Schizophrenia and HIV—Study underscores serious issues associated with dual diagnoses

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Several studies have found that some people with HIV are more likely to have mental health issues compared to HIV-negative people. Most of these studies have focused on mental health issues such as anxiety and depression.

A team of researchers in Denmark has completed a massive study to understand the relationship(s) between schizophrenia, HIV and episodes of psychosis. The research team also assessed the overall impact of substance use to determine if it had any impact on mental health. Also, the Danish team sought to understand the potential impact of the anti-HIV medicine efavirenz (Sustiva, Stocrin and in Atripla) on schizophrenia and episodes of psychosis.

The Danish researchers made use of databases that collect extensive health-related information about Danish citizens and residents. This allowed researchers to track the health of participants before they were diagnosed with either HIV or schizophrenia.

In an analysis of data gathered from more than 2.6 million participants (only 1,369 of whom became HIV positive) over an average of 17 years, researchers reached the following conclusions:

- A diagnosis of HIV was associated with a significantly increased risk of developing schizophrenia or an episode of psychosis.
- The increased risk was greatest during the first 12 months after a diagnosis of HIV. However, an elevated risk for schizophrenia or psychosis persisted for the first five years after an HIV diagnosis.
- Schizophrenia was not linked to an increased risk for becoming HIV positive unless participants were also engaged in substance use.
- Once HIV-positive participants took treatment for HIV, their risk of subsequently developing schizophrenia or having an episode of psychosis fell significantly.
- There was no increased risk for developing psychosis when participants took efavirenz-containing regimens.
- In the years 1999 to 2011 (a period when HIV-positive people in Denmark were at generally low risk of death because of widespread use of anti-HIV treatment), HIV-positive people who had been diagnosed with schizophrenia had a hugely increased risk of death compared to HIV-negative people without schizophrenia.

Before we delve into the study and explain some of the researchers’ findings, we first explain some terms used.

About schizophrenia and psychosis

The Canadian Mental Health Association has excellent materials about schizophrenia on its website. Here is an excerpt that explains schizophrenia and psychosis:

“Schizophrenia is a mental illness that affects the way you understand and interact with the world around you. At the beginning of an episode, people may feel that things around them seem different or strange. They may start to experience problems concentrating, thinking or communicating clearly, or taking part in their usual activities. At the height of the episode, people may experience breaks from reality called psychosis. These could be hallucinations (sensations, like voices, that aren’t real) and delusions (strong beliefs that aren’t true, like the belief that they have superpowers). Some people feel ‘flat’ or numb. They may also experience changes in mood, motivation, and the ability to complete tasks. After an episode, signs can continue for some time. People may feel restless, withdraw
from others, or have a hard time concentrating.”

**Study details**

Researchers focused on people born in Denmark between January 1, 1955 and December 31, 1995 or people who were residents of Denmark from their 16th birthday or January 1, 1995, whichever occurred last. Anyone who was diagnosed with schizophrenia or psychosis before 1995 was excluded from the study.

The researchers reviewed data from the following people whose health was being monitored by databases:

- 2,646,154 people who could, in theory, later develop schizophrenia or psychosis
- 2,658,662 people who could, in theory, later become HIV positive

Most participants entered the study around the age of 21, and 51% were men and 49% were women.

**Results**

After an average of 17 years of monitoring, the distribution of the key diagnoses made was as follows:

- HIV infection – 1,369 people
- schizophrenia or psychosis – 23,599 people

Overall, HIV-positive people had between a two-and four-fold elevated risk for developing schizophrenia compared to HIV-negative people. They also had a four- to seven-fold elevated risk for developing psychosis.

However, according to the research team, the increased risk for a diagnosis of schizophrenia or psychosis was “substantially higher in the first year after an HIV diagnosis than in subsequent years.”

Also, the risk of a diagnosis of psychotic episode was increased in HIV-positive people, particularly during the first year after a diagnosis of HIV.

**HIV treatment**

Researchers found that HIV-positive participants who were taking potent combination anti-HIV therapy (also known as ART) had “a significantly lower risk of being diagnosed with schizophrenia or psychosis than those with HIV who had not started ART.”

Researchers found no link between schizophrenia and psychosis and the use of efavirenz. An explanation of this finding appears later in this report.

**Substance use**

Researchers found that there were nearly 150,000 people whose disclosure of substance use was captured in Danish databases. Among these people who also had schizophrenia, there was a statistically significant almost two-fold increased risk of getting HIV.

Among people who had schizophrenia but who did not engage in substance use, there was no significantly increased risk for acquiring HIV.

**Strikingly increased risks of death**

According to the researchers, rates of death were “six to eight times higher in people with HIV or schizophrenia than in those with neither of these diagnoses.”

What’s more, among people with both HIV and schizophrenia, the researchers found that “the risk of death was substantially higher [about 26-fold] than in those with neither of these diagnoses or only one.” The increased risk of death did not significantly differ between men and women.

**Points to consider**
1. Exploring the risk for schizophrenia and psychosis among HIV-positive people

It is possible that once a diagnosis of HIV has been made, patients come under greater medical scrutiny—more visits to doctors where more questions about health issues are discussed. This enhanced medical scrutiny could have unmasked pre-existing cases of schizophrenia. Such an impact of increased medical scrutiny on the study is called “surveillance bias.”

