In the first 15 years of the AIDS pandemic, the medical focus was on preventing and treating life-threatening infections that were commonly seen in AIDS. In the present era, at least in high-income countries, combination therapy for HIV—called highly active antiretroviral therapy, or HAART—is widely available. This treatment puts HIV disease into remission. And as long as there are no severe co-existing illnesses, researchers expect that HIV positive people who are engaged in their care and treatment will have near-normal life spans.

But as HIV positive people live longer, researchers, doctors and patients wonder about the long-term impact of HIV on an ageing body as well as potential side effects of HIV treatment. In this issue of Treatment Update, we review studies on the health of the kidneys in HIV.

Focus on the kidneys

The kidneys are two organs each about the size of a fist, located on either side of the spine, just below the ribs.

These organs perform many vital functions, such as the following:

- maintaining blood pressure
- converting vitamin D that was made in the skin into its active form, vitamin D₃
- monitoring oxygen levels in the blood and stimulating the bone marrow to produce more oxygen-carrying red blood cells should the need arise
• balancing ions and minerals in the body, such as calcium, potassium, phosphorus and magnesium
• filtering waste materials from the blood

Inside each kidney are millions of cells called nephrons. And inside each nephron are tiny filtering units; each unit is called a glomerulus. Each of these filtering units is made up of a blood vessel wrapped around a collection tube.

Filter, filter
Perhaps the most important function of the kidneys is to filter waste materials from the blood. These are produced from many everyday activities as cells carry out their functions, repair themselves and, in some cases, die. Wastes are also produced when food is broken down to release energy. Cells release their wastes into the blood.

Checking up on the kidneys
Kidney health can be assessed in a number of ways. Perhaps the most common way is a method of assessing how efficiently the glomerulus is able to filter blood. This method is called the glomerular filtration rate, written as GFR. However, because measuring the GFR is cumbersome, time-consuming and expensive, doctors most often order tests to estimate the GFR and the results are the eGFR.

A bit about creatinine
Before we can discuss eGFR we must first give you some background information on a substance called creatinine. This is a waste product produced when muscles are broken down. In healthy people, levels of creatinine in the blood are usually fairly constant. Because creatinine is filtered by the kidneys, levels of this substance in the blood can be used to estimate GFR. Creatinine levels are usually put into one of two formulas named as follows:

• MDRD (modification of diet in renal disease)
• Cockcroft-Gault

MDRD is often used to calculate the eGFR because in addition to factors such as age and gender it can take into account race. The Cockcroft-Gault formula does not take into account a person’s race.

Sometimes, often for research purposes, levels of a protein called cystatin C are used to estimate eGFR (more about this protein later).

Test results
eGFR results are expressed as a number followed by the units mL/min (for example, 90 mL/min). In most cases, people with healthy kidneys will usually have a normal eGFR result of 90 or higher. However, lower values for eGFR may stress kidney damage as indicated below:

• An eGFR between 89 and 60 suggests mild kidney disease.
• An eGFR less than 60 for three consecutive months suggests chronic kidney disease.
• An eGFR between 30 and 59 suggests a moderate degree of kidney damage. If this persists, low levels of red blood cells and thin bones can occur. Low levels of red blood cells can lead to fatigue and fewer minerals in the blood can affect the strength of bones.
• An eGFR that falls between 15 and 29 suggests severe kidney damage. Artificial filtration of the blood—dialysis—is needed to remove wastes from the body.
• When the eGFR falls below 15 the kidneys have largely stopped working and without dialysis or a kidney transplant death can occur. In Canada, transplanted organs are not available to HIV positive people.

Other tests
In addition to eGFR, other tests are useful when trying to assess the risk for or the presence of kidney dysfunction. These tests can include the following:

• Blood pressure
  Because the kidneys regulate blood pressure, having high blood pressure may be a sign of kidney damage. Prolonged periods of high blood pressure can also damage the kidneys.

• Urine tests
  Normally, the kidneys send wastes to the urine and reabsorb useful nutrients. However, damaged kidneys can inadvertently leak key nutrients, such as the protein albumin, into the urine. When a small amount of albumin is detected in the urine, this is called microalbuminuria. If the kidneys continue to degrade and more protein leaks into the urine, this is called proteinuria.

• Kidney biopsy
  A small amount of kidney tissue is removed for analysis.
• Scans
  Depending on the situation, ultrasound, CAT scans or MRIs may be taken to assess kidney health.

