TreatmentUpdate 195

Vol. 25, No. 1
February 2013

Available online at
www.catie.ca/en/treatmentupdate

Contents

I COMPLICATIONS AND SIDE EFFECTS

A. Aging, HIV and the possible effect of nukes

In high-income countries such as Canada, Australia and the U.S. and in regions such as Western Europe, huge advances have been made in the treatment of HIV disease. Researchers increasingly expect that a young person who is diagnosed today and who initiates potent combination anti-HIV therapy (commonly called ART or HAART) and who has minimal co-existing health conditions should have several additional decades of life expectancy.

The combinations of therapies available for the initial treatment of HIV are plentiful. Furthermore, pill taking has been simplified by the availability of the co-formulation of several drugs into one pill, creating an entire regimen in a single tablet. Such single-tablet regimens need only be taken once daily. However, things were not always this way.

A look at the past

Initial treatment for HIV infection, when it became available in the late 1980s, consisted of a single drug—the nuke (nucleoside reverse transcriptase inhibitor) AZT (zidovudine, Retrovir)—given at high doses and taken every four hours. Such a regimen frequently caused headache, nausea, vomiting and damaged the bone marrow.

produced by

CATIE
Canada's source for HIV and hepatitis C information

555 Richmond Street West, Suite 505
Box 1104
Toronto, Ontario M5V 3B1 Canada
phone: 416.203.7122
toll-free: 1.800.263.1638
fax: 416.203.8284
www.catie.ca
charitable registration number: 13225 8740 RR

In the early 1990s, other anti-HIV drugs in the same class became available, including the following nukes:

- ddC (zalcitabine, Hivid)
- ddI (didanosine, Videx)
- d4T (stavudine, Zerit)

These three drugs, commonly called d-drugs, initially appeared to be better tolerated but soon showed their own side effects, such as peripheral neuropathy (painful nerves in the hands, feet and legs). ddC is no longer manufactured and treatment guidelines in high-income countries now discourage the use of d4T and ddI.

In 1996, a new class of anti-HIV drugs became available—protease inhibitors (PIs). When used in combination with nukes, the results were dramatic. For the first time in the history of the AIDS pandemic, people showed sustained recovery from AIDS-related infections.

However, shortly after HAART became available, reports emerged of a strange syndrome of changes in body shape sometimes associated with the loss of the fatty layer just under the skin. This loss of fat, called lipoatrophy, affected all parts of the body but its effect on the face could become most distressing.

Initially, because PIs were the latest class of anti-HIV therapy, they were suspected as the culprits. However, a few years later, researchers began to realize that exposure to d4T and, to a lesser extent, AZT, was linked to lipoatrophy. Today, drugs such as d4T and AZT are generally not recommended as first-line therapy in high-income countries.

Nukes today

In the current era, nukes remain the backbone of many regimens. Nukes commonly used today include the following combinations:

- abacavir + 3TC – sold as a fixed-dose formulation called Kivexa (or Epzicom) and also found in Trizivir
- tenofovir + FTC – sold as a fixed-dose formulation called Truvada and also found in other combinations such as Atripla, Complera and Stribild

A lingering sense of caution

Decisions about starting therapy for HIV infection have always been challenging; both doctors and their patients have weighed the risks and benefits, as well as a person's ability to take HIV medicines exactly as directed for many years. In the current era, with safer, simpler therapies and more results from clinical trials, the risk–benefit ratio has swung strongly in favour of very early initiation of therapy. The most recent version of the U.S. Department of Health and Human Services' (DHHS) HIV/AIDS Treatment Guidelines recommends early therapy for all HIV-positive people, for two reasons, as follows:

- At the level of the individual, early treatment can help preserve the immune system and improve health.
- From a public health point of view, treating more HIV-positive people reduces the amount of HIV in their blood, other tissues, and genital fluids. The result is decreased sexual infectiousness. As a result of this reduced infectiousness, at the level of a large urban area or region, widespread use of ART can help to reduce new cases of HIV transmission. This approach of treating people to reduce their infectiousness is called TasP—treatment as prevention.

Despite the general tolerability and safety of Kivexa and Truvada, some HIV-positive people and their doctors remain somewhat wary of nukes in general, given their checkered history, and wonder about the potential of these drugs for causing new, unknown side effects. This latter concern is increased as HIV-positive people age and need to take multiple medications, heightening the potential for drug interactions and side effects.

Emerging research suggests the possibility that nukes can affect the energy-producing parts of cells (mitochondria). However, nuke combinations commonly used in the initiation of therapy today have not been proven to cause mitochondrial damage that is directly linked to the ill health of ART users.

