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I HIV AND BRAIN-RELATED ISSUES

A. HIV, survival and mental and emotional health

The HIV epidemic has always been associated with deeply emotional issues. In part this was caused by the way the new syndrome AIDS made its debut in high-income countries in the early 1980s—with reports of the sudden and mysterious onset of unusual life-threatening infections in previously healthy young men, many of whom were gay and bisexual. Cases also quickly appeared in people who injected street drugs and, later, in other populations. These affected communities—already deeply despised by larger society and, in the case of gay men, struggling to repeal legal restrictions on their rights—could hardly be expected to solve the problem of an emerging epidemic. The initial arrival of AIDS was met largely with silence from governments around the world, and communities affected by the new epidemic felt a deep sense of isolation and abandonment.

The seemingly inevitable association between AIDS and death, combined with initial uncertainty about precisely who was susceptible and exactly how the new syndrome was spread, were sufficiently disturbing to understandably cause a range of emotions in some people with AIDS—*anxiety, fear, hopelessness and depression*. The same fear triggered other feelings in some members of the public, such as *panic, hysteria and hatred*.

American physician Richard Glass who observed the impact of the arrival of the HIV pandemic proposed that “the intensity of emotional responses to AIDS may be at least partially due

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to its linkage with two of life's most powerful experiences— sex and death.”

The initial response to AIDS by health authorities in 1980 and 1981 was at best indifferent compared to responses in that era to outbreaks of Legionnaires' disease, toxic shock syndrome and other public health issues. This governmental and institutional indifference resulted in shock and anger that incited citizens to create the AIDS movement. This movement helped to mobilize communities and scientists to begin to find ways to deal with the health and research needs of people living with HIV.

Focus on the brain

In the mid-1980s scientists and doctors gained insight about HIV's impact on the brain and it became likely that this virus could be responsible for the sometimes subtle, sometimes serious effects on this organ that were seen in HIV-positive people. The impact of this virus could result in changes in mood and personality, impaired memory and difficulty thinking clearly.

Massive change for the better

In 1996 powerful combinations of anti-HIV drugs (commonly called ART or HAART) became increasingly available in high-income countries and prospects for better health and survival with HIV improved tremendously. The power of ART is so profound that researchers estimate that a young adult who becomes HIV positive today and who begins treatment shortly thereafter and who is engaged in his/her care and who does not have unrecognized and/or untreated or poorly managed co-existing health issues (such as serious co-infections with liver-injuring germs, addiction, severe mental health and emotional issues) is expected to survive into his/her 80s.

The closet of mental and emotional health

Although ART is widely available in high-income countries and the overall risk of death from AIDS-related infections is greatly reduced, some HIV-positive people, even those adherent users whose CD4+ cell counts rise significantly, experience challenges to their emotional well-being. Many HIV-positive people who have survived the initial wave of AIDS in the 1980s and 1990s may still have unresolved issues, including the emotional toll exacted by witnessing the loss of friends and

loved ones. Issues such as survivor guilt and post-traumatic stress disorder can occur. Furthermore, ART allows people to reach older age, a period when friendship networks can gradually dwindle, which can lead to loneliness and isolation that may trigger depression. HIV is still a stigmatized condition and this can place an additional psychological burden on people; not everyone can cope well with this without adequate support. Also, mental and emotional health issues are stigmatized in the larger society, so it may be difficult for affected HIV-positive people to recognize changes in their mental health or to even seek help to relieve the distress of emotional issues. HIV-positive people who use street drugs (injected or otherwise) also have unique mental health needs.

Gender

Research suggests that some women living with HIV today are at heightened risk for depression and anxiety. In some cases, the reasons for this are psychosocial and in other cases they are biological; in some cases, there is a mix of factors at play. Below are some examples:

- A research team in Alberta identified that HIV-positive women who experience violence are at heightened risk for depression and poor health.
- Another team in the U.S. found that some HIV-positive women are at greater risk for experiencing anxiety compared to HIV-negative women.
- Researchers in British Columbia found that some HIV-positive women, particularly women from marginalized communities, do not receive high-quality care.
- Researchers in Ontario found that some HIV-positive women are more likely to have episodes of more intense depression than HIV-positive men.

