may be an important therapeutic target." This statement is supported by their findings that getting the CD4+ count to about 900 cells/mm^3 and keeping viral loads low greatly reduces the risk of subsequently developing AIDS and also reduces immunological dysfunction and activation and inflammation of the immune system.

More studies need to be done to find safe ways to further reduce the excess inflammation that persists in ART users and to help raise their CD4+ cell counts.

Normalizing CD4+ cell counts

The researchers found that participants had "the capacity for CD4+ cell normalization" if the following two conditions were met:

- the duration of untreated HIV infection is short (less than 12 months)
- the CD4+ count when ART is initiated is 500 cells/mm^3 or greater

In the U.S. study, researchers found that participants whose CD4+ counts were at least 500 cells/mm^3 when they initiated ART generally had large subsequent increases in cell counts. However, the advantage of starting ART with a high CD4+ count was, according to the researchers, "greatly diminished" if participants initiated ART more than 12 months after they became HIV positive.

The present study has uncovered what some scientists and doctors had long suspected: Untreated HIV infection can cause significant injury to the immune system in a relatively short span of time, long before CD4+ counts fall and AIDS symptoms appear.

Public policy—Reaping the benefits of early ART

Most people are not aware when they became infected with HIV. In large part this problem arises because the symptoms of initial HIV infection are generally similar to a cold or flu and in some cases can be very mild. However, if newly diagnosed people are to be in a position to take advantage of the benefits of early ART, sexually active adults need to have frequent access to barrier-free and confidential counselling and HIV testing. The U.S. researchers hope that such testing will uncover some previously unrecognized HIV infections so that "prompt initiation of ART after diagnosis occurs." According to the U.S. researchers, "such a strategy may offer the best chance for [quickly halting injury to the immune system that can otherwise occur because of untreated HIV infection]."

The researchers also stated that "an added advantage of earlier [initiation of] ART would be reductions in HIV transmission" because, in their experience,

early ART quickly reduces the amount of HIV in the blood.

People who test negative for HIV need to take steps to continue to stay that way. Such steps include the correct and consistent use of condoms and, in some cases, discussion with their doctor about the use of pre-exposure prophylaxis (PrEP).

Possible limitations

The analysis from the U.S. study is supported by the results of the START study, discussed earlier in this issue of *TreatmentUpdate*.

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F. Starting ART on the same day as an HIV diagnosis in British Columbia

It is likely that immediate HIV treatment will become the standard of care in high-income countries when this viral infection is diagnosed in the future. It is therefore important to assess programs that offer immediate HIV treatment in order to determine their effectiveness and the attitudes toward them by newly diagnosed people.

Before we delve into the main part of this report, we first provide some background information about acute or very early HIV infection.

About acute HIV infection

After HIV has invaded the ano-genital tract, it infects cells of the immune system that are present in that location. These infected cells produce many more copies of HIV and the cycle of infection continues as new cells are converted into mini-virus factories. Within days of entering the body, HIV-infected cells spread first to nearby lymph nodes and lymphatic tissues, and shortly after to many organ-systems, including the brain. During the period when the virus is spreading from the ano-genital tract and reaching other parts of the body, the immune system is overwhelmed—both by the scale of infection and the chemical signals released by HIV-infected cells that hamper its ability to control the virus.

It takes the immune system some time to reduce the amount of HIV that is being produced during acute infection. As a result, it may take a few weeks after initial exposure and infection before anti-HIV antibodies are detectable in the blood. To assess blood samples for the presence of HIV very early in acute infection, laboratories can use tests called NAATs (nucleic acid amplification tests) that can detect the genetic material of HIV in blood.

In British Columbia

Two clinics that screen for sexually transmitted infections (STIs) in Vancouver used NAATs to help identify people undergoing acute HIV infection. As mentioned earlier in this issue of *TreatmentUpdate*, offering immediate treatment for HIV infection has many benefits. Researchers in B.C. therefore decided to assess their program that offered immediate ART upon HIV diagnosis.

Study details

Researchers with the BC Centre for Disease Control (BCCDC) and the BC Centre for Excellence in HIV/AIDS in Vancouver assessed a program in which participants were offered two choices after an HIV diagnosis:

- counselling and referral to care (as has traditionally been the case)
- counselling and referral to rapid, same-day connection to an HIV specialist and, if needed, additional resources such as peer navigators, primary care doctors and social workers

The research team reviewed health-related information collected between January 2013 and October 2014 from two STI clinics in Vancouver. As part of this study, participants were also briefly interviewed.