Aging and HIV

Some researchers have found hints of apparently accelerated aging in some HIV-positive people. Specifically, some organ-systems, such as the brain, heart, blood vessels and bones, appear to have aged more quickly than they should.

The cause of this apparent aging is not clear.

If premature or accelerated aging does exist in HIV infection, there may be several potential causes affecting different people, including the following:

- long-term exposure to specific proteins produced by HIV-infected cells
- higher-than-normal levels of inflammation, which accompanies chronic viral infections such as HIV
- substance use
- tobacco smoking
- co-infection with other germs, such as members of the herpes virus family—CMV (cytomegalovirus) and EBV (Epstein-Barr virus)

The immune system and aging

Several research teams have found that, if left untreated, HIV infection does prematurely age the immune system. HIV appears to cause this by repeatedly activating the immune system and producing inflammation. This virus also appears to cause complex and poorly understood changes to the immune system shortly after it enters the body.

ART greatly reduces HIV-related inflammation but cannot entirely eliminate it. Prolonged exposure to higher-than-normal levels of inflammation is associated with many chronic illnesses and it is possible that such inflammation over the long-term may play a role in reports of accelerated aging seen in some HIV-positive people in studies. However, it is important to bear in mind that exposure to unhealthy behaviours—particularly tobacco smoking—also causes inflammation. Separating all the positive drivers of accelerated aging in HIV-positive people will not be easy and will require many studies, some of them quite expensive and daunting in their complexity.

Much caution needed

A research team in Australia has been exploring the theory that nukes somehow contribute to the apparent acceleration in aging in HIV-positive people. Their work, conducted in complex laboratory experiments on cells from HIV-negative and HIV-positive people suggests the possibility that the drug tenofovir (Viread) may accelerate the aging of the immune system. However, we urge our readers to treat this finding with a great deal of caution, if only because the results from the Australian experiments are not definitive. Furthermore, due to built-in limitations of their study's design (it is cross-sectional in nature), questions remain about the significance of their findings. Next up, we will explore some of the issues related to the Australian study.

REFERENCES:

1. Boasso A, Royle CM, Doumazos S, et al. Overactivation of plasmacytoid dendritic cells inhibits antiviral T-cell responses: a model for HIV immunopathogenesis. *Blood*. 2011 Nov 10;118(19):5152-62.

2. Herbeuval JP, Nilsson J, Boasso A, et al. HAART reduces death ligand but not death receptors in lymphoid tissue of HIV-infected patients and simian immunodeficiency virus-infected macaques. *AIDS*. 2009 Jan 2;23(1):35-40.

3. Bestilny LJ, Gill MJ, Mody CH, et al. Accelerated replicative senescence of the peripheral immune system induced by HIV infection. *AIDS*. 2000 May 5;14(7):771-80.

4. Leeansyah E, Cameron PU, Solomon A, et al. Inhibition of telomerase activity by HIV Nucleos(t)ide Reverse Transcriptase Inhibitors: a potential factor contributing to HIV-associated accelerated ageing. *Journal of Infectious Diseases*. 2013; *in press*.

5. Payne BA, Wilson IJ, Hateley CA, et al. Mitochondrial aging is accelerated by anti-retroviral therapy through the clonal expansion of mtDNA mutations. *Nature Genetics*. 2011 Jun 26;43(8):806-10.

6. Helleberg M, Afzal S, Kronborg G, et al. Mortality Attributable to Smoking Among HIV-1-Infected Individuals: A Nationwide, Population-Based Cohort Study. *Clinical Infectious Diseases*. 2013; *in press*.

7. Rasmussen LD, Kessel L, Molander LD, et al. Risk of cataract surgery in HIV-infected individuals: a Danish nationwide population-based cohort study. *Clinical Infectious Diseases*. 2011 Dec;53(11):1156-63.

8. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clinical Infectious Diseases*. 2011 Dec;53(11):1120-6.

9. Pathai S, Lawn SD, Weiss HA, et al. Increased ocular lens density in HIV-infected individuals with low nadir CD4 counts in South Africa: evidence of accelerated aging. *Journal of Acquired Immune Deficiency Syndromes*. 2013; *in press*.

10. Smith RL, de Boer R, Brul S, et al. Premature and accelerated aging: HIV or HAART? *Frontiers in Genetics*. 2012;3:328.

11. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS*. 1998 May 7;12(7):F51-8.

12. van der Valk M, Gisolf EH, et al. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. *AIDS*. 2001 May 4;15(7):847-55.

