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### I ANTI-HIV AGENTS

#### A. Longer life expectancy for HIV-positive people in North America

Large studies, primarily from Western Europe, the U.S. and Australia, have found that potent combination anti-HIV therapy (commonly called ART or HAART) has led to tremendous improvement in the health of HIV-positive people. In Canada and other high-income countries, AIDS-related infections are uncommon for HIV-positive people who are in care and who are taking ART. As a result, researchers increasingly expect that a young adult who is infected with HIV today *and* who begins ART shortly thereafter *and* who takes his or her medicine every day exactly as directed *and* who does not have untreated co-existing health issues—such as addiction, depression, schizophrenia, co-infection with hepatitis C virus—is likely to live for several decades.

Until recently, analyses of life expectancy for large numbers of HIV-positive people in Canada and the U.S. were not available. Now a consortium of researchers across the continent has pooled health-related data collected from HIV-positive people and analysed their life expectancy. The researchers found that overall the life expectancy for HIV-positive people has increased over the past decade and is approaching that of HIV-negative people. However, not all key groups affected by HIV are experiencing the same degree of life expectancy. In this bulletin we explain which groups are affected and offer possible reasons for the observed differences.

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## Study details

Researchers across North America with the NA-ACCORD database analysed health-related information from 22,937 participants who initiated ART between January 1, 2000 and December 31, 2007.

The average profile of participants was as follows:

- 77% were male, 23% were women

Participants were distributed across the following age ranges:

- 20 to 34 years – 25%
- 35 to 44 years – 42%
- 45 to 54 years – 25%
- 55+ years – 8%

Route of infection

- sharing equipment for injecting street drugs (IDUs) – 20%
- having unprotected sex with another man (MSM) – 39%
- other, unspecified routes of infection – 41%

Race/ethnicity

- people of colour – 62%
- white people – 38%

CD4+ count at the time ART was initiated:

- less than 350 cells – 72%
- 350 or more cells – 28%

## Results—Overall

A total of 1,622 people died during the study; details about causes of death were not provided.

In general, rates of death were high among groups of people with the following features/characteristics:

- a history of injecting street drugs
- people of colour
- people who started ART when their CD4+ count was 350 or less

## Life expectancy – The numbers

Based on its analysis, the research team predicted that the average life expectancy of a 20-year-old person in the U.S. or Canada who began ART shortly after he or she became HIV positive should be around 70. However, this is just an average figure, and some groups will have

shorter or longer life expectancy. Below are the estimated life expectancies of a 20-year-old person in different groups in 2009, starting with HIV-negative people for comparison. At the end of the figures we provide possible explanations for these results:

- HIV-negative men in Canada – 80 years
- HIV-negative men in the U.S. – 77 years
- HIV-negative women in Canada – 84 years
- HIV-negative women in the U.S. – 82 years

Gender

- HIV-positive men – 62 years
- HIV-positive women – 64 years

Route of infection

- IDUs – 49 years
- MSM – 77 years
- other risk groups – 70 years

Race/ethnicity

- people of colour – 58 years
- white people – 72 years

CD4+ count when ART was initiated

- less than 350 cells – 59 years
- 350 or more cells – 75 years

These life expectancies should be compared to the time before ART became available when, on average, HIV-positive people in high-income countries lived for between 10 and 12 years after diagnosis.

## Reasons for the gaps:

### Women

The overall life expectancy of HIV-positive women in this study was less than that of MSM and HIV-negative women. The researchers suggested several possibilities for their findings. It is possible that “women may be accessing HIV-related care at later stages of HIV disease than [some] men.” The study enrolled large numbers of women who had a history of injecting street drugs (IDUs). In general, people who inject street drugs have worse survival, regardless of HIV status, than non-IDUs. Women in this study may have had less education, lower incomes and more difficulty interacting with the healthcare system and may have experienced more social stigma and isolation than HIV-positive MSM in the study.

Unmentioned by the researchers are the many roles that women have thrust upon them, including caring for children and other family

members, running a household and working outside the home. Due to these multiple roles, women sometimes are forced to prioritize the care of others and have insufficient time to care for themselves. All of these factors could have impacted the overall health and survival of women in this study.

### People who inject street drugs

The research team suggested that the following factors likely played a role in the poorer life expectancy of people who inject street drugs in this study:

- having co-morbidities such as hepatitis C virus (HCV)
- difficulty taking ART every day exactly as directed
- the destabilizing effect of active drug use
- unstable housing
- low income

### Race/ethnicity

The study team stated that the differences in life expectancy between people of colour and white people may reflect the impact of a number of factors, such as “underlying socioeconomic conditions, access to care and health insurance coverage....” The researchers found that at the beginning of the study the gap in life expectancy between the two racial groups was huge—23 years. However, toward the end of the study period, it had fallen to nine years.