**Signs and symptoms**
In early cases of kidney damage there may be no noticeable symptoms. However, as the kidney degrades the following may occur:

• increased or decreased urination
• decreased appetite
• nausea
• vomiting
• muscle cramps
• itchiness
• difficulty concentrating

**Risk factors for kidney disease**
There are a number of factors that increase the risk of developing kidney damage, including the following:

• Uncontrolled HIV infection
  This virus infects the cells of the immune system, but it also infects and weakens the kidneys. Moreover, some researchers suggest that the kidneys can become a reservoir for HIV, a place where new copies of HIV are regularly made inside HIV-infected cells. Taking anti-HIV treatment so that levels of HIV fall to very low levels helps reduce viral damage to this organ.

• High blood sugar and high blood pressure
  Diabetes and high blood pressure are the leading causes of kidney disease in HIV negative people and likely play a major role in HIV positive people.

• Race
  For reasons that are not clear, people of African ancestry are at increased risk for HIV-related kidney damage.

• Age
  As people (and their kidneys) age, these organs become less effective at filtering wastes from the body.

The good news is that diabetes, high blood pressure and HIV viral load can often be controlled, which reduces the risk of kidney disease.

**B. Drugs and the kidneys**
As the kidneys help to filter wastes (including drugs) from the blood, the tiny filtering units, each of which is called a glomerulus, get exposed to high concentrations of drugs as part of the filtering process. As a result, the glomerulus is vulnerable to drug toxicity.

Also, the kidneys normally receive about 25% of the blood supply, and as blood carries medicines, these can also accumulate in the kidney.

Therefore, a huge range of drugs has the potential to cause kidney damage. The types of damage to kidney cells (nephrons) and their filtering tubes can vary, but here are some examples of the results of drug toxicity on nephrons:

• reduced energy output
• excessive production of damaging molecules
• damage to the surface of cells
• dehydration
• death of the tubes used by the kidney to eject wastes or reabsorb nutrients

In some cases, signs or symptoms of kidney injury will at first be subtle.
**Drugs and the kidneys—caution**

Below is a list of some drugs and herbs with the potential to cause kidney injury; in some cases this problem is rare. In the case of the listed herbs, kidney toxicity can be severe and readers should avoid using the specific herbs or ingredients listed. For the listed drugs, in general, most otherwise-healthy HIV positive people should not have severe or life-threatening kidney problems as a result of taking these drugs. However, some of these drugs are used in very ill people, and in such cases kidney toxicity can occur. Note that this list is not exhaustive:

- **Antibiotics:** Several groups, or classes, of antibiotics have the potential to injure the kidneys, including the following:
  - aminoglycosides – amikacin, gentamycin, spectinomycin
  - cephalosporins – ciprofloxacin (Cipro)
  - sulfa drugs – Bactrim/Septra (trimethoprim-sulfamethoxazole)
- **Antidepressants** – lithium
- **Antifungal drugs** – amphotericin B
- **Antiseizure drugs** – valproic acid
- **Antiviral drugs** – acyclovir or valacyclovir, adeovir (Hepsera), cidovir (Vistide), tenofovir (Viread and in Truvada and Atripla), foscarnet (Foscavir) and indinavir (Crixivan)
- **Chinese herbs** that contain aristolochic acid. These are found in herbs of the Aristolochia species. Some herbal remedies that contain aristolochic acid include Mu-Tong and Fangchi.
- **Blood pressure medicines** such as ACE inhibitors (angiotensin converting enzyme), including: benazepril, cilazapril, fosinopril, lisinopril, quinapril, ramipril (Altase), perindopril, trandolopril
- **Illicit drugs** – cocaine, heroin
- **Immunomodulators** – interleukin-2 and interferon (Pegasys and Peginteron)
- **Lipid-lowering medicines** – rosuvastatin (Crestor)
- **Pain medications** – acetaminophen (Tylenol), ibuprofen (Advil, Motrin) and some drugs used to treat inflammation
- **Transplant medicines** – cyclosporine, tacrolimus

Because initial kidney injury can be mild, regular monitoring of the kidneys is necessary when these drugs are prescribed. It is important to stay hydrated, drinking at least a litre of healthful fluids—water, juice, herbal teas—each day. Liquids containing alcohol or caffeine increase the need for drinking more water.

**REFERENCES:**


**C. HIV and the kidneys – a look over time**

To get an idea of what effect HIV infection has on the kidneys, researchers in the United States and European Union have been conducting studies. One American study is called FRAM—Fat Redistribution and Metabolic change in HIV infection. Researchers with this study have been monitoring the health of HIV positive and HIV negative people for several years. During this time, study participants have physical examinations, blood tests, X-ray scans and so on.

A recent analysis of the FRAM database focused on the relationship between kidney health and HIV viral load. The findings suggest that HIV infection can degrade the kidneys and that reducing viral load as much as possible helps to improve kidney health.

**Study details**

The study team compared health-related information collected over five years on 337 HIV positive people and 230 HIV negative people. Our report will focus on the changes in HIV positive people.