Change for the better

Prospects for a long healthy life for people living with HIV have never been better. HIV-positive people (and people at high risk for HIV) need regular checkups and screening for mental health and emotional issues. Identifying such issues is a first step toward fortifying a person's ability to understand, cope with and successfully triumph over some of the challenges that can occur in life.

In this *TreatmentUpdate* we continue to explore some issues related to the functioning of the brain as well as selected mental and emotional health issues that we reported on in *TreatmentUpdate* 203.

Resources

HIV and Emotional Wellness – CATIE’s guide to how people with HIV can cultivate their emotional well-being

Canadian Mental Health Association

Strengthening the aging brain – *TreatmentUpdate*

Good for the brain—advice from neuroscientists – *TreatmentUpdate*

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B. Pushing back against challenges to mental health and emotional wellness

There are many biological and psychological factors faced by people living with HIV that can from time to time challenge their sense of mental health and emotional well-being. Researchers have found that people living with chronic conditions such as HIV are at increased risk for experiencing mental and emotional health issues. These issues reduce a person’s ability to engage in the daily work of looking after him or herself.

Different studies have found different rates of depression among HIV-positive people; however, overall rates of depression are generally higher than among HIV-negative people.

Psychosocial support plays a vital role in acting as a buffer against stress. Counselling can make people more resilient by enabling them to deal with past trauma and by teaching helpful responses to difficult situations.

Biological issues

HIV can cause changes to the way brain cells process and send chemical signals to each other. Also, due to the ongoing inflammation incited by HIV and only partially suppressed by ART, the brain may benefit from additional doctor-recommended or prescribed therapy from time to time, including the following:

- regular aerobic exercise (several times weekly)
- relaxation practices – yoga, meditation, Tai Chi
- counselling – on an individual basis or with a group
- treating underlying mental health and emotional issues such as anxiety, depression, mood swings and addiction

All of these steps can go a long way to helping HIV-positive people lead longer and healthier lives and improve their quality of life.

In some cases it may be necessary for family doctors, nurses and pharmacists to refer patients to different healthcare providers as appropriate, including the following:

- social workers
- psychologists
- psychiatrists

Anxiety

Researchers have found that anxiety—including such symptoms as excess worry, episodes of panic, nervousness, paralyzing fear—can occur in some HIV-positive people. Anxiety can also occur as part of the spectrum of depressive illness.

If left untreated, persistent anxiety can degrade a person's quality of life and affect their energy and ability to have restful sleep.

If you think that you might suffer from anxiety, speak to your doctor to get help.

Anxiety can be successfully managed with one or more of the following:

- counselling
- stress reduction and relaxation techniques (as mentioned earlier in this report)
- temporary use of anti-anxiety medicines or antidepressants

Bipolar disorder

Also called manic depressive illness, bipolar disorder causes “unusual shifts in mood, energy, activity levels and the ability to carry out day-to-day tasks,” according to mental health experts. Furthermore, these experts add that “symptoms of bipolar disorder can be quite severe and can result in a manic state where thinking and judgment are severely impaired.” Some researchers suggest that rates of bipolar disorder are elevated among HIV-positive people.

People living with bipolar disorder can go through periods of high energy for weeks or months and can have symptoms such as the following:

- little need for sleep
- poor concentration (easily distracted by irrelevant events)
- impulsive behaviour, such as extended bouts of substance use (including alcohol), increased sexual activity, uncontrolled spending
- changes in mood
- excessive talking

After a period of weeks or months the affected person may become depressed and experience symptoms such as the following:

- unexpected lack of energy
- difficulty concentrating
- poor memory
- feelings of unexpected sadness, guilt or hopelessness
- losing pleasure in activities that were once fun
- difficulty falling or staying asleep or sleeping too much
- avoiding friends

If you have these or other symptoms suggestive of bipolar disorder, contact your doctor right away.

Diagnosis of bipolar disorder can only be done by a healthcare professional. There are many treatment options for bipolar disorder and the goals of treatment are to minimize shifts in mood and enable people to become functional.

People with bipolar disorder are at high risk for severe depression and thoughts of self-harm. In such cases, preventing suicide with medication becomes an important short-term goal.