### CD4+ count at the start of ART

The findings from the present study support recommendations by leading treatment guidelines in Canada and the U.S. that HIV-positive people should initiate ART as early as possible regardless of their CD4+ count.

### Limitations and strengths

It is possible that researchers may have underestimated recent or future developments in technology, care and medicine that could extend the life expectancy of HIV-positive people.

It is also possible that in the future HIV-positive people may develop age-related problems faster than HIV-negative people that cause their life expectancy to stagnate or even decrease.

Researchers were unable to follow each participant from the age of 20 until they reached their 70s. This is a reasonable limitation, as ART only became available in 1996 in most high-income

countries. However, there are other databases that have monitored the health of HIV-positive people who began taking ART in 1996 (note that this is merely four years earlier than the start of the present study). These other studies have found broadly similar trends as the present NA-ACCORD analysis. The researchers in the present study used similar methodology as is routinely used to estimate the average life expectancy in HIV-negative people and so the findings from the present study are reasonable and are based on ongoing trends.

### The benefits of regular care

Bear in mind that compared to HIV-negative people, many HIV-positive people in Canada and similar countries are under a relatively high degree of medical scrutiny—they undergo visits to the clinic for interviews and laboratory tests several times each year. This degree of heightened medical surveillance is likely to detect any complications early on, before they can become serious. This is yet another factor that may help extend the lifespan of HIV-positive people.

In the next article, we explore trends in survival among HIV-positive people in countries with healthcare systems similar to Canada and issues that can be addressed to help prolong survival.

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Samji H, Cescon A, Hogg RS, et al. Closing the Gap: Increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One*. 2013 Dec 18;8(12):e81355.

## B. Exploring factors linked to longer survival among ART users

In the UK, Professor Caroline Sabin, PhD, from University College London has been analysing different studies of HIV-positive people and how such studies estimate life expectancy. She has confirmed in a recent analysis that many studies conducted in high-income countries have found a dramatic reduction in AIDS-related deaths among ART users since 1996.

### Factors unrelated to HIV

In drilling deeper into the data, Professor Sabin has found that factors *unrelated* to HIV can have

a major impact on survival in the recent era. Those factors include the following:

- smoking (significantly increases the risk for serious cardiovascular disease, cancers and diabetes)
- excessive alcohol use
- substance use

Studies have found that some HIV-positive people tend to have higher rates of those factors than HIV-negative people. Furthermore, smoking tobacco can have such a profound impact on survival that it may shorten people's lifespan in ART users more than HIV does.

One large observational study called ART-CC comprises 70,000 HIV-positive participants from Europe and North America. In one analysis of health-related information, researchers with ART-CC examined data on life expectancy and found that the proportions of ART users with a life expectancy similar to that of HIV-negative people were as follows:

- 46% of MSM
- 42% of heterosexuals
- 0% of IDU

Analysing the data slightly differently, looking for the proportions of participants with the greatest risk of death, researchers found this distribution:

- 4% of MSM
- 14% of heterosexuals
- 47% of IDU

In a Danish study examining clinical events in the period from 1995 to 2008, researchers found that non-AIDS-related causes of death fell significantly among people who did not inject street drugs, while such deaths rose over the same period among IDUs.

These findings confirm the serious effect of injecting drugs—overdoses, accidents and exposure to germs with major consequences, such as serious bacterial infections and viruses that cause hepatitis which can lead to liver failure and, in some cases, liver cancer.

Professor Sabin also calls attention to another study, done in Alabama, which found that patients who missed clinic appointments in the first year after initiating ART “had over twice the rate of long-term [death] compared with those attending all scheduled appointments....”

## Factors related to HIV:

### Late diagnosis

Studies in Brazil, Western Europe and North America suggest that a diagnosis late in the course of HIV disease is a factor associated with an increased risk of death. This risk arises because the body and the immune system have been severely weakened.

### Getting to 500 cells with ART

In one European study called COHERE, with more than 80,000 HIV-positive participants, researchers found that the risk of subsequent death fell tremendously among men who achieved a CD4+ count of at least 500 cells after starting ART, approaching the risk seen in HIV-negative men. However, for HIV-positive women, even when they maintained CD4+ counts of 500 cells or more for over five years, the results were not the same. The reasons for this may be that HIV-positive women are more likely than HIV-negative women to smoke tobacco and to have a history of injecting street drugs.

When researchers segregated their analysis of survival among women who were **not** IDU, then their survival after three years of attaining and maintaining a CD4+ count of 500 cells or more became similar to that of HIV-negative women.

