TreatmentUpdate 192

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I ANTI-HIV AGENTS

A. The Quad and changes to assessments of kidney health

In *TreatmentUpdate 191*, we extensively reviewed available data from clinical trials on the Quad. This is the nickname given to a combination of the following four drugs in one pill:

- elvitegravir – an experimental integrase inhibitor
- cobicistat – a drug used to boost and maintain the concentration of elvitegravir in the blood so that once-daily dosing of the Quad is possible
- tenofovir – a popular anti-HIV drug sold under the brand name Viread and found in co-formulations with other drugs under the brand names Truvada, Atripla and Complera
- FTC (emtricitabine) – found in some co-formulations such as Truvada, Atripla and Complera

The Quad is expected to be licensed in the U.S. in August 2012 and in Canada and the European Union in the autumn of 2012.

Focus on the kidneys

The kidneys are two bean-shaped organs near the lower back. These organs filter blood, removing wastes, diverting waste into urine and returning vital substances back to the blood. The Quad contains tenofovir and because tenofovir (and many other drugs and health conditions) can affect the kidneys, monitoring kidney health from time to time is routinely done as part of the care of HIV-positive people, including those who take tenofovir-containing regimens.

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A routine method of assessing kidney health is to calculate the estimated glomerular filtration rate, or eGFR. This relies on a measurement of a waste product called creatinine and one of several equations. Creatinine plays a major role in routine assessments of kidney health because when kidneys become dysfunctional, levels of creatinine in the blood rise. To measure the actual GFR (aGFR), a person's output of urine over 24 hours would need to be collected and later analysed. When performing aGFR assessments, patients receive a non-radioactive substance called iohexol, which is filtered by the kidneys. Iohexol is given intravenously over a few minutes.

In experiments with 54 healthy HIV-negative volunteers (almost evenly balanced between men and women), researchers gave them either cobicistat, ritonavir (Norvir and in Kaletra) or placebo for seven days. Participants had either normal or mildly dysfunctional kidneys.

In analyzing participants' kidney function, researchers found that among cobicistat users there were small decreases in eGFR, (around 10 ml/minute) and small increases in the amount of creatinine in the blood, suggestive of very mild kidney dysfunction. However, when aGFR was assessed, there were no statistically significant changes detected in cobicistat users. This shows that short-term exposure to cobicistat is safe and that eGFR is not a reliable way of assessing kidney health in cobicistat users.

Neither ritonavir nor placebo resulted in any significant changes to kidney function.

Monitoring the kidney health of Quad users will be an important part of their regular care. eGFR is the mainstay of routine kidney assessment, but if exposure to cobicistat alters eGFR in an apparently harmless way, physicians will need other ways of assessing kidney health.

What are doctors to do?

Researchers who conducted phase III clinical trials using cobicistat have suggested that doctors assess the kidney health of Quad users in the following way:

- monitor the amount of sugar in the urine
- monitor the amount of protein in the urine
- check blood samples for levels of phosphorus

These tests are highly specific and abnormal results would strongly suggest kidney dysfunction, particularly if such abnormal results persist.

A long-term view

One clinical trial testing the Quad is called GS-US-236-0102. In this study, researchers are analyzing data from nearly 700 participants who are taking either the Quad or a triple-drug co-formulation called Atripla (efavirenz + tenofovir + FTC). Gilead Sciences is continuing its trial of GS-US-236-0102 for a total of 192 weeks (four years). This study is double blind and placebo controlled—participants will not be told which combination of drugs they are taking until they leave the study. This long-term monitoring will provide important data about the safety of the Quad, as both elvitegravir and cobicistat are new drugs.

Such monitoring is important because cobicistat modestly increases the concentration of tenofovir in the blood. As a result, it is possible that in some people with pre-existing kidney issues caused by co-infection with hepatitis C virus, type 2 diabetes and higher-than-normal blood pressure, tenofovir may accumulate in the filtering apparatus (the tubules) of the kidneys. This could, in theory, result in the malfunctioning of the kidneys' ability to filter and reabsorb substances from the blood.

Special populations

In the trials used to generate data to license the Quad, women comprised only about 10% of participants. Gilead plans future studies to explore the issues of safety and effectiveness in women and people with varying degrees of kidney dysfunction.

Overall

The looming arrival of the Quad will usher in a new, potent and attractive option in HIV therapy. However, regular monitoring will be needed to assess kidney health and the potential for drug-drug interactions. Studies have found the Quad to be as effective as other commonly used therapies. Common side effects with the Quad include mild headache and nausea. Kidney dysfunction occurred in a minority of Quad users and was rarely serious. When it was serious, it was typically in participants with risk factors for kidney dysfunction. Researchers who have reviewed data on the Quad recommend that this product only be used in

patients who have normal kidney function (an eGFR of 70 or more). To ensure maximum absorption, the Quad must be taken with a meal.

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II SIDE EFFECTS AND COMPLICATIONS

A. Understanding sudden cardiac death

The heart is a large muscular pump that helps push blood around the body. The pumping action of the heart is driven by regular waves of tiny electrical currents. When disturbances in the electrical currents of the heart occur, heartbeats can become irregular and in some cases can even stop. When the heart stops beating and pumping blood the brain and lungs are immediately affected. People quickly become unconscious and, if standing, suddenly collapse and stop breathing. There is no pulse because the heart has stopped beating. This is called sudden cardiac death, or SCD.

Not a heart attack

Sudden cardiac death is different from a heart attack. In the latter condition, a blood vessel that brings oxygen-rich blood from the lungs to the heart becomes blocked, perhaps because of a large blood clot. During a heart attack, pain and distress occur yet the heart continues to beat. During SCD, the heart stops beating.

Sudden cardiac death usually occurs without a warning but in some cases the following symptoms may occur:

- unexpected tiredness or lack of energy
- fainting
- dizziness
- chest pain
- shortness of breath

Changes in risk

In general, among HIV-negative people, the risk of SCD is generally very low (0.001% per year) in otherwise healthy teenagers and young adults. After the age of 30, the risk of SCD begins to rise and increases to about 0.1% per year. From this point, the risk gradually increases with age. In people with serious heart disease who are 50 or older, the risk of SCD may be much greater, reaching between 10% and 25% per year.

Focus on the heart

Disturbances in the heart's electrical system are likely to occur in people who have or have had the following conditions:

- heart attack
- coronary artery disease
- abnormally thickened heart muscle (cardiomyopathy)
- abnormal heart valves
- inherited heart disease
- problems with the electrical system of the heart

As sudden cardiac death is linked to cardiovascular disease (CVD), the same factors that place a person at risk for CVD also increase the risk for SCD, as follows:

- a family history of cardiovascular disease
- smoking tobacco
- higher-than-normal blood pressure
- abnormal levels of cholesterol in the blood
- obesity
- diabetes
- insufficient exercise
- excessive intake of alcohol
- age – SCD risk increases with age, particularly among men over the age of 45 and women over the age of 55
- gender – men are between two and three times more likely to experience SCD
- use of stimulants – cocaine and crystal meth

- hyperthyroidism
- an imbalance of nutrients such as potassium and magnesium

Consequences

In cases of SCD, the flow of oxygen-rich blood to the brain stops and a person immediately loses consciousness. Unless the heart quickly resumes its normal rhythm and beats within about 10 minutes, the oxygen-starved brain undergoes serious damage and death occurs. People who survive SCD may show signs of brain damage.

Tests

A common test to monitor heart rhythms is the ECG—electrocardiogram (commonly called a cardiogram). For this non-invasive test, technicians place sensors on the chest and limbs and the ECG can detect abnormalities in the electrical wave produced by the heart.