According to American psychiatrist Daniel Hall-Flavin, approaches to the treatment of bipolar disorder can include the following groups of medicines:

- mood stabilizers – lithium
- some anti-seizure drugs (valproic acid, carbamazepine, lamotrigine)

Some doctors and patients also find another class of drugs called antipsychotics helpful for bipolar disorder. These can include the following drugs:

- quetiapine (Seroquel)
- olanzapine (Zyprexa)
- risperidone (Risperdal)
- aripiprazole (Abilify)
- ziprasidone (Zeldox, Geodon)
- asenapine (Saphris)

According to Dr. Hall-Flavin, antipsychotics can be helpful in cases where persistent depression or mania occur despite the use of mood stabilizers. Antipsychotics may be used either alone or in combination with a mood stabilizer.

In cases of persistent depression despite the use of a mood stabilizer or antipsychotic, doctors may then also add an antidepressant to a person's regimen. However, antidepressants need to be used cautiously, as they may inadvertently trigger an episode of mania in susceptible people.

In addition to medications, and depending on the severity of illness, doctors may recommend the following courses of action:

- a temporary stay in a hospital or regular visits to a hospital where the response to treatment is monitored
- lifestyle changes – healthier eating, more regular exercise

Successfully managing bipolar illness takes time and patience to find the right drug or combinations of drugs. Dose adjustments or other changes to medications may be necessary from time to time to avoid or minimize side effects.

Depression

It is normal to feel temporary and mild sadness after learning about unfortunate events that have happened to friends and loved ones. However,

in some people, sadness can persist for more than a few weeks and can lead to a serious condition called depression. This can be caused by psychological issues, biological issues or a combination of factors.

Not everyone with depression will have the same signs and symptoms, so trying to self-diagnose depression is tricky and can lead to problems. The best person to help you diagnose depression is your doctor.

According to the U.S. National Institute of Mental Health, people with depression can experience some or all of the following:

- feeling sad
- feeling hopeless, anxious or guilty
- getting easily irritated or angry
- feeling tired without having expended energy
- difficulty concentrating
- difficulty making decisions
- memory problems
- difficulty falling asleep or staying asleep
- waking up prematurely in the early morning
- unexpected muscle pain, cramps, headache
- sudden changes in appetite that result in weight loss or gain
- loss of interest in regular activities, including sex

If you think you may be suffering from depression, talk to your doctor as soon as possible.

Medical factors that can affect a person's mood can include the following:

- abnormal levels of thyroid hormone
- less-than-normal levels of testosterone in men
- presence of type 2 diabetes
- untreated hepatitis C virus infection
- exposure to certain anti-HIV medicines, particularly efavirenz (sold as Sustiva, Stocrin and found in Atripla)
- exposure to biological agents that affect the immune system, such as interferons (sometimes used in the treatment of hepatitis C) and interleukins

Major depression

If depression is left untreated it can become severe, leading to major depression. In such cases, some people may develop additional feelings such

as thoughts of self-harm or suicide. If this occurs do the following **right away**:

- call your doctor
- if your doctor is not **immediately** available go to the emergency room of the nearest hospital right away
- if you are unable to get yourself right away to the emergency room of the nearest hospital, **dial emergency services at 911**

There are many therapies for depression and your doctor can help you find one that is right for you. It may take some time to find the right medication or dosage that is best for you, so some patience is necessary. Doctors and their patients have found that using a combination of approaches, such as counselling and antidepressants, can be very useful.

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Good for the brain—advice from neuroscientists – *TreatmentUpdate*

Mindfulness-based therapy found helpful for stress and the immune system – *CATIE News*

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C. Denmark—unexpected trends in use of psychotropic medicines

Psychotropic medicines are drugs that affect the chemical signals used by brain cells to communicate. These drugs can have an effect on behaviour and mood. Commonly prescribed classes of psychotropic meds include the following:

- anti-anxiety drugs
- antidepressants
- antipsychotics
- hypnotics
- mood stabilizers
- sedatives

As part of a study, researchers at major clinics in Denmark reviewed health-related information collected from more than 3,000 HIV-positive people in several databases. The researchers had access to data on the filling of prescriptions for psychotropic medicines in pharmacies by both HIV-positive and HIV-negative Danes.