Results

For comparison, in 2013, before the implementation of the rapid referral program for care and treatment, there was an average of 21 days before patients saw a doctor after a diagnosis of HIV was made.

In 2014, 19 people were diagnosed with acute HIV infection and 16 (84%) of them chose the rapid referral program. On average, these participants were linked to care within one day after an HIV diagnosis.

Also in 2014, 14 cases of chronic HIV infection were uncovered. These participants took an average of 14 days to connect with care and treatment.

Satisfaction and interest

According to the B.C. team, "the majority of [participants with acute HIV] expressed a high degree of satisfaction with immediate linkage to care and chose to initiate ART on the same day."

Doctors and nurses reported that patients had "strong" interest in immediate treatment of HIV. However, these clinicians were somewhat concerned that patients who immediately initiated ART might somehow not be able to sustain their ability to take ART every day, exactly as directed, over the long-term.

Room for expansion

Based on the promising results obtained so far, the BCCDC researchers have found additional issues related to the immediate initiation of ART that could be expanded, including the following:

- informing partners and sexual contacts that they may have recently been exposed to HIV and that testing would be a good idea for their health
- offering HIV post-exposure prophylaxis (PEP) to the sexual partners and contacts of people who have tested positive

The present analysis is based on a relatively small number of participants. However, it is an important and vital first step in assessing the impact of immediate initiation of ART. Other steps would include assessing adherence over the long-term.

Some readers may be surprised that the majority of newly diagnosed participants chose same-day initiation of ART. This will likely be the way that HIV will be treated in the years ahead, particularly since the release of the results of the START study.

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G. Uncovering HIV by looking for indicator conditions

In Canada and some other high-income countries, researchers estimate that a large proportion of HIV-positive people are not aware of their infection status. The Public Health Agency of Canada estimates this figure at 25%. Researchers from the Netherlands have made a similar estimate for their country.

This lack of awareness of one's HIV status poses at least two issues, as follows:

- People may not take steps to prevent the spread of HIV.
- The immune system degrades without treatment. This can result in the development of serious illness, including AIDS-related infections and cancers that can greatly weaken a person and in some cases lead to death.

Research with people who have been diagnosed late in the course of HIV disease has revealed that for several years prior to their HIV diagnosis there were opportunities for HIV testing that were missed. For instance, these people had visited doctors in family practice units, community clinics or the emergency department of hospitals. During such visits HIV testing was not discussed or offered.

If progress is to be made by uncovering undiagnosed HIV infection, opportunities for HIV testing need to be made more available.

Indicator conditions

In high-income countries, people generally seek care for non-life-threatening conditions from doctors and nurses who specialize in primary care or family medicine. During the early years of undiagnosed HIV infection people can develop conditions that are generally not life threatening but have become highly associated with underlying HIV infection. These conditions—infections and complications—are called indicator diseases or indicator conditions (a list of these appears later in this report).

In Amsterdam

Researchers in Amsterdam have been studying people whose HIV infection was once undiagnosed. This means that once this population tests positive, some researchers in that city have access to medical records and databases that have collected health-related information over several years. By doing so, researchers are able to examine the medical histories of people before they became aware that they had HIV. By looking at a person's medical history, researchers found that people who were diagnosed late in the course of HIV were much more likely to have an indicator condition than people who remained HIV negative in the same community over the same period.

The Dutch research has revealed that there are likely opportunities in primary care clinics where family doctors and nurses can help uncover HIV with the offer of HIV testing and counselling.

Study details

Researchers in Amsterdam extracted health-related information from medical databases in that city. They focused on adults and used data from 102 HIV-positive and 299 HIV-negative people (the latter group acted as a control or comparison group).

Indicator conditions sought by the researchers from medical records included the following:

General sexually transmitted infections
- Chlamydia
- gonorrhea
- syphilis
- hepatitis B
- genital herpes
- LGV (lymphogranuloma venereum)
- genital warts
- trichomoniasis (caused by a parasite)

Other infections or complications
- acute hepatitis A or C viral infection
- shingles
- severe or unusual forms of psoriasis
- seborrheic dermatitis
- abnormal growths on the cervix
- community-acquired pneumonia
- oral yeast infections
- nerve injury that can cause weakness, intermittent sensation, numbness, tingling
- symptoms of a mononucleosis-like illness (suggestive of a viral infection) that included at least two of the following symptoms—rash, fever, swollen lymph nodes; with or without muscle pain, sore throat and feeling unwell
- fever
- unintentional weight loss
- persistently swollen lymph nodes

Blood tests
- persistently decreased levels of white blood cells
- less-than-normal levels of platelets
- chronic kidney dysfunction or injury

Results—Visits to a family doctor

In the year prior to testing positive for HIV, the majority of people (62%) visited a family doctor an average of three times. Among people who tested HIV negative, 39% visited their family doctor on three occasions during the same period.