Among IDUs who achieved a CD4+ count of 500 cells, death rates were elevated compared to non-IDU HIV-negative people “even after five years of maintaining a CD4+ count of [at least 500 cells],” the COHERE researchers reported.

The COHERE team also explored survival among older HIV-positive ART users. Among people aged 60 or older who had a CD4+ count of at least 500 cells, both men and women had a risk of death similar to that seen among HIV-negative people. The COHERE researchers explained that this finding was due to at least the following two factors:

- fewer IDUs among older HIV-positive people
- increasing risk of death among HIV-negative people

### Are neighbourhoods a factor?

Another study in British Columbia has found that HIV-positive people living in different neighbourhoods have different rates of death. They compared one neighbourhood where there was a relatively high concentration of people who

injected street drugs to another neighbourhood with a relatively high concentration of gay men. The researchers said, “We found significant differences between patients from the two neighbourhoods for all socioeconomic variables. Patients in the neighbourhood with a high concentration of injecting drug users were more likely to be female, have a history of injecting drug use, have a less HIV-experienced physician and be less adherent.” They also found that even among those who used ART the risk of death for IDUs in that neighbourhood was threefold greater than that of gay men using ART in another neighbourhood.

### Making the right comparisons

Regardless of HIV infection status, differences in survival by neighbourhood can vary by city, region or even within a country. For instance, Professor Sabin stated that overall male life expectancy at birth in the years 2007 to 2009 was about 84 years in parts of London, compared to 73 years for males who were living in parts of Glasgow. She said that this and other differences in life expectancy among HIV-negative people can be explained by “differences in the characteristics of those living in different regions, particularly socioeconomic status, lifestyle factors and dietary factors.” Thus, she argues that when making comparisons between HIV-negative and HIV-positive people, it is probably useful to match each HIV-positive person to an HIV-negative person who has similar “lifestyle and behavioural characteristics...” so that a more accurate estimation of life expectancy can be obtained.

In one study comparing HIV-positive and HIV-negative people in the U.S. several years ago, researchers found that life expectancy for the average HIV-negative person was about 76 years. When researchers recalculated the life expectancy in their study using HIV-negative people with similar behaviours and characteristics of their HIV-positive population, the average life expectancy of this group of HIV-negative people fell to 68 years. Adjusting estimations of life expectancy—taking into account alcohol use, tobacco smoking, use of other substances, consequences of sexually transmitted infections (STIs)—is an important point that needs to be considered. When the U.S. researchers took these factors into account and estimated the life expectancy of their HIV-positive population, they arrived at a figure of about 56 years.

### Increasing life expectancy for HIV-positive people

The studies that we have reported on in this issue of *TreatmentUpdate* suggest that there is still much work to be done raising the life expectancy of key populations who have HIV. Such work needs to be focused on care and treatment issues mainly *unrelated* to HIV, likely including at least the following themes:

- screening for and treatment of anxiety, depression, post-traumatic stress disorder and schizophrenia
- help with recovery from addiction and substance use
- among people with hepatitis B or C co-infections, reducing alcohol consumption is particularly important for maintaining liver health
- encouragement and support for quitting smoking
- maintaining a healthy weight
- monitoring of and assistance with taking medicines every day exactly as directed
- screening for and treatment of HCV and other co-infections
- screening for and preventing and treating cardiovascular and kidney disease as well as diabetes
- getting vaccinations against common infections
- regular cancer screening and, when necessary, treatment
- screening and treatment of STIs as well as vaccination against hepatitis A and B and human papillomavirus (HPV)

Until these and other measures become routine across North America for *all* groups hit hard by HIV, gaps in survival between the different groups mentioned in these and other studies will persist.

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### C. Why some people don't want to start HIV treatment

When ART became available in Canada and other high-income countries in 1996, regimens were complex—they had specific food and water requirements, contained many pills, had to be taken up to three times a day on an exact schedule and had many side effects.

Surveys of HIV-positive people around that time found that there were at least the following barriers to starting treatment:

- fear of side effects
- not wanting to take many pills several times a day
- difficulty integrating pill-taking into their lives

Nearly 20 years after ART became available, therapy is much simpler (often once a day and there are entire regimens available in one pill), safer and more effective. However, there are still HIV-positive people who do not wish to start therapy, though there are many benefits to starting early. At the level of the individual, early use of ART can reduce the amount of HIV in the body. This reduction in HIV helps relieve ongoing damage to the immune system, brain, heart, lungs, kidneys and other vital organs and systems. At the level of thousands of people in a city or region (what researchers call “population level”), taking ART every day exactly as directed and getting regular checkups for sexually transmitted infections helps to greatly reduce the future risk for spreading HIV. This is an important benefit for the community.

Researchers in the European Union and Australia conducted a survey of HIV-positive patients and their doctors about perceived barriers to starting ART. Analysis of the survey results suggest that in the current era barriers to initiating therapy still exist but are different from those of the late 1990s. A primary barrier among HIV-positive people today is that they may not feel sufficiently unwell and they lack serious symptoms that would hasten their entry to treatment. Major reasons by doctors for delaying the initiation of ART include that they perceived some of their patients to be suffering from a degree of depression, that there was active substance use and that patients did not understand the need to adhere to HIV medicines.

### Study details

Between November 2011 and October 2012 researchers recruited 508 HIV-positive patients with the following average profile:

- age – 37 years
- 84% men, 16% women
- time since HIV diagnosis – between one and four years

### Transmission groups

- 67% men who have sex with men (MSM)
- 6% people who shared equipment for injecting drugs (IDUs)
- 25% heterosexual
- 2% were classed by researchers as unspecified “other”
- HIV viral load – 10,000 copies/ml
- CD4+ count – 568 cells

Most participants had none or very mild symptoms of HIV disease and were distributed into the following CD4+ cell count ranges:

- less than 350 cells – 8%
- between 350 and 499 cells – 27%
- 500 or more cells – 65%

During the same period, 114 doctors were recruited, 60% of whom had at least 10 years of experience treating people with HIV.

All participants were administered an extensive survey about perceived barriers to initiating ART.

### Results—HIV-positive people

The main reason that HIV-positive people gave for delaying the start of ART was as follows:

- “I rely on my body to tell me when to start.”

This reason was relatively common regardless of CD4+ cell counts.

Another answer was that they would delay starting ART until symptoms occurred.

Interestingly, researchers stated that 47% of respondents did not wish to start therapy because they did not want to be reminded about their HIV status. This wish was also relatively common regardless of CD4+ count.

### When to start

Treatment guidelines increasingly call for considering initiating ART shortly after testing HIV positive, regardless of CD4+ count. When participants were queried about starting ART the distribution of some of their responses was as follows:

- 50% of participants with a CD4+ count less than 500 cells were not ready to start
- 30% of participants with a CD4+ cell count less than 500 cells were “ambivalent” about starting

### Doctors

Most doctors (93%) said that the recommendations in ART guidelines about starting therapy were suitable for their patients. When researchers asked if patients who have less than 350 CD4+ cells should start therapy, 46% of physicians said

“no.” Researchers were surprised by this response because all guidelines in high-income countries recommend that ART be initiated if the CD4+ count falls below this threshold. So they asked physicians about their reluctance to prescribe ART according to patients’ cell counts. Here is what they found:

Below 350 CD4+ cells

- patient is too depressed
- patient does not understand key issues about HIV treatment
- patient uses harmful substances

CD4+ count between 350 and 499 cells

- have not known patient for a long enough time
- patient is too depressed
- patient does not understand key issues about HIV treatment

500 or more CD4+ cells

- have not known patient long enough
- family, relatives not aware of patient’s HIV infection
- job prevents good adherence to medicines

The researchers conducting the survey were surprised by the reluctance of some doctors to treat substance users because studies have shown that with appropriate intervention and support people can be safely transitioned from substance use to opiate substitution (methadone, buprenorphine) and with psychosocial support and education, they can successfully use and adhere to ART and demonstrate long-term recovery from addiction.

### Limitations and strengths

The survey had a relatively small proportion of participants with less than 350 CD4+ cells. This problem may arise because ART is being initiated at higher CD4+ counts. Also, the researchers did not collect data on cultural differences that may have existed among countries about medicines and health.

On the other hand, the survey was one of the largest exploring these themes in high-income countries.

### For the future

The survey’s findings are important and provide valuable clues as to how some doctors and patients perceive barriers around the initiation of ART. As programs to expand the offer of an HIV test followed by counselling and swift referral

for treatment are increasingly implemented as ways of not only improving the health of HIV-positive people but also reducing the general spread of HIV, the issues raised in the survey will increasingly be encountered. Finding ways to address the themes raised in the survey will be essential if ART is to be more widely used.

As a follow-up to this type of research, focused interviews with a small group of patients about their feelings on starting ART have the ability to uncover deeper and perhaps more meaningful psychological issues that underpin their stated reluctance and ambivalence about initiating therapy.

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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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© CATIE, Vol. 26, No. 1  
January 2014

ISSN 1181-7186 (print)  
ISSN 1927-8918 (online)  
CATIE Ordering Centre Catalogue Number ATI-60214E  
(Aussi disponible en français, ATI-60214F)

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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#### *A Practical Guide to HIV Drug Side Effects*

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#### Fact Sheets

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