The researchers’ analysis found that 55% of these HIV-positive people filled prescriptions for a wide range of psychotropic medicines. Among HIV-negative people of the same age and gender, only 30% filled prescriptions for psychotropic medicines. Prescription patterns varied among the populations studied, affected by factors such as age and co-existing health conditions. The filling of prescriptions revealed that there are mental health and emotional issues among some HIV-positive people that need to be addressed.

Study details

Researchers reviewed and analysed information held in several databases dealing with HIV-positive people and their use of prescribed medications.

Data on 3,615 HIV-positive participants who were not co-infected with hepatitis C virus were analysed. Data from each HIV-positive person were compared to data from nine HIV-negative Danish people of the same age and gender.

At the time they entered the study, between 1995 and 2009, participants were on average about 38 years old and were mostly male (83% men, 17% women). The majority of men were gay or bisexual. No participants in this study injected street drugs.

Participants were in the study for between two and four years.

Results

Psychotropic drugs were used at least once by the following populations:

- HIV-positive people – 55%
- HIV-negative people – 30%

The most commonly used classes of psychotropic drugs were either hypnotics or sedatives. These drugs are generally used to help people fall asleep or stay asleep. Sedatives are also used to relieve temporary distress from anxiety.

The researchers found that the following categories of medicines were distributed as follows:

- antipsychotics were more likely to be prescribed to women and people of colour
- antidepressants were more likely to be prescribed to men who had sex with men (MSM)

Changes over time

Over the course of the study, the use of antipsychotics rose in both HIV-positive and HIV-negative people.

The pattern over time was different with antidepressants, as follows:

- HIV-positive people – use of antidepressants increased rapidly
- HIV-negative people – use of antidepressants increased slowly

The use of anti-anxiety medicines decreased then stabilized among HIV-positive people. However, rates of use were still greater than among HIV-negative people. The use of this category of medicines was stable among HIV-negative people.

The use of hypnotics and sedatives decreased then stabilized among HIV-positive people but still remained greater than among HIV-negative people. Among the latter group, rates of use of hypnotics and sedatives were stable throughout the study.

Putting it all together

The Danish team found that HIV-positive people had an overall greater use of psychotropic medicines than HIV-negative people of the same gender.

As the Danish national databases are comprehensive, the researchers were able to monitor prescription patterns before and after HIV infection occurred in some participants. In this sub-group of participants, they found that there was a greater rate of use of hypnotics and sedatives both before and after HIV infection compared to people who did not become HIV positive.

In general, the researchers found that the longer a person had HIV, the more likely they were to be prescribed psychotropic medicines. In other words, as HIV-positive people grew older, they were more likely to use antidepressants than HIV-negative people.

More than one use

The rise in the prescribing and use of antipsychotics is not likely due to a large increase in psychosis. Rather, researchers point out that this class of medicines has been found to be useful by both doctors and patients for helping to treat a broad range of mental health issues including depression, anxiety, bipolar disorders and so on. Therefore, the increased prescribing of this class of medicines is likely because doctors are using them to treat several conditions.

Focus on hypnotics and sedatives

As mentioned earlier, hypnotics and sedatives are used to treat sleeping problems and anxiety. Although their use declined over time among HIV-positive people, rates of using these classes of drugs were between two- and four-fold greater in people with HIV than in their HIV-negative counterparts. Furthermore, as HIV-positive participants grew older, their use of these drugs increased.

Ideally these drugs should only be used for short periods of time. One of the reasons for this is that some sedatives related to Valium (known as benzodiazepines), as well as others, can become addictive. As a result, in many high-income countries health authorities discourage the routine prescribing of this class of drugs for

prolonged use. The relatively high rate of hypnotic and sedative use by HIV-positive people caused concern among the researchers.

Due to their overall findings, the Danish researchers encourage doctors everywhere who are caring for HIV-positive people to “focus on the diagnosis and treatment of [mental health and emotional issues] among their HIV-positive patients, including MSM.”