Furthermore, at such visits people who subsequently tested HIV positive were more likely to have lab tests done on their blood (39%) compared to HIV-negative people (19%).

Indicator conditions prior to an HIV diagnosis

Five years prior to an HIV diagnosis, researchers found that nearly 60% of people had been diagnosed with one or more indicator condition compared to only 7% of people who remained HIV negative.

During the five-year period, common indicator conditions that occurred in people included the following:

- syphilis
- Chlamydia
- pneumonia
- mononucleosis-like illness
- shingles

During the same period, common HIV-related symptoms that doctors recorded were as follows:

- unintentional weight loss
- persistently swollen lymph nodes

Taking many factors into account, the indicator conditions most strongly associated with a subsequent diagnosis of HIV were as follows:

- unintentional weight loss
- persistently swollen lymph nodes
- syphilis
- gonorrhea
- nerve injury

Key findings

One year prior to their HIV diagnosis, most patients with HIV in this study had seen a doctor. However, HIV testing was not discussed during that appointment.

Five years prior to their HIV diagnosis, more than half of the patients in this study had a condition suggestive of either underlying HIV infection or a high risk for HIV infection.

Bear in mind

Several years ago, Danish researchers conducted a much larger study with 2,000 people subsequently diagnosed with HIV and 35,000 people who did not have this infection. The Danish researchers made similar findings to the Dutch study. Furthermore, the Danes flagged the use of opioids and/or the diagnosis of addiction as conditions that should prompt doctors and nurses to offer HIV testing.

The results of both studies underscore the importance of making an offer of an HIV test to patients who are seeking care and who have indicator conditions.

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H. Beyond testing positive—issues with getting care and taking treatment

The following report previously appeared in *CATIE News*. We are putting it in this issue of *TreatmentUpdate* to underscore some of the issues related to care and treatment after HIV has been diagnosed.

Alberta—Reducing deaths by strengthening the HIV Treatment Cascade [http://www.catie.ca/en/catienews/2014-05-20/alberta-reducing-deaths-strengthening-hiv-treatment-cascade]

I. Why some HIV-positive people may be reluctant to start therapy

Researchers in Australia conducted a study to understand the reasons why some HIV-positive people have either not started potent combination anti-HIV therapy (commonly called ART) or did initiate therapy but later interrupted it and have not resumed taking it.

Note well

It is very important to bear in mind that these interviews took place before the results of START became available. As the news about START

diffuses over time, it is possible that more people may become accepting of the need to begin ART as early as possible. However, it is also possible that despite the results from START and other studies, a minority of newly diagnosed people may not wish, at least initially, to take ART. Therefore, it may be useful to consider the results of the Australian study below when treatment-reluctant patients are encountered. The Australian researchers also provide helpful approaches to engage with such patients.

Study details

Researchers recruited 27 participants (23 men, four women) by placing advertisements on the websites of community-based agencies. Interviews were conducted by telephone or in person between September 2012 and February 2014.

All participants were HIV positive. Ten people had never taken ART. Most of the remaining participants had taken ART for less than a year, such as during pregnancy or during post-exposure prophylaxis (PEP). Slightly more than half of the participants had a CD4+ count greater than 500 cells/mm^3.

Results

The researchers gathered the responses from participants and found several themes, which are reproduced here.

Why not take ART?

In some cases participants had not received what the researchers called "a strong recommendation" to initiate ART from their doctors.

Some participants reported that their doctors had encouraged them to consider taking ART. These participants reported that they were indeed considering it and continued to visit their doctor and had blood drawn for analysis. These participants and their doctors monitored CD4+ counts and HIV viral load and watched the trends in these measures over time.

A few participants disclosed that they had been diagnosed as "non-progressors"—rare cases where the immune system slowly degrades despite untreated HIV infection. These participants embraced the belief that somehow their immune systems would never degrade and that they would never have to use ART. Readers should note that some research suggests that so-called "non-progressors" do develop immunological injury arising from HIV infection. Thus, it is very likely that at some point in their future such people will have to initiate ART to avoid ill health and complications related to inflammation triggered by chronic HIV infection.