To find the underlying cause of SCD there are many additional tests that a cardiologist may order, including analyses of blood samples, ultrasound and other scans of the heart and its vessels, and more complex tests of the heart's electrical system. Some tests and procedures used in assessing the risk for SCD and heart disease may be invasive.

Preventing SCD

To help prevent SCD, regular checkups with a focus on screening for heart disease are necessary. Leading a life that is good for your heart is also crucial. For more tips about how to do this, see CATIE's in-depth Fact Sheet on heart health.

Treatment

If a person has a high risk for abnormal heart rhythms or has abnormalities of the heart's electrical system, cardiologists may prescribe drugs. Classes of drugs used to treat abnormal heart rhythms include the following:

- beta blockers
- ACE (angiotensin-converting enzyme) inhibitors
- calcium channel blockers

In some cases, a tiny device called an implantable cardioverter defibrillator (ICD) may be surgically emplaced near the collarbone. The ICD has wires that are connected to the heart. The purpose of the ICD is to monitor the heart's rhythms. It can release tiny electrical signals that adjust the heart's rhythm.

As part of the assessment of the underlying cause of abnormal heart rhythm, if blood vessels that supply the heart with oxygen-rich blood narrow or are blocked, cardiologists may perform coronary angioplasty. In this procedure, a long, thin, flexible tube is inserted into an artery. The end of the tube can inflate like a very small balloon. This opens up the artery. Doctors may also insert a small tube (called a stent) to keep the artery open on a longer basis.

Other surgeries may be performed, including the following:

- coronary bypass surgery
- heart surgery to correct any inherited abnormalities
- heart transplant

B. Sudden cardiac death and HIV

Studies have found that HIV-positive people are at heightened risk for cardiovascular disease—heart attack, stroke and other complications. The reasons for this heightened risk are not clear, but here are some possibilities:

- HIV infection causes the release of chemical signals that trigger inflammation and ultimately weaken blood vessels and may accelerate cardiovascular disease (CVD).
- Surveys have found that there are high rates of tobacco smoking among some HIV-positive people.
- Problems associated with sudden cardiac death (SCD) may be relatively common among HIV-positive people, including pulmonary hypertension, an enlarged heart and abnormal electrical activity in the heart.

The risk for many CVD-related issues appears or grows worse as people age. So, as HIV-positive people live longer because of the effects of potent combination therapy for HIV (commonly called ART or HAART) heart problems may become more of a concern.

Researchers at San Francisco General Hospital reviewed the medical records of nearly 3,000 patients with HIV, searching for cases of SCD.

Among 230 deaths that occurred between the years 2000 and 2009, 13% of deaths were caused by SCD. People who died from SCD, compared to other causes, were more likely to have a history of heart problems.

Study details

The research team reviewed medical records of 2,860 HIV-positive patients from San Francisco General Hospital. All were adults and were enrolled in the study between April 2000 and August 2009.

Researchers reviewed medical records and death certificates. Deaths that occurred "in a hospice or due to overdose, violence, suicide, a cancer or opportunistic infections were excluded" from analysis for SCD, according to the researchers. After these exclusions, there were 230 deaths to analyse.

The average profile of participants was as follows:

- 87% men, 13% women
- age – 39 years
- CD4+ count – 353 cells
- viral load – 13,000 copies/ml
- 21% of participants had undetectable viral load in their blood

On average, they were monitored by the hospital for four years.

Results

Out of a total of 230 deaths, 35 were heart related, of which 30 were caused by SCD.

Other causes of death among patients who died during the study were as follows:

- AIDS-related infections and cancers – 57%
- other natural causes of death (lumped into this category were deaths due to non-AIDS cancers, liver disease and blood poisoning from bacterial infections) – 11%
- overdoses, suicides, unknown causes – 19%
- sudden cardiac death – 13%

Focus on SCD

During the course of the study, the proportion of deaths due to SCD did not increase. However, by 2003 researchers noticed that SCD "was often the leading cause of non-AIDS natural deaths."

The researchers found that "more than half of [participants] had histories of tobacco, alcohol or drug use." All of these could have contributed to poor overall health.

At their last clinic visit before dying, 33% of participants who subsequently died from SCD reported the following symptoms:

- chest pain
- palpitations
- fainting
- shortness of breath

Overall, 83% of participants who subsequently died from SCD were prescribed cardiac medicines. Many also underwent cardiac ultrasound scans, which revealed further heart problems. Cardiograms also showed disturbances in heart rhythms in 60% of participants and uncovered evidence of prior heart attacks in four people.

Comparing deaths

Researchers compared the medical profiles of participants who had SCD with those who died of AIDS-related complications.

People with SCD tended to have higher CD4+ counts (321 cells vs. 87 cells) and lower viral loads (6,000 copies/ml vs. 63,000 copies/ml) compared to those who died from AIDS-related causes.

The researchers found that factors such as ethnicity and gender were not significantly different between people who had SCD and those who died from other causes. People who had SCD were slightly older (49 years) compared to other people who died (45 years).

Importantly, people who died from SCD were significantly more likely to have the following issues:

- previous heart attack
- swollen heart muscles
- weak hearts
- abnormal heart rhythms
- higher-than-normal blood pressure
- abnormal levels of cholesterol in the blood

Factors such as the following affected a similar proportion of patients in each group:

- type 2 diabetes
- chronic kidney disease
- chronic lung disease

The rate of death due to SCD was nearly five-fold greater than expected in a group of HIV-negative people of similar age and ethnicity.

Why these findings?

What are the reasons for this relatively larger rate of SCD in HIV-positive people? Researchers are not certain but they note that among HIV-negative people SCD is associated with heart disease. In the present study, many people who were found to have had SCD had cardiovascular disease risk factors associated with SCD.

More than half of people with SCD had modest CD4+ cell counts (312 cells) and suppressed viral loads. The research team suggests that even "patients on effective ART remain at risk [for SCD]."

The present study was retrospective in nature and designed to assess and document causes of death. The study was not designed to find out why SCD occurred.

Research teams in North America and Western Europe who have also investigated causes of death need to confirm that SCD is elevated among their HIV-positive patients. If this is the case, research into inflammation as a possible underlying cause of SCD may be a useful approach. The potential impact of specific anti-HIV medicines on SCD risk would require a different study.

What to do?

The study authors note that because many participants who developed SCD commonly had cardiac symptoms they encourage health care providers to consider "aggressive primary prevention of cardiovascular disease…in HIV-infected patients, especially those with traditional CVD risk factors."

They also note that implantable cardioverter defibrillators (ICDs) have saved the lives of some HIV-positive people at high risk for SCD. Studies of these devices used in HIV-positive people need to be conducted.

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C. Understanding pulmonary arterial hypertension

Although potent combination anti-HIV therapy (commonly called ART or HAART) is good at suppressing the production of HIV by infected cells, it does not cure HIV infection. Chronic HIV infection causes inflammation that is only partially suppressed by ART. Some researchers worry that prolonged inflammation incited by HIV may slowly degrade the health of the body's organ-systems. This damage caused by chronic inflammation could lead to the intensification of pre-existing health problems or to the onset of new ones. It may, in part, explain the reason for the elevated risk of cardiovascular disease faced by HIV-positive people. Another problem that can occur among HIV-positive people that is probably related to inflammation is pulmonary arterial hypertension (PAH).

Origins

In the time before potent combination therapy for HIV became available, researchers noticed that some HIV-positive people developed PAH. Monkeys infected with simian immunodeficiency virus (SIV), which can cause an AIDS-like disease in susceptible animals, can also develop a PAH-like condition. Some researchers theorize that HIV-infected cells of the immune system that circulate within the lungs release chemical signals that cause inflammation in these organs, particularly in the main blood vessels that supply oxygen-rich blood to the heart. Yet, so far most HIV-positive people do not appear to get PAH.