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Rasmussen L, Obel D, Kronborg G, et al. Utilization of psychotropic drugs prescribed to persons with and without HIV infection: a Danish nationwide population-based cohort study. *HIV Medicine*. 2014 Sep;15(8):458-69.

D. Mood stabilizers and metabolic issues

As previously mentioned in this issue of *TreatmentUpdate*, HIV-positive people are at increased risk for issues affecting their mental health and emotional well-being. In cases of severe mental health issues, a class of drugs called antipsychotics is sometimes used. Healthcare providers and some patients have found that these drugs are useful for the following conditions:

- schizophrenia
- mania
- bipolar disease
- treatment-resistant depression

The second generation of this class of antipsychotics (SGA) is associated with a reduction in certain side effects that were seen with the first generation of these medicines:

- muscle spasms
- twitchiness
- restlessness
- involuntary movements

However, SGAs can also have side effects, particularly metabolic issues such as these:

- elevated blood sugar
- unintentional weight gain, particularly belly fat
- elevated levels of fatty substances (lipids) in the blood
- increased blood pressure

Together these issues make up what is called the metabolic syndrome and can increase the risk for cardiovascular disease.

Research suggests that the reasons for weight gain and other metabolic issues in people with serious mental health conditions are likely complex and related to an intersection of factors such as the following:

- behavioural – smoking tobacco, poor eating habits, insufficient exercise
- additional medical issues (called comorbidities) prior to the diagnosis of serious mental health issues
- an underlying predisposition to develop the metabolic syndrome among some people with schizophrenia and bipolar disorder

Researchers in Modena, Italy, and in San Diego, California, have collaborated on a study of the impact of SGA on the health of HIV-positive people, particularly among people who use potent combination anti-HIV therapy (commonly called ART or HAART). They have found that exposure to SGA is probably linked to an increase in elements of the metabolic syndrome. We caution readers that this does not mean SGA should be abandoned. Rather, the international team of researchers has released helpful recommendations about the use of SGA when caring for HIV-positive people. These recommendations appear later in this report.

Study details

Researchers recruited 2,229 HIV-positive people for the study and divided them into two groups as follows:

- taking SGA – 258 people
- not taking SGA – 1,971 people

Participants had the following average profile upon entering the study:

- age – 45 years
- gender – 80% men, 20% women
- duration of HIV infection – 7 years
- current CD4+ cell count – 435 cells/mm³
- current viral load – 50 copies/ml

Results

On average, participants had been taking antipsychotics for 15 months. Here are the drugs that were used:

- aripiprazole (Abilify)
- clozapine (Clozaril)
- paliperidone (Invega)
- quetiapine (Seroquel)
- risperidone (Risperdal)
- olanzapine (Zyprexa)

Researchers found that, in general, exposure to SGA was associated with certain elements of the metabolic syndrome, such as the following:

- increased levels of fatty substances in the blood (triglycerides)
- increased weight
- increased blood pressure
- new cases of type 2 diabetes

These results have also been found in studies of SGA in HIV-negative people.

There are several possible reasons for the occurrence of these side effects in the present study:

- Both SGA and some anti-HIV meds could have interfered with the hormone insulin. This hormone is used to help regulate blood sugar. Excess sugar is turned into fat and leads to weight gain.
- Both SGA and some anti-HIV meds could have interfered with the growth and development of fat cells, causing fat cells to concentrate and grow in the belly.

Researcher recommendations

The study team, which included psychologists, psychiatrists and neurologists, made the following recommendations:

- When prescribing or using SGA, healthcare providers and patients should note that many factors contribute to metabolic side effects.
- Non-drug therapies that can be considered for SGA-related side effects can include the following: “individual or group psycho-education, self-monitoring, cognitive behavioural therapy, nutritional intervention, supervised exercise programs and/or nutritionist and dietician counselling.”