Doubts about medicine and science

According to the researchers, some participants expressed "a range of doubts and concerns [about] the science, politics and economics of HIV medicine." The researchers added that "these participants were explicitly critical of biomedicine, and viewed HIV management practices as unduly influenced by the pharmaceutical industry."

Despite disagreement and conflict with their doctors, participants who were critical of HIV treatment and related issues continued to visit their doctors for monitoring. These participants were all aware of their CD4+ cell counts and viral load.

Some of these participants also stated that they were interested in complementary and alternative approaches to ART. The researchers found that many participants who were distrustful of doctors and medicine viewed ART as "chemicals that were toxic."

Concerns about well-being

Some participants felt that their immune systems were functioning adequately without help [from ART]. Furthermore, as they did not have any apparent symptoms of HIV-related complications, these participants felt that they could defer the use of ART.

Holding on to a way of life

Several participants expressed concern around the following issues:

- their ability to attend clinic appointments
- being able to visit pharmacies to fill prescriptions
- adherence—the ability to take HIV medicines every day exactly as directed

The researchers stated that some participants, due to fears of being "locked into a strict routine of medicine-taking," also had issues about a possible

loss of autonomy. One participant expressed his concerns as follows:

> "I just feel a certain level of independence not having to take [ART]…I still am living and achieving and in control. And I feel as though I would become dependent on something to stay alive and battle the virus."

Fears of change and disclosure
Some participants were concerned about how ART might change the way they viewed themselves or how others viewed them. As one participant said:

> "I don't want treatment to define who I am. And I don't let the virus define me either."

Participants were concerned that initiating ART would increase the risk of others discovering their HIV status. These fears were expressed in regard to filling a prescription, carrying it on their person and storing medicines at home or during travel.

Engagement with treatment also represented what researchers called "a major psychological and emotional hurdle in coming to accept…living with HIV." According to the research team, participants who were concerned about this issue "expressed… avoiding any reminders of their HIV status at all."

Views on ART

Researchers found that participants' reasons for not taking ART could be grouped into the following themes:

Treatment acceptance
ART initiation was inevitable and they would begin treatment once their doctors recommended doing so. Participants who were recently diagnosed or who had never taken ART were likely to express this view.

According to researchers, "the framing of ART use as 'inevitable' was common across most of our interviews and speaks to a culture and context in which pharmaceutical treatment plays a central role in shaping the story of HIV diagnosis and care."

Treatment deferred
The research team stated that this view (of deferral) can be described as "a more explicitly recalcitrant version of treatment acceptance." Furthermore, researchers stated that "those participants accepted there were probably good reasons to start ART but expressed a strong desire to avoid that outcome as long as possible." Here's how one participant expressed this idea:

> "I was given a script [a prescription]…and it took me a good six weeks and push from my family to even get it filled. And those tablets are currently sitting under my bed in their boxes. And yeah, I've just been very hesitant to start taking them…I think that time will come, but for me it's obviously taking a very long time! I think everybody knows it's inevitable, know what I mean? It's going to happen, right? [But] it's like, 'No! Not until I'm absolutely half-dead and have to.'"

Treatment refusal
According to researchers, "many who took up this position [of refusing to take ART] held deep fears regarding the potential side effects of ART…some had witnessed the highs and lows of HIV medicine since early in the epidemic, and therefore found it hard to place their trust in HIV medicines."

Despite these feelings among some participants, researchers found that "almost all of these participants remained engaged with HIV clinical care, including some who had deliberately sought out new [doctors and/or nurses] willing to provide them with clinical services to monitor their HIV and manage symptomatic illness without the use of ART."

Treatment as a low priority
Participants in this group gave a variety of reasons for avoiding initiation of ART such as these:

- child-care responsibilities
- experiencing significant emotional and mental distress
- criminal proceedings

An ideal future

By interviewing participants, researchers gained insight into the issues participants felt needed to be addressed before ART could begin. The research team divided these issues into the following themes:

Treating sickness
In this category, people could foresee a time when they would become sufficiently ill and require treatment. Some people imagined a future

with significant "physical deterioration." As one participant stated, "I'd have to feel a lot worse."

Treating for others

In this category, participants felt that other people (partner, spouse, family member) would strongly encourage them to take ART so as to greatly reduce the possibility of the sexual spread of HIV and/or so that their health would improve.

An impossible ideal

On hearing some participants' wishes about the type of treatment they would prefer in the future, researchers described these views as "remarkably utopian." Researchers stated that some participants' demands about future treatment options were framed in way as to seem extremely unlikely to be realized. As one participant said about his willingness to take treatment in the future:

> "If they came up with a tablet that, one tablet that [did] the job of all the others, and made me feel good? [But] that's not likely to happen, so no."