Risks for PAH

Researchers do not know all the causes of PAH but have found that the following factors affect a person's risk for developing it:

- gender – women are generally at greater risk for PAH than men, the precise reasons for this are not known
- stimulants – use of stimulants such as amphetamine, methamphetamine (crystal meth) and cocaine
- blood clots – people whose blood clots faster than normal
- genes – people whose parents or siblings have PAH

Symptoms

Initially, people with PAH may be symptom free. However, over time, PAH causes abnormalities in the arteries of the lungs, and so the following symptoms can develop:

- shortness of breath
- lack of energy
- chest pain
- swelling in the lower legs

According to surveys in the U.S., historically research suggests that less than 1% of HIV-positive people develop PAH. However, surveys in Western Europe have found greater rates of PAH among people with HIV. The reasons for this difference are not clear.

As part of the medical assessment of patients with potential PAH, a range of tests and procedures can be performed. Initially non-invasive tests may be used, such as an echocardiogram (also known as Doppler echocardiography). Although cardiograms may not yield precise measures of blood pressure within the lungs' arteries, some doctors find them a useful first step before moving on to more invasive procedures.

Treatment

As part of recovery from symptoms of PAH, doctors may prescribe gentle exercise, such as walking. Changes to the diet can also be helpful, such as lowering the intake of sodium. Treatment options for PAH can include the following:

- bosentan (Tracleer)
- ambrisentan (Volibris)
- sildenafil (Revatio)
- tadalafil (Adcirca)

Note that the last two drugs listed above have different brand names and doses when used for the treatment of erectile dysfunction.

In some cases, doctors may recommend heart surgery to maintain a person's quality of life and stabilize the course of PAH until a heart or lung transplant can be performed.

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D. Pulmonary arterial hypertension and HIV

Researchers in Madrid, Spain, investigated almost 400 HIV-positive people for the presence of pulmonary arterial hypertension (PAH) using cardiac ultrasound scans. They found a relatively high rate of PAH—about 10%. PAH was most likely to occur in the following groups of people:

- women
- people co-infected with HIV and hepatitis C virus (HCV)
- people with untreated HIV infection

Study details

Researchers recruited 392 participants at random between October 2009 and April 2011 for this study. The average profile of participants when they entered the study was as follows:

- 83% men, 17% women
- age – 47 years
- duration of HIV infection – 13 years
- CD4+ count – 577 cells
- lowest-ever CD4+ count – 277 cells
- proportion taking ART – 84%
- proportion of ART users with an undetectable viral load – 76%
- HCV co-infection – 29%
- HBV co-infection – 5%

Results

A total of 39 people (about 10% of participants) had a diagnosis of PAH based on echocardiography graded as follows:

- mild – 25 participants
- moderate – 11 participants
- severe – 3 participants

Most participants (30 out of 39) were symptom free and their PAH was graded as mild or moderate. Symptoms in the remaining nine participants were as follows:

- shortness of breath
- chest pain
- fainting

In conducting their analysis, researchers found that factors such as age, length of HIV infection, CD4+ counts (current or lowest ever), duration of ART, presence of type 2 diabetes, smoking tobacco, high

blood pressure and co-infection with HBV were **not** linked to PAH. No specific anti-HIV therapy or class of therapy was associated with PAH. However, the following factors were linked to an increased risk for PAH:

- gender – being female
- having HCV co-infection
- having a detectable HIV viral load

Chronic HCV infection damages the liver, and in cases of cirrhosis (severe liver damage) other research teams have found that PAH can occur, affecting between 4% and 16% of people.

The Madrid team recommends that all HIV-positive patients be evaluated for PAH, particularly those who are co-infected with HCV and also those whose HIV infection remains untreated. Echocardiograms could be an initial non-invasive method of assessing this, although such scans are not wholly accurate.

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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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