- If a change to drug therapy must be made, the researchers advise doctors to consider switching therapy to an SGA less likely to cause an increase in appetite or weight. They added that doctors might also consider changing their patients’ ART regimen. However, the researchers warn that any changes to existing SGA “should be weighed against potential worsening of psychopathology” and, in the case of ART, new side effects and/or the potential development of HIV that is resistant to therapy.
- Additional therapies, such as cholesterol-lowering medicines, may be deployed to deal with metabolic side effects of SGA.
- The drug metformin (Glucophage) works by making the body more sensitive to the effect of the hormone insulin. Along with exercise and diet, metformin can help people to normalize blood sugar levels. The researchers suggested that doctors consider the use of metformin to help reduce SGA-related side effects.

Looking ahead

Another important outcome of the present research on SGA is that the scientists involved have realized that long-term prospective studies are needed to assess the impact of SGA as well as interventions (exercise, nutritional advice, drugs such as metformin) to reduce the side effects of these antipsychotics and improve the health of people who use them.

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E. Efavirenz and suicide risk

The non-nuke efavirenz—sold as Sustiva, Stocrin and found in Atripla—has been commonly used as part of HIV treatment since the late 1990s. Efavirenz can be taken in a single dose and has potent anti-HIV activity when used as part of combination therapy (commonly called ART or HAART) in many studies. When used as directed, efavirenz is generally safe. However, this drug can cause side effects that affect the brain, including the following:

- abnormal dreams
- changes in mood
- irritability
- difficulty falling asleep
- anxiety
- dizziness

Researchers refer to these and other side effects that affect the brain as neuropsychiatric symptoms. These side effects are supposed to fade within the first two to four weeks of initiating therapy with efavirenz. However, several studies from Europe suggest that efavirenz-related side effects can persist. Furthermore, a UK study found that about 20% of participants given the efavirenz-containing medicine Atripla quit because of side effects that affected their brain.

A robustly designed (randomized, placebo-controlled, cross-over) clinical trial in Switzerland found that 50% of participants who were taking an efavirenz-based regimen preferred to switch to a combination that was better tolerated, in this case with the integrase inhibitor raltegravir (Isentress).

A less common side effect associated with efavirenz is the development of depression. For many years in high-income countries, the prescribing information for efavirenz has included warnings about the possibility, in rare cases, of self-harm and attempted suicide.

Researchers with the U.S. AIDS Clinical Trials Group (ACTG) decided to investigate any possible link between the use of efavirenz and suicidal thoughts or behaviour in several well-designed clinical trials that they conducted. In their work, the researchers focused on four randomized clinical trials and found that the use of efavirenz was associated with a two-fold increased risk of suicidal thoughts or behaviours.

Study details

The ACTG team reviewed data from four studies comparing efavirenz-based regimens to efavirenz-free regimens involving 5,332 participants. None of these people had previously been exposed to anti-HIV drugs. They were distributed as follows:

- efavirenz-containing regimens – 3,241 participants
- efavirenz-free regimens – 2,091 participants

Although these four trials were held in different countries, nearly three-quarters of participants were from the U.S. Half of the participants were between the ages of 18 and 37 years; 73% were men and 27% were women.

Here are key points related to the mental health of participants:

- 8% disclosed a history of injecting street drugs
- 10% had received an antidepressant in the past
- 32% had a history of mental health and emotional issues or had recently received what doctors called “psychoactive” medicines prior to entering the study. Such medicines would include treatments for anxiety, depression, bipolar illness, psychosis, schizophrenia and difficulty sleeping.

Most participants were monitored for up to three years.

Results

Researchers assessed participants for suicidality, which they defined as any of the following:

- thoughts of suicide
- attempted suicide
- completed suicide

In their analysis, the researchers found that 83 participants had reported suicidal thoughts or behaviours. The overall distribution of people

who had thoughts of, attempted or completed suicide was as follows:

- efavirenz-containing regimens – 47 events
- efavirenz-free regimens – 15 events

The distribution of attempted suicides was as follows:

- efavirenz-containing regimens – 17 events
- efavirenz-free regimens – 5 events

The distribution of completed suicides was as follows:

- efavirenz-containing regimens – 8 events
- efavirenz-free regimens – 1 event

Statistical analysis revealed that participants taking efavirenz were at least twice as likely as participants not taking this drug to have thoughts of or attempted or completed suicide. This difference was statistically significant; that is, not likely due to chance alone.

In general, the length of time it took for a participant to develop thoughts of suicidal behaviours was shorter among people taking efavirenz than among people who did not take this drug.

