Canadian study explores the possible effect of abacavir on liver health in co-infection

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Due to shared routes of infection, co-infection with HIV and hepatitis C virus (HCV) is relatively common. Chronic infection with HCV injures the liver and causes this vital organ to eventually become dysfunctional. Serious complications can arise from chronic HCV infection, including death.

Studies have found that co-infected people who take potent combination anti-HIV therapy (commonly called ART) to reduce the amount of HIV in their blood to very low levels can generally slow the pace of HCV-related liver injury.

Long-term studies of modern ART are needed to assess the safety of these medicines in co-infected people. To determine the potential impact of ART on the rate of progress of liver injury, researchers with the Canadian Co-infection Cohort (CCC) study analysed health-related information from more than 300 participants collected in their database. The researchers found that some ART regimens containing the anti-HIV drugs abacavir and 3TC (both drugs are co-formulated and sold in one pill called Kivexa in Canada and the European Union, and Epzicom in the United States) were associated with an increase in blood tests suggestive of accelerated liver injury. The researchers suspect that abacavir may be the drug responsible. The implications of this finding are discussed later in this CATIE News bulletin but first some background information.

About the CCC

As of October 2015, the CCC study has recruited 1,498 participants from 18 sites across Canada: 72% men, 27% women and 1% transgender people. All participants have both HIV and HCV and are regularly monitored by researchers.

Co-infection, HCV and assessment of liver injury

Chronic HCV infection causes inflammation in the liver as the immune system tries to rid this organ of HCV. The inflammation resulting from the struggle between the immune system and HCV injures the liver. Over time, this causes healthy liver cells to be replaced with useless scar tissue. If HCV infection is left untreated the liver degrades, resulting in liver dysfunction, reduced quality of life, serious complications, infections and death. Chronic HCV infection increases the risk for the development of liver cancer.

There are many factors that can speed up the pace of scarring in the liver. One such factor is inflammation. HIV infection causes a great deal of inflammation that degrades many organs, including the liver. ART significantly reduces the amount of HIV in the blood. As HIV levels fall so does HIV-related inflammation. As a result, in cases of HIV-HCV co-infection, ART also can slow down the pace of liver injury. Treatment for HCV infection is also important.

Historically, assessment of liver health and the extent of scarring in this organ have relied on a liver biopsy, the removal of a tiny piece of the liver for analysis. However, in the past decade an alternative method of assessing the liver has been developed. Using a specialized ultrasound scan called Fibroscan, doctors can now get a generally reliable idea of the extent of scarring within the liver. Also, over the past decade doctors have found that when used in an equation some blood test results can, in many cases, let doctors know if scarring in the liver has become worse. The equation is called the AST to platelet ratio index (APRI) and the result is called an APRI score. Increasing values for APRI are highly suggestive of serious liver injury. APRI requires a blood test to measure the levels of the
liver enzyme AST and the platelet count.

**Study details**

Researchers with the CCC combed through their database and selected participants who were taking as part of their regimens one of the following classes of HIV medicines: a protease inhibitor or non-nuke.

Examples of protease inhibitors include the following:

- atazanavir (Reyataz)
- darunavir (Prezista and in Prezcobix)
- ritonavir (Norvir and in Kaletra)
- lopinavir + ritonavir (Kaletra)

Examples of non-nukes include the following:

- efavirenz (Sustiva, Stocrin and in Atripla)
- etravirine (Intelence)
- nevirapine (Viramune)
- rilpivirine (Edurant and in Complera)

In addition, researchers also took note of which nucleoside analogues (commonly called nukes) participants were using. Usually they were the following combinations:

- tenofovir + FTC (sold as Truvada and found in Atripla and Complera)
- abacavir + 3TC (sold as Kivexa and found in Triumeq and Trizivir)

The researchers found 314 participants who were taking only the nukes listed above with either a protease inhibitor or a non-nuke.

To reduce the potential for bias when analysing their results, the researchers took into account many factors that could have affected their results, including the following:

- age
- gender
- length of time infected with HCV
- whether or not participants injected street drugs
- CD4+ count
- whether or not HIV viral load was less than 50 copies/ml

The researchers also took into account the fact that the vast majority of participants who used a non-nuke were taking Atripla (efavirenz + tenofovir + FTC).

Researchers then matched the data from each participant taking a protease inhibitor-based regimen with data from another co-infected person taking a non-nuke-based regimen, and vice versa.

Using all of these data, researchers created a mathematical model to explore links to an accelerated pace of liver disease.