At the start of the study, the average profile of participants was as follows:

- 32% female, 68% male
- CD4+ count – 400 cells
- 45% had an undetectable viral load
- 88% were taking HAART
- 43% smoked tobacco
- estimated glomerular filtration rate (eGFR) – 87
Anti-HIV drugs
Two anti-HIV drugs are generally thought to have the potential to cause kidney damage—indinavir (Crixivan) and tenofovir (Viread). In high-income countries, indinavir is seldom prescribed anymore. However, tenofovir is a widely prescribed drug. Despite its wide use in the FRAM study, tenofovir exposure was not linked to declining kidney health.

People who used the anti-HIV drug saquinavir (Invirase) had modest improvements in eGFR.

The study team encourages other researchers to use eGFR and understand its relationship not only on kidney health but cardiovascular disease as well.

REFERENCE:

D. Cystatin C for monitoring kidney health
Although the level of creatinine in the blood is often used to estimate the glomerular filtration rate (eGFR)—and thereby kidney health—creatinine may not always be the ideal substance to use for this purpose.

Creatinine is produced when muscle cells break down, therefore, creatinine levels are dependant on the amount of muscle in the body. Also, creatinine and eGFR calculations can be affected by other factors such as posture, thyroid disease, pregnancy, exercise, blood sugar levels and so on. As a result, researchers have sought another substance with levels that are more stable in the blood, which can be used to estimate eGFR. That substance may be cystatin C.

About cystatin C
Cystatin C is a protein produced by many of the body’s cells. It helps to protect connective tissue from breaking down and may help protect the body from infection.

Under normal conditions, cystatin C levels in the blood are relatively stable, particularly under conditions where creatinine is not. Moreover, cystatin C may be particularly useful in attempting to assess cases of early or subtle kidney damage when using creatinine levels cannot reveal this damage.
Cystatin C may also have other uses—high levels of this protein in the blood have been linked to an increased risk of stroke, heart attack and death. This is because high cystatin C levels suggest that inflammation is taking place, inflammation that can damage whole organ-systems.

Cystatin C measurements may have multiple potential uses, but in this issue of Treatment Update we focus on its use for estimating GFR.

REFERENCES:

E. Comparing viruses – HIV and hepatitis C in mostly men

In high-income countries today, HIV is most commonly transmitted in the following ways:

- unprotected sex
- sharing equipment for substance use

Hepatitis C virus (HCV) is also transmitted in similar ways, particularly among HIV positive men. Co-infection with both of these viruses can affect the immune system and liver. Researchers have wondered what impact co-infection might have on the kidneys. To find out more about this issue, doctors in France conducted a study. Their findings suggest that HCV co-infection can make kidney health worse.

Study details

In the span of nine years 100 people underwent a kidney biopsy because of various complaints at the Pitie-Salpetriere Hospital in Paris. Researchers there reviewed the health records of these people and were able to perform an analysis of their kidney health based on their viral infection history.

The average profile of participants when they first sought medical care was as follows:

- 33% female, 67% male
- age – 50 years
- 55% of participants were White and no further ethno-racial information was available
- 50% of participants had high blood pressure
- most patients had chronic kidney disease, with an average eGFR of 51

Participants were divided into the following three groups:

- HIV positive – 40 people
- HCV positive – 30 people
- both infections – 30 people

Results

Biopsies of the kidneys revealed that some participants had kidney inflammation, particularly the parts of the kidney that filter blood. Inflammation of this part of the kidney is called MPGN (membranoproliferative glomerulonephritis).

MPGN can occur because antibodies get deposited in the membranes of the filtering units of the kidney—the glomerulus. These membranes help to filter wastes out of the blood into the urine. MPGN can happen in some cases of chronic viral infections. The proportion of people with MPGN in each of the three groups was as follows:

- HIV positive – 34%
- HCV positive – 9%
- both infections – 57%

Biopsies revealed that the blood vessels in the kidneys of some of the people with HIV mono-infection were prematurely stiffened, suggesting cardiovascular disease.

When the kidneys are severely injured, wastes can build up in the body. To help remove waste materials artificial filtration of the blood can be done. This is called dialysis. Only a small number of people needed this procedure, as follows:

- HIV positive – 6 people
- HCV positive – 6 people
- both infections – 5 people

Not all people co-infected with HCV and HIV received treatment for these infections in the French study. However, those co-infected people who were treated had their kidney health improve.
Deaths
Twenty-one people in this study subsequently died, most of whom had either HCV or HCV and HIV. Participants who had MPGN and HCV infection were at heightened risk of death. Other factors that played a role in contributing to the death of HCV-HIV co-infected people were as follows:

- delays in getting a kidney biopsy
- being relatively young
- having a diagnosis of MPGN

Aces
Medicines called ACE-inhibitors (angiotensin-converting enzyme) are used to reduce blood pressure and were commonly prescribed to participants along with lipid-lowering medications called statins. Neither group of drugs seemed to have any negative impact on participants’ survival.

