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Inflammation-related illness among HIV-positive people

Chronic HIV infection is associated with increased levels of inflammation. Researchers suspect that over the long-term this inflammation may be associated with an increased risk of health problems. To explore this idea, rather than launch a new and expensive clinical trial, researchers in Europe and the U.S. re-analysed data from two large, well-designed studies of the cytokine IL-2 (interleukin-2) in people with HIV. Specifically, researchers sought to assess the impact of chronic inflammation on major clinical events—heart attack, stroke, cancer, other serious complications and the risk of death. Both studies were randomized; participants received either IL-2 and HIV therapy (ART) or continued use of ART. The researchers who re-analysed the data focused on participants who continued to use ART alone (no IL-2). They found that some of the participants who continued to take ART and who had higher levels of inflammation had an increased risk of serious complications. An increased level of the chemical signal IL-6 (interleukin-6) in the blood of participants over time was linked to an increased risk for serious inflammation-related problems. The researchers say that potent anti-inflammatory treatment that is able to suppress chronic HIV-related inflammation “could greatly impact the health of people with HIV.”

Study details

Researchers reviewed data from the following two studies:

- SMART - a study assessing the impact of continuous ART vs. interrupting ART. All participants had at least 300 CD4+ cells/mm³ when they entered the study.
- ESPRIT - a study comparing IL-2 + ART vs. ART alone. All participants had at least 300 CD4+ cells/mm³ when they entered the study.

Researchers focused on the following outcomes:

- heart attack, stroke, hospitalization to undergo cardiovascular procedures/surgery
- severe liver injury (cirrhosis)
- severe kidney dysfunction (end-stage renal disease)
- cancers unrelated to HIV
- serious or other potentially life-threatening events

Researchers reported that their re-analysis focused on data collected from 3,568 patients whose average profile at the time they entered the parent studies was as follows:

- 77% men, 23% women
- age - 42 years
- CD4+ count - 547 cells/mm³
- lowest-ever CD4+ count - 210 cells/mm³
- duration of ART before entering the parent studies - five years

Results

In total, 252 participants had at least one of the following diagnoses:

- AIDS-related complications
- severe cardiovascular disease (heart attack, stroke or hospitalization for cardiac procedure/surgery)
- cancer unrelated to AIDS

In general, complications due to cardiovascular disease were more common than AIDS-related complications.

A total of 339 participants experienced signs/symptoms of a potentially life-threatening health complication; such complications are sometimes called “grade 4” events by researchers. These grade 4 events were unrelated to the problems mentioned above. In half of the 339 people, grade 4 events were related to chronic inflammation. Examples of chronic inflammation that were found were as follows:

- gastrointestinal inflammation
- severe liver injury
- acute kidney failure
- acute inflammation of the pancreas gland

The researchers gave the following examples of health issues that occurred that were not related to chronic inflammation:

- depression
- back pain
- groin hernia
- attempted suicide

Grade 4 events and diminished survival

Overall, people who experienced grade 4 events were at heightened risk of death. The greater the number of such events, the greater the risk of death. People with a diagnosis of cancer unrelated to HIV were at very high risk of death in this study.

Researchers found that people who entered the studies with high levels of proteins associated with inflammation (IL-6, D-dimer) in their blood were more likely to die when they developed complications.

Taking many factors into account, researchers found that people who developed grade 4 events were more likely to have the following characteristics/features:

- of African descent
- use medications to help normalize blood pressure
- co-infected with hepatitis-causing viruses

Note that this does not mean that taking blood pressure medicines caused grade 4 events. Rather, it suggests that people who were using such medicines in this analysis were likely in very poor health and therefore likely to develop serious complications.

Why did grade 4 problems occur?

Researchers strongly suspect that grade 4 events in this study were likely caused by an intersection of several factors, including the following:

- underlying HIV infection
- co-infection with hepatitis-causing viruses
- age (some older people had poorer health)
- hypertension

The researchers did not have data on participants’ history of exposure to tobacco, alcohol and other substances.

The researchers noted that elevated levels of IL-6 and D-dimer occurred several years before life-threatening complications happened. This strongly suggests that chronic inflammation plays a role in the life-threatening complications that the study examined.

Note that researchers did not have detailed information about the general health of participants from the distant past. This could have affected their interpretation of the data. For instance, some people who experienced grade 4 events could have been experiencing recurrent problems, not new ones. It is possible that some grade 4 events were scheduled hospitalizations for procedures or conditions that were not life threatening.

However, there is a clear trend in the re-analysis: Over time, elevated inflammation is linked to an increased risk for some complications in HIV-positive people even if they are using ART.

—Sean R. Hosein

REFERENCE:

Hart BB, Nordell AD, Okulicz JF, et al. Inflammation-related morbidity and mortality among HIV-positive adults: How extensive is it? *Journal of Acquired Immune Deficiency Syndromes* . 2018; *in press* .

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