However, the increased risk for developing schizophrenia persisted for at least five years after a diagnosis of HIV was made. The researchers stated that during this period most patients would have been taking ART and would have had low viral loads. Therefore, surveillance bias is unlikely to have played a role in the relatively high rate of schizophrenia and psychosis revealed in the present study.

2. Focus on psychosis

Researchers found that having a diagnosis of HIV was linked to “a substantially increased risk for a subsequent diagnosis of psychosis.” Furthermore, in this population, the risk of developing psychotic episodes was greatest among people who used substances.

In the era before ART became widely available in high-income countries like Denmark, there are reports of psychotic episodes in people who were ill with severe HIV-related complications. The researchers stated that such episodes were probably caused by the following factors:

- life-threatening infections
- harmful proteins produced by HIV-infected cells in the brain
- disturbed metabolism brought about by unremitting HIV-related weight loss

These same biomedical factors that likely played a role in HIV-related psychosis in the past are unlikely to have any major role in the present era, now that ART is widely available. Therefore, the researchers made the following statement:

“The psychological distress associated with a diagnosis of HIV might [trigger] overt psychoses in susceptible people.”

3. Concerning efavirenz

The anti-HIV drug efavirenz can cause what the Danish team called “neuropsychiatric” side effects, including dizziness, difficulty falling asleep, nightmares, feeling stoned and depression. In very rare cases, use of efavirenz has been linked to an increased risk for thoughts of suicide and suicidal behaviour. There have even been reports of psychotic episodes associated with the use of this drug. Whether efavirenz was the cause of such behaviour is not clear from these reports.

However, in the present study, researchers did not find any link between exposure to efavirenz and an increased risk for schizophrenia or psychotic episodes. Furthermore, researchers found that participants who received efavirenz were less likely to develop such problems. Why would such a counter-intuitive result occur? There are at least two reasons:

- Bear in mind that this was not a randomized clinical trial but an observational study. As such, it may arrive at unexpected conclusions (such as efavirenz not being linked to psychosis) due to issues with the study design.
- The researchers stated that it was very likely that doctors caring for patients knew about the side effects of efavirenz and steered patients who had or who were at risk for mental health issues toward efavirenz-free regimens.

4. Why such a high risk of death?

The researchers found a greatly elevated risk of death among HIV-positive people who had schizophrenia. The team did not find any differences between HIV-positive people with and without schizophrenia when it came to CD4+ cell counts, initiation of ART or suppression of HIV (while taking ART).

Therefore, the researchers concluded that there were factors not directly related to HIV that likely played a role in
the demise of people with a dual diagnosis.

In searching for an explanation for the excess deaths among HIV-positive people with schizophrenia, the team reviewed studies of HIV-negative people with schizophrenia and noted that the following factors associated with poor health (and an increased risk for death) can occur in this population:

“Unhealthy lifestyle (smoking, [excessive drinking of alcohol], and substance use, high prevalence of [pre-diabetes, early cardiovascular disease, elevated blood pressure and excess weight], side effect of antipsychotic drugs, late diagnosis and insufficient treatment of co-morbidities, accelerated aging, and high rates of suicide and accidents)…”

The team proposed two possible explanations for the elevated death rates in HIV-positive people with schizophrenia:

- Some of the same factors associated with poor health seen in HIV-negative people are present among HIV-positive people. Furthermore, it is likely that HIV infection heightens the effects of these risk factors.
- The researchers state that HIV infection “might be a marker for a subgroup of people with schizophrenia with an increased rate of risk-taking behaviour and [unhealthy behaviours].” To support this idea, they noted that “78% of people diagnosed with both HIV and schizophrenia [used substances].”

For the future

Clearly more research is needed to uncover and understand the drivers of death in people with schizophrenia and HIV.

Psychologists at the University of Pennsylvania who have reviewed the Danish data find the results credible. They are also troubled by the finding that schizophrenia and psychosis tended to be diagnosed only after HIV had been diagnosed. Their concern arises because before schizophrenia and psychosis develop, there is usually a long period where signs of these disorders gradually appear. This period before the development of frank schizophrenia is called a prodrome. According to the Pennsylvania psychologists, the prodromal phase of schizophrenia “typically occurs during late adolescence and early adulthood for both men and women.”

The Danish findings underscore the need for a close linkage of mental health and HIV services. The Pennsylvania psychologists argue that, based on the work of the Danish researchers, an offer of HIV testing should be available in mental health clinics. Furthermore, people who test positive should receive swift referral to HIV care and treatment.

Places that offer HIV testing programs also need to refer people who test positive for HIV for swift screening and treatment for mental health issues, including schizophrenia.

The Danish researchers should be praised for undertaking an important study. Hopefully, their findings will encourage other researchers to investigate connections between HIV and mental health issues, including schizophrenia.

A note on syphilis and psychosis

Unmentioned by the Danish researchers is the issue of syphilis. Presumably the participants were screened for this illness. The germs—called treponemes—that cause syphilis penetrate the central nervous system (the brain and spinal cord) shortly after exposure. These germs can slowly degrade the brain and, in some cases, cause a range of symptoms that mimic other conditions, including psychosis. Thus screening tests for syphilis can sometimes be useful in uncovering unexpected underlying causes of psychosis.

Resources

Canadian Mental Health Association
Schizophrenia Society of Canada
Centre for Addiction and Mental Health

REFERENCES:

—Sean R. Hosein


Decision 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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