The factors statistically linked to death (in general) in this study were as follows:

- HCV-HIV co-infection
- having water retention

This latter problem occurs when the kidneys are not able to flush water out of the body.

The findings from this study highlight the kidney-damaging potential of HCV infection and the need to help HCV positive people engage in and access the care that they need. The French study was done with a group made up mostly of males. Our next report focuses on co-infected women and the impact HCV might have on their kidney health.

REFERENCE:

F. The kidneys and hep C in women
Historically, most studies in HIV research and treatment have been done using male volunteers. As a result, the precise impact of HIV and many HIV medicines on the health of HIV positive women may not be clear or may take a long time to uncover. In an attempt to begin to resolve this situation, researchers in the U.S. established the Women’s Interagency HIV Study (WIHS). This study enrolled HIV positive women as well as women at high risk for this infection. Researchers noted the effects of HIV infection and, later, anti-HIV drugs on the women over a period of years. Health-related information collected on the women was entered into the WIHS database.

Recently, researchers completed an analysis of the impact of HCV co-infection on the kidney health of women in WIHS. Their findings suggest that in some HIV positive women, HCV co-infection increased the risk of kidney damage.

Study details
Researchers analysed information on 2,684 HIV positive women, 945 (35%) of whom were co-infected with HCV. On average, the HCV co-infected women were described in this way by the research team:

“They were more likely to be older, African American, poor and drug users” at the time they entered the WIHS.

Results
At the start of the study, about 8% of the co-infected women had an eGFR of about 60, suggesting that they had chronic kidney disease (CKD). Moreover, co-infected women were twice as likely to have CKD as women who had HIV only.

Women who entered the study with CKD (an eGFR of less than 60) continued to have detectable kidney damage over the next five years. What’s more, with each passing year their eGFR continued to fall, suggesting that CKD grew worse. On average, eGFRs fell by 5% each year among these women.

Even when researchers took into account many factors, they still found that having HCV co-infection was statistically a more powerful predictor of declining kidney health over time than any of the following factors:

- illicit substance use
- diabetes
- high blood pressure
- CD4+ counts
- HAART use
- HIV viral load

The findings from this study should not be entirely surprising—larger studies of HCV positive people who don’t have HIV have found similar results.
HCV infection might play a role in declining kidney health through the following ways:

- HCV could damage the membrane used in the filtering units of the kidney.
- HCV could accelerate kidney injury caused by HIV, diabetes or hypertension, which are likely pre-existing conditions in some people with HCV.

The findings from the WIHS study need to be confirmed and extended in other co-infected women.

REFERENCE:

H. A large study looks at tenofovir and kidney health

Researchers in the United Kingdom recently conducted a large review of health records at two major HIV treating centres. Over a period of eight years their findings suggest that, for the most part, tenofovir (Viread) is a safe drug for the kidneys. However, tenofovir was associated with kidney damage among a subset of patients. The kidney damage cleared when the patients stopped taking the drug. Factors that placed tenofovir users at risk for kidney dysfunction are discussed later in this report.

Study details
Over a period of eight years, data from 3,439 HIV positive people (28% female, 72% male) who sought care were collected at the study hospitals in London and Brighton. Below are the results from an analysis of that data.

Results
Among 843 people who took tenofovir during the study, 21 (or 2.5%) developed chronic kidney disease (CKD).

Although four tenofovir users died during the study period, this drug was not linked to their demise.

Risk factors
Most people who take tenofovir do not develop any kidney problems, so the doctors were curious as to what factors these people might have had that made them susceptible to kidney disease. Among patients with pre-existing CKD (eGFR less than 60), tenofovir appeared to accelerate the decline of their kidneys. Among patients without...
pre-existing CKD, here is what the doctors found that likely played a role:

- being at least 50 years of age
- having mild kidney dysfunction (an eGFR greater than 60 but less than 90) before starting tenofovir
- having had prolonged HIV infection (for about 10 years)

This last point is interesting because it suggests the possibility that HIV itself may have played a role in affecting their kidney health prior to taking tenofovir.

The research team proposes that because the kidneys of these patients were not completely functional they could not rid the body of tenofovir, and so levels of this drug accumulated. In some cases, the doctors reduced the tenofovir dosage so that the eGFR could improve.

The study team noted that the results from this study “underscore” the need for monitoring kidney health, perhaps as soon as HIV positive people enter the medical health care system. Moreover, the researchers add that in people with certain features (such as diabetes, being 50 years or older, high blood pressure) perhaps frequent monitoring of eGFR and adjustment of tenofovir dosage may be necessary.

REFERENCE:
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Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.
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