Missing or misjudged

Sometimes death due to suicide may be misclassified or attributed to drug overdose, accidents or murder. When researchers reanalyzed the data taking into account these other possible misclassifications, exposure to efavirenz was still associated with a two-fold increased risk of death.

Additional risk factors

Taking into account several factors and their relationship to thoughts of or suicidal behaviours, the researchers found that the following factors were linked to an increased risk for suicidality in participants:

- taking efavirenz
- having a history of injecting street drugs
- having a documented history of mental health and severe emotional disorders, including thoughts of or attempts at suicide

Note that the researchers found that participants with a documented history of mental and severe emotional disorders were not common in these

studies. They were limited to 25 people and distributed as follows:

- efavirenz-containing regimens – 0.5% of participants (16 people)
- efavirenz-free regimens – 0.4% of participants (nine people)

Furthermore, among these 25 people (particularly five of the 16 who were taking efavirenz and one of the nine on an efavirenz-free regimen), thoughts of suicide or suicidal behaviour occurred.

Rates of suicidality were similar whether or not analyses were restricted to participants based in the U.S. or elsewhere.

Bear in mind

The results of the ACTG analysis show that in four clinical trials where regimens were randomly assigned, exposure to efavirenz was linked to a two-fold increased risk of suicidal thoughts or behaviours. Furthermore, eight out of nine participants who completed suicide were taking efavirenz.

Factors associated with an increased risk of thoughts of suicide or suicidal behaviour included the following:

- exposure to efavirenz
- history of injecting street drugs
- prior to entering the studies analysed, a recent history of using medicines for treating anxiety, depression, bipolar illness or psychosis

The findings from the ACTG analysis should not be entirely surprising. Initial studies with efavirenz suggested that about 0.7% of 1,008 participants taking this drug vs. 0.3% of 635 participants who took an efavirenz-free regimen reported thoughts of suicide.

The ACTG researchers found and reviewed publicly available data used by the U.S. Food and Drug Administration (FDA) when reviewing the emerging data from efavirenz in clinical trials many years ago. In these early clinical trials, there were cases of “serious nervous system or psychiatric experiences” that could include the following outcomes arising from exposure to efavirenz:

- aggravated or severe depression
- hallucinations
- thoughts of suicide
- attempted suicide

- outbursts of anger
- paranoia
- mania

Other studies

The overall level of suicidality found in the ACTG's analysis is similar to that seen in an earlier French study. Bear in mind that in either the ACTG or French study, it is possible that given the stigma surrounding mental health issues, including suicide, some participants may have chosen not to report such suicidality.

Suicidality occurred throughout the monitoring period of the ACTG's trials—three years.

Strengths and weaknesses

The analysis by the ACTG was done on four randomized clinical trials. The number of participants was large and diverse.

However, the ACTG's methods did have some relative weaknesses. Three of the four studies were not double blind; that is, participants and their doctors and nurses knew who was taking which regimens.

Another important weakness was that the trials were not originally designed to assess the potential for suicide. Bear in mind that clinical trials for HIV drugs are generally not designed for the purpose of assessing the potential of anti-HIV drugs for suicidality. Such trials would have to be very large (several thousand people) and run for many years and would therefore be very expensive. Furthermore, as safer, better tolerated and more potent regimens than efavirenz are available today, clinical trials exploring the adverse effects of efavirenz are unlikely to be launched in high-income countries.

Recommendations

Despite the previously mentioned weaknesses of the ACTG's reanalysis of clinical trial data, it is likely that there *is* a relationship between exposure to efavirenz and an increased risk for suicide in a relatively small number of people who use it. The U.S. researchers stated that the risk for suicidality that they found associated with efavirenz is "clinically relevant." They therefore encourage

doctors and nurses treating HIV-positive patients who use efavirenz to do the following:

- Such patients "should be monitored carefully for [signs or symptoms of worsening] depression or evidence of suicidal thoughts or behaviour."

Furthermore, the editors of the journal *The Annals of Internal Medicine*, in which the ACTG report was published, made this statement:

- "An increased risk for suicidality should be considered when choosing efavirenz as part of an initial antiretroviral regimen."

