Lung cancer risk linked to immunological dysfunction and bacterial pneumonia

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In Canada and other high-income countries, the widespread availability of HIV treatment (ART) has made deaths due to AIDS-related complications significantly less common than in the 1980s and 1990s. In the current era, doctors are finding that issues generally unrelated to AIDS are affecting the health and survival of HIV-positive people who take ART. As an example, research teams in Canada, Denmark, France and the U.S. are finding that some HIV-positive people are at elevated risk for lung cancer. In part, this problem of elevated lung cancer risk arises from the high rates of smoking among HIV-positive people. However, researchers have suspected that there may be additional risk factors for lung cancer in this population.

Recently, a team of researchers at several clinics in the U.S. has moved closer to uncovering these additional risk factors. The researchers analysed health-related data collected from nearly 22,000 HIV-positive people who were monitored for about seven years. The team found that, as would be expected, smokers were at elevated risk for lung cancer. In addition, they found that people who had a low ratio of two types of immunological cells (CD4+ cells and CD8+ cells) and others who had a history of bacterial pneumonia were at elevated risk for lung cancer. Later in this bulletin we explore these two additional factors and how they could have affected the risk for lung cancer.

Study details

The research team collected data between January 1, 1998 and December 31, 2012. The researchers focused on 21,666 HIV-positive veterans, 277 of whom ultimately developed confirmed cases of lung cancer.

The vast majority (98%) of participants were male and had between two and four T-cell counts done each year that they were in the study (in addition to other tests).

Results

Over the course of the study, 277 participants (1.3%) developed lung cancer.

According to the researchers, participants who developed lung cancer were statistically more likely to have the following features upon entering the study:

- past or current tobacco smoking
- a low CD4/CD8 ratio
- older age – on average 50 years among participants with lung cancer vs. 45 years among participants without lung cancer
- a diagnosis of COPD (chronic obstructive pulmonary disease; problems breathing, most commonly bronchitis and emphysema) or occupational lung disease (this can arise because of inhaling dust in certain occupations in mining, processing and manufacturing)

In arriving at these results, the researchers also took into account the following factors from participants’ medical records:

- a diagnosis of problematic use of alcohol and/or drugs
- hepatitis C virus co-infection
About the CD4/CD8 ratio

Two important groups of T-cells involved in the immune response to germs and tumours are CD4+ and CD8+ cells. Monitoring the level of CD4+ cells in the blood has been a key part of assessing the health of the immune system in people with HIV and other immunological disorders. In untreated HIV infection, the number of CD4+ cells falls and the CD8+ cell count rises.

The ratio of CD4/CD8 cells is used as a crude way of assessing the overall health of the immune system. In healthy HIV-negative adults, the lower end of the normal range for a CD4/CD8 ratio is usually around 1.0. However, in HIV infection the CD4/CD8 ratio is often less than this and can fall even lower the longer this infection remains untreated. Once ART is initiated, the CD4+ count often rises, usually at a slow pace over several years, and the CD8+ count often decreases, also sometimes at a slow pace. One study in Italy with more than 3,000 HIV-positive participants found that over a period of five years the use of ART led to a slow but steady improvement in initially very abnormal CD4/CD8 ratios. However, after five years, only about 30% of ART users had a CD4/CD8 ratio of at least 1.0.

Note that not everyone responds to ART in the same manner. For instance, in a minority of cases, the CD4+ count rises after ART is initiated but the CD8+ count does not fall. The net result is that the ratio of these two cells is less than normal, even if the viral load becomes undetectable. A low CD4/CD8 ratio despite good adherence to ART (as shown by an undetectable viral load) is a signal that the immune system is dysfunctional, and if low ratios persist it may require further investigation by a specialist in infectious diseases or immunology.

Possible reasons for an abnormal CD4/CD8 ratio

The reasons for minor or no significant improvement in the CD4/CD8 ratio despite good adherence to ART over several years are not clear and may differ from one person to another. Some research suggests that the longer the time period between HIV infection and the initiation of ART, the more time HIV has to damage the immune system. A study in the UK and several other countries has found that among 573 people who had recently become HIV positive, 84% had abnormal CD4/CD8 ratios. Furthermore, the longer that HIV remained untreated, the less likely it was for participants’ CD4/CD8 ratio to normalize after initiation of ART. Similar findings were seen in a study in Montreal with 84 participants who began early initiation of ART vs. 49 participants who started later.

Therefore, several research teams have suggested initiating ART as soon as possible after HIV infection to help prevent the CD4/CD8 ratio from becoming very abnormal and to make it more likely that the immune system can have a better response to ART.