**Results**

**abacavir + 3TC**

When researchers took into account the length of time that participants were taking nukes, they found that “the rates of change in APRI scores appeared to be driven by [the use of abacavir + 3TC].” On average, the researchers found that among people who took abacavir + 3TC and at least one protease inhibitor, APRI scores increased by 16% over five years. When abacavir + 3TC was used with a non-nuke, APRI scores increased by an average of 11% over five years. These increases were statistically significant; that is, not likely due to chance alone.
Among participants who used tenofovir + FTC and a protease inhibitor, APRI scores increased by 8% over five years. In participants who used these drugs with a non-nuke, APRI scores increased by an average of 3% over five years. These changes in APRI scores among participants who used tenofovir + FTC were not statistically significant.

**Bear in mind**

1. The report from the CCC is likely the first to explore the rate of fibrosis in HIV-HCV co-infected people and how some ART regimens interact with the pace of liver injury. The findings are interesting and suggest a possible cautionary signal with abacavir (researchers suspect that this drug could be affecting the livers of some participants). The study had several strengths, including its prospective nature and, in a broad sense, was representative of the co-infection population accessing care in Canada because of its inclusion of women, Aboriginal people and people who injected street drugs.

The results of the study are relevant to co-infection studies in the modern era, as none of the participants had taken nukes notorious for their general toxicity (so-called “d-drugs”), such as the following:

- ddC (Hivid)
- d4T (stavudine, Zerit)
- ddl (didanosine, Videx)

2. The CCC research team should be lauded for exploring the issue of liver fibrosis and co-infection. Although the researchers took great pains to reduce the possibility that some factor(s) might have inadvertently biased (or confounded) their conclusion(s), such a possibility can never truly be ruled out. This arises because the study’s design is that of a cohort study—essentially an observational study. Such studies are good at finding associations between a drug and an event, but they are unable to prove that, in this case, abacavir accelerated liver fibrosis when used with a protease inhibitor. Furthermore, the researchers generously acknowledge that it is also possible that exposure to protease inhibitors themselves may have accelerated the pace of liver injury in their study. Unfortunately, the CCC does not have the statistical power to discern the impact of protease inhibitors on the pace of liver injury. A much larger study is needed to explore this potential effect of protease inhibitors.

3. Potential sources of bias

There may be several sources of potential bias in this study. The researchers mentioned that protease inhibitors “are often favoured for persons with poor adherence in order to lower risks of [HIV developing resistance to treatment].” Confounding is possible because the researchers stated that “if more [users of protease inhibitors] had unstable lives” this could have impaired their ability to take ART exactly as directed and exposed participants “to potential risk factors for liver injury such as alcohol use and uncontrolled [HIV] replication.”

4. Why suspect abacavir?

Abacavir is broken down, or metabolized, by the liver. It is possible that during the process of breaking down abacavir highly reactive molecules are released with the potential to cause toxicity. However, abacavir is a widely prescribed drug. Regulatory agencies consider it a generally safe and effective part of ART regimens when it is used according to treatment guidelines. In the past decade, there appear to have been only three cases of abacavir-associated liver injury reported in biomedical journals. In all three cases, participants had been taking nevirapine for some time without any problems. Note that nevirapine use is associated with an increased risk for liver injury. At any rate, published reports of abacavir-associated liver injury seem to be exceedingly rare.

The other drug commonly used with abacavir is 3TC, and doctors consider this to be quite safe.

5. Next steps

Cohort or observational studies are a good first step to explore an idea or theory. If an association is found in a study of an observational design, then it needs to be studied and understood, both at the laboratory level with cells, viruses and drugs and also in a study of a more robust statistical design. A more robust study will be expensive, and in an era of enforced austerity such a study may not be possible or may take many years of fundraising and would be time-consuming for all concerned. Thus, no simple answers as to the potential role of abacavir in
accelerating liver injury will become available anytime soon.

In the meantime, the CCC team has not suggested that co-infected people avoid abacavir. They have found a signal of potential concern, but it requires verification in at least another study.

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Resources

- Hepatitis C – CATIE’s hepatitis C information
- Living with HIV and Hepatitis C Co-infection – CATIE
- Canadian Co-Infection Cohort
- The CTN – CIHR Canadian HIV Trials Network
- Canadian Institutes of Health Research (CIHR)
- Fonds de recherche du Québec (FRSQ)

REFERENCES:


—Sean R. Hosein
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