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F. How might efavirenz affect the brain?

Researchers are not certain precisely why efavirenz or the compounds into which it is broken down by the body affect the brain. In part, this problem arises because the action of efavirenz on the brain, at least at the molecular level, is disputed by some researchers.

However, clues about how efavirenz interacts with brain cells are emerging from laboratory experiments with cells and animals. We now present some findings from lab research on

cells and animals. Until this information is confirmed in studies in people, it should be considered preliminary.

The benzo link

Valium and chemically related drugs belong to a class of drugs commonly called benzodiazepines (benzos). Efavirenz belongs to the class of anti-HIV medicines called non-nukes. These drugs are somewhat similar in shape to benzos. This is an advantage because benzos can penetrate the brain and, not surprisingly, so can efavirenz.

Getting drugs inside the brain is important because this organ plays host to visiting cells of the immune system that can be infected with HIV. In other words, the brain can act as a reservoir or sanctuary for HIV. Efavirenz, as part of combination anti-HIV therapy, can help reduce the amount of HIV in the blood and brain.

Not all non-nukes cause identical side effects. For instance, other non-nukes such as nevirapine (Viramune), rilpivirine (Edurant) and etravirine (Intelence) can penetrate the brain and can cause side effects, but they are generally not associated with the same degree of neuropsychiatric side effects as efavirenz.

Cannabinoids

Many of the natural chemicals in marijuana responsible for its effect on the brain are called cannabinoids. These chemicals stimulate the body's receptors for cannabinoids. Efavirenz or the compounds into which the body breaks it down may also stimulate the body's receptors for cannabinoids. The evidence for this is indirect, as follows:

- There are reports that people taking efavirenz sometimes falsely test positive for marijuana use.
- Studies with cancer cells in the lab suggest that efavirenz interacts with them via cannabinoid receptors.

LSD

Recently, researchers in Texas conducted extensive lab experiments with rats, trying to identify receptors that these animals have that could be affected by efavirenz. The researchers found that efavirenz had the potential to stimulate the

receptors used by several substances when they entered the brain, including the following:

- Valium-type drugs
- barbiturates
- cocaine
- LSD (acid)
- methamphetamine

However, efavirenz did not cause addiction in these experiments with rats. This suggests that efavirenz's effects may be somewhat different from the substances tested.

Although efavirenz can stimulate receptors for several substances, at least in rats, the Texas researchers found that the drug's main effect on the behaviour of rats occurs through a receptor called 5-HT_{2A}. This is the same receptor used by LSD and related compounds. The Texas researchers found that the behaviour of rats that were fed efavirenz seemed similar to when they were fed LSD. They suspected that the interaction between efavirenz and the receptor 5-HT_{2A} might in part be responsible for some of the side effects—hallucinations, psychosis, flashbacks and nightmares—reported by some efavirenz users.

Abuse

A recent report by researchers in South Africa has documented that some substance users likely make use of efavirenz by crushing it and mixing it with other substances and then smoking the mixture to get high.

Brain cells

Researchers in Spain have conducted lab experiments with human and rat brain cells and efavirenz. They found that in some cases efavirenz can impair the parts of the cell used to generate energy (called mitochondria). This occurs because efavirenz has apparently injured brain cells in lab experiments. Researchers suspect that this effect of efavirenz may help to explain some of the neuropsychiatric side effects reported.

Bear in mind

For now, all of these different research findings we presented are just that. Scientists have not been able to prove that any of the molecular mechanisms discussed here are indeed the source of efavirenz-related problems that can occur in people.

Doctors have found that efavirenz can be a very useful part of combination anti-HIV therapy when used in the right patients. However, earlier in the summer, a trio of leading researchers in Canada, France and the U.K. reviewed clinical data on efavirenz. Due to a combination of factors—side effects, reduced overall effectiveness compared to newer drugs, concern about the potential for birth defects, and the presence of efavirenz-resistant HIV—they suggested that the time has come to reconsider “the routine use of efavirenz” in high-income countries.

As many HIV treatment options are now available in Canada and other high-income countries, it will be interesting to see if efavirenz will still be widely used five years from now.

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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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