Researchers found that that one of their participants who had low CD4+ counts, "considerable ill health, and significant conflict with care providers regarding the decision to refuse treatment," made the following statement about initiating ART:

> "I would need to be ill and it would need to be definitely linked to HIV and you [would have to] show me why the specific medications recommended would benefit me."

Taken together, many of the findings in the interviews revealed what the researchers called "an enduring set of fears" about ART among some HIV-positive people. By categorizing responses and issues about starting ART, these interviews provide a point of view that doctors, nurses and pharmacists can consider when counselling treatment-reluctant patients.

The way forward

According to the researchers, participants for the most part appreciated their relationships with doctors and nurses whom they saw on a regular basis. Many participants had chosen not to take ART with the support of their care providers. Thus, it is possible that as care providers' views on when to start ART evolve, so will their patients' views. However, these patients will likely only begin ART after much discussion.

Some participants sought what researchers called "convincing proof" that they should begin ART. Researchers also recognized that some participants sought an impossible ideal—guaranteed efficacy with zero side effects. This information can be used to guide conversations about the use of medicines.

Not necessarily irrational

The researchers cautioned that patients who do not wish to start ART should not simply be dismissed as irrational. Rather, many participants in this study had general fears about the safety of medicines. These fears were in part based on the early history of anti-HIV therapy. However, treatment has changed tremendously since potent treatment became available in 1996. In 2015, guidelines by the U.S. Department of Health and Human Services (DHHS) recommended that doctors prescribe combinations of drugs that are generally safer, better tolerated and more effective for the initial therapy of HIV. Many of these regimens are available in one pill that can be taken once daily. These guidelines could be used as a starting point for discussion with and education of patients.

Advice for care providers

In taking into account their findings, the research team made the following statement for doctors, nurses and pharmacists:

> "…the best way forward, in supporting people being asked to make treatment decisions, is to continue to appreciate the breadth and diversity of beliefs that shape their thinking, and to provide specific forms of support and understanding regarding [what it means to take medicines and how it affects the bodies and lives of patients]."

Caring for oneself

The Australian researchers found that many of the participants thought carefully about their health; they were focused on "well-being, way of life and sense of self."

A clue to psychological issues

The research team noted that while many participants "feared the use of HIV medicine… [they] did not report similar concerns about other forms of medical care and treatment including [therapy with antibiotics or antifungals]."

What is interesting is that the researchers stated that participants felt the following way:

> "HIV medicines were invested with a particular potency, representing a greater risk to the self than other medical interventions, which needs to be better appreciated in policy and clinical activities relating to treatment uptake."

Not more time

Researchers strongly cautioned that care providers should not assume that some reluctant patients "simply need more time before they are ready [to initiate ART]." Rather, researchers encouraged doctors, nurses and pharmacists to view their patients' reluctance to initiate ART as something that may shift. Patients are engaged in a "process of deliberation which draws on their own particular past (treatment histories), present (contemporary concerns) and future (ideal conditions) perspectives on ART." By recognizing these issues, care providers can begin helpful and ongoing dialogue about treatment.

The researchers also advised care providers to engage in "respectful interactions…so as to avoid excessive…adversarial debates."

For the future

The research team specifically sought people who were reluctant to take HIV medicines, and so this may bias their findings. On the other hand, it is this specific group of people whose views on treatment need to be heard and understood, so we are lucky that the researchers were able to find this group. The Australian work provides valuable insight into the views of treatment-reluctant people and some of the psychological issues that underpin a desire to avoid or defer taking ART. Conducting analyses of interviews—qualitative research—is difficult and time consuming. The Australian researchers should be congratulated for engaging with their participants and gaining more insight into treatment reluctance. The findings from the Australian study can help a broad range of people working in the field of health and health education. It is very likely that in high-income countries in the future, there will be further emphasis on early initiation of ART. This emphasis will be both for the health of the individual and to reduce the further spread of HIV. It is in this regard that the Australian findings will be very valuable.

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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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© CATIE, Vol. 27, No. 5
August/September 2015

ISSN 1181-7186 (print)
ISSN 1927-8918 (online)
CATIE Ordering Centre Catalogue Number ATI-60231E
(*Aussi disponible en français, ATI-60231F*)

Production of this newsletter has been made possible through a financial contribution from the Public Health Agency of Canada.

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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.

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