13. Cohen S, Janicki-Deverts D, Turner RB, et al. Association between telomere length and experimentally induced upper respiratory viral infection in healthy adults. *JAMA*. 2013 Feb 20;309(7):699-705.

B. Tenofovir and telomeres – is there a link?

Chromosomes, found in the centre of our cells, are the structures that house our genetic information (genes). The ends of the chromosomes are called telomeres. Every time a cell divides in two to make a copy of itself, the telomeres become slightly shorter. Over time, as people age, researchers have found that their cells have shortened telomeres compared to those of younger people.

Shrinking telomeres in the lab

In lab experiments, cells with shortened telomeres do not function as well as cells with longer telomeres.

Researchers have found shortened telomeres in the following groups of people when they examined cells of the immune system:

- HIV-positive people who were **not** taking potent combination anti-HIV therapy (commonly called ART or HAART)
- people with other chronic viral infections, such as those caused by members of the herpes virus family—CMV (cytomegalovirus) and EBV (Epstein-Barr virus)
- people with certain inflammatory conditions, such as rheumatoid arthritis and type 1 and 2 diabetes
- some people who developed cancer

Why are shortened telomeres a problem?

Every time you have an infection, inflammation occurs and cells of the immune system are activated and mobilized. T-cells divide several times, forming large numbers of cells to contain and fight the infection. Every time T-cells in the blood divide to form new cells, their telomeres become shorter and these cells become less effective at doing their job of protecting the body from infections and cancers.

With short-term viral infections, telomeres do not significantly shrink in T-cells because such cells can produce an enzyme (called telomerase) that helps maintain the length of telomeres. However, over time, the effectiveness of telomerase wanes as people age and so their telomeres shorten.

Shortened telomeres, HIV and nukes

Telomerase contains a small amount of an enzyme called reverse transcriptase (RT). This enzyme is also used by HIV-infected cells. Nukes (nucleoside reverse transcriptase inhibitors) and non-nukes interfere with RT. Therefore, some researchers think that nukes (and possibly non-nukes) interfere with telomerase and its ability to maintain the length of telomeres in cells of the immune system, particularly CD8+ cells. Such cells are the body's main means of fighting virus-infected cells and tumours.

Results—Lab experiments

The Australian team obtained blood samples from HIV-positive participants who were taking ART containing the following nukes:

- 3TC (lamivudine), also found in Kivexa and Trizivir
- tenofovir and FTC (Truvada), also found in Atripla, Complera and Stribild
- abacavir (Ziagen), also found in Kivexa and Trizivir
- AZT (zidovudine, Retrovir), also found in Combivir and Trizivir

The researchers tested varying concentrations of these nukes in cultures of immune cells and found that all drugs inhibited the enzyme telomerase. However, tenofovir was the only nuke to do so at concentrations that can be achieved with oral use. Furthermore, cells grown in the lab in the presence of tenofovir had shortened telomeres.

Results—PEP and telomeres

In cases of possible exposure to HIV, doctors can prescribe a combination of anti-HIV drugs that is taken for 28 consecutive days. This is called post-exposure prophylaxis (PEP). Generally, if PEP is taken within 72 hours of exposure to HIV, it can help to contain the virus and help keep the person from becoming infected. PEP combinations vary from one region to another but generally consist of between two and three anti-HIV agents.

The Australian team collected blood samples before, during and after PEP from 11 HIV-negative people who had taken two of the following nukes:

- tenofovir
- FTC
- 3TC
- AZT

Additionally, some participants took the protease inhibitors lopinavir and ritonavir, sold as a fixed-dose combination pill called Kaletra.

Technicians found that there were no significant differences in telomere length before, during and after PEP. This suggests that short-term exposure to nukes does not have a significant effect on telomeres.

A note on children

In a separate study, Canadian researchers led by Hélène Côté, PhD, in British Columbia, have investigated the impact of nukes on the telomeres of children (both HIV positive and HIV negative) born to HIV-positive mothers and compared them to telomeres of children born to HIV-negative mothers. They found that, overall, there were no differences in telomere length. For babies exposed to nukes during their mother's pregnancy, this confirms the findings from the Australian team that short-term exposure to nukes does not affect telomere length.

The team later assessed telomere lengths in HIV-positive children up to 19 years of age. They found that those children who had detectable viral loads tended to have shorter telomeres. This suggests that HIV itself, rather than ART, may have shortened the telomeres.