Another potential factor that may be associated with a prolonged low CD4/CD8 ratio despite the use of ART could be older age. As a person ages, so does their immune system. People who become infected later in life and who then initiate ART may sustain more immunological injury than a younger person. A French study of 399 HIV-positive people monitored for 10 years found that participants who initiated ART when they were 40 years or older were less likely to eventually normalize their CD4/CD8 ratio than younger people.

In the same French study, researchers found that those participants who interrupted ART were more likely to have a low CD4/CD8 ratio.

Several teams of researchers, including ones based in Canada, have found evidence suggesting that the virus called CMV (cytomegalovirus; a member of the herpes virus family and relatively common among gay, bisexual and other men who have sex with men) may be linked to an abnormal CD4/CD8 ratio in some ART users. Research teams in France and the U.S. have also pointed a finger at CMV co-infection as a possible reason for persistent abnormal CD4/CD8 ratios despite the use of ART with suppressed viral loads.

The U.S. team studying lung cancer risk did not explore possible co-infection with CMV or other herpes viruses and their potential impact on the CD4/CD8 ratio.

Keep in mind that the complexity of the immune system is immense and scientists do not know everything about it.

Immunological and infection-related findings in the study
The research team studying HIV-positive veterans found that having a prolonged low CD4/CD8 ratio (1.0 or less) was significantly associated with an increased risk for lung cancer.

Another finding was that participants with a history of bacterial pneumonia were also at elevated risk for lung cancer.

**Why bacterial pneumonia?**

The U.S. team studying lung cancer risk found that a history of bacterial pneumonia was linked to an increased risk for lung cancer. The team is not certain why this relationship exists but thinks that the inflammation in the lungs triggered by bacterial pneumonia may in some cases incite the development of abnormal growth among lung cells. Ultimately, these abnormal cells may become pre-cancers and, in some people, cancers, particularly in the context of smoking tobacco.

**Bear in mind**

The present study had several drawbacks, including the following:

- Participants were U.S. veterans who were overwhelmingly male. The findings may therefore not be applicable to HIV-positive women.
- There was an absence of detailed information about the smoking habits of participants, such as the number of cigarettes smoked daily and the duration (in years) that people engaged in smoking.
- There was little detailed information on other inhaled drugs, such as cocaine and marijuana, which also could have affected the health of the lungs.

Despite these shortcomings, the study among veterans with HIV adds important knowledge about risk factors for lung cancer.

**Marijuana—an understudied drug**

In reviewing the U.S. research on lung cancer risk in veterans, scientists in France who also study lung cancer risk in HIV-positive people made the following comment:

“inhaled [marijuana smoke] is probably an underestimated risk factor for lung cancer, because [the cancer-causing chemicals in marijuana smoke] are qualitatively similar to those in tobacco smoke but are present at much higher concentrations.” Furthermore, they stated that marijuana use is “high in subpopulations of people living with HIV.”

**What to do?**

The American and French researchers propose the following ideas related to treatment and research that could be implemented to help find ways to reduce the risk of lung cancer in HIV-positive people:

*Offer smoking cessation*

In reviewing the U.S. data, French scientists found that “most lung cancers occurred in current or former smokers.” They stated that this “underscores that smoking cessation is probably the most effective method to reduce [the] risk of lung cancer in people with HIV.”

*Offer early initiation of ART*

Both the U.S. and French researchers recommended the early initiation of ART to help protect the immune system and reduce the chances of the CD4/CD8 ratio falling very low. By protecting the immune system with ART, the chance of developing bacterial pneumonia would also be reduced. Many HIV care guidelines also recommend that doctors and nurses vaccinate their patients to help protect them from bacterial pneumonia.

*Consider lung cancer screening*

It may be useful to establish lung cancer screening programs for HIV-positive people using low-dose CT scans.

*Develop lung cancer risk assessment scores*
French scientists encourage the development and validation of a lung cancer risk scoring system. Such a measure could include putting information about the following factors into a simple formula:

- age
- smoking status
- presence of COPD
- history of bacterial pneumonia
- CD4/CD8 ratio

The CD4/CD8 ratio was once widely used in assessing the health of the immune system in the time before ART became widely available. Now that HIV-positive people are living longer and are at increased risk for health-related issues as they age, there will likely be a resurgence of interest in this ratio.

Resources

**Smoking, addiction and breaking free:**

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

**CMV**

- Canadian researchers point to CMV as a problem for the immune system — CATIE News
- Current and future therapies for CMV — CATIE News

**Issues affecting health and survival:**

- What reduces survival 10 years after starting ART in North America and Europe? — TreatmentUpdate 217
- Challenges in achieving a longer life — TreatmentUpdate 214

—Sean R. Hosein

REFERENCES:


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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