Results—Experiments with HIV-positive people

Back to the Australian study: Researchers obtained cells of the immune system from 36 HIV-positive ART users. These participants had been taking ART for at least a year and during that time their viral load was less than 50 copies/ml. Researchers also obtained cells of the immune system from 42 healthy HIV-negative people of similar age to the HIV-positive group.

The researchers found that levels of telomerase were reduced in the HIV-positive group. Furthermore, telomeres were significantly shortened in the cells of HIV-positive people.

Researchers also found that older HIV-positive people had shorter telomeres compared to HIV-negative people of the same age.

Making sense of the findings

1. Due to built-in limitations of the study's design (it was cross-sectional in nature), the Australian researchers were **not** able to prove that exposure to nukes, particularly tenofovir, was the principle cause of shortened telomeres found in cells of the immune systems of HIV-positive people.
2. In some experiments, the number of samples tested was relatively small, so these results require confirmation in another study.
3. The Australian researchers focused on telomere length. However, tests are required to prove that shortened telomeres in ART users have an effect, such as a reduced capacity of the immune system's cells to carry out their functions. Such assessments were not done by the researchers.
4. The cells of the immune system that were tested (mostly T-cells) were from what immunologists call the periphery—the blood. The vast majority of the body's T-cells are found in lymph nodes and lymph tissues and not in the blood. Moreover, T-cells in the blood are often at the end stages of their life cycle and may not be fully functional.

   A more interesting (and time-consuming, expensive and, for volunteers, somewhat painful) experiment would have been to assess telomere length using cells of the immune system taken from lymph nodes and tissues, perhaps even the bone marrow or thymus gland. Cells from such locations would be more likely to undergo replication, so telomere length would be very important for these cells.
5. The study did not take into account certain other factors in participants that could have shortened telomeres, such as the following:
   - the level of immune activation
   - co-infection with members of the herpes virus family, such as CMV and EBV
   - tobacco smoking
   - the amount of exercise they did

Also, the use of cholesterol-lowering medicines (commonly called statins) can have an anti-inflammatory effect. Many HIV-positive people take statins and this could have affected the interpretation of the study's results.

6. Tenofovir has been available in many high-income countries for at least the past decade. It is a common part of ART. If tenofovir were prematurely aging the cells of the immune system, there should be a high proportion of tenofovir users developing cancers and serious, even life-threatening, infections. Yet there are no reports of such problems in long-term ART users arising from exposure to tenofovir. This is perhaps the most obvious and practical counterpoint to the Australian research.

Based on the results of the Australian study and its limitations, there is no data to support not prescribing tenofovir or for HIV-positive people to stop using this important medicine.

For the future

The present Australian study is interesting, but future studies exploring the issue of aging, HIV and exposure to nukes and other medicines need to do at least the following:

- monitor ART users for longer periods
- assess the impact of nukes (and other drugs) on cells that are not at the end stage of their life cycle; such cells are found in lymph nodes, lymphatic tissue, bone marrow, the thymus gland and so on
- examine the effect of anti-HIV drugs on the *functioning* of the immune system's cells
- determine the overall impact of nukes on the aging of cells from other organ-systems such as muscles, nerves, fat, kidneys, liver, etc.
- explore the impact of nukes on the energy-producing parts of cells (the mitochondria) in different organ-systems

REFERENCES:

1. Wong JM, Collins K. Telomere maintenance and disease. *Lancet*. 2003 Sep 20;362(9388):983-8.

2. Bestilny LJ, Gill MJ, Mody CH, et al. Accelerated replicative senescence of the peripheral immune system induced by HIV infection. *AIDS*. 2000 May 5;14(7):771-80.

3. Leeansyah E, Cameron PU, Solomon A, et al. Inhibition of telomerase activity by HIV Nucleos(t)ide Reverse Transcriptase Inhibitors: a potential factor contributing to HIV-associated accelerated ageing. *Journal of Infectious Diseases*. 2013; *in press*.

4. Côté HC, Soudeyns H, Thorne A, et al. Leukocyte telomere length in HIV-infected and HIV-exposed uninfected children: shorter telomeres with uncontrolled HIV viremia. *PLoS One*. 2012;7(7):e39266.

5. Payne BA, Wilson IJ, Hateley CA, et al. Mitochondrial aging is accelerated by anti-retroviral therapy through the clonal expansion of mtDNA mutations. *Nature Genetics*. 2011 Jun 26;43(8):806-10.

6. Hearps AC, Maisa A, Cheng WJ, et al. HIV infection induces age-related changes to monocytes and innate immune activation in young men that persist despite combination antiretroviral therapy. *AIDS*. 2012 Apr 24;26(7):843-53.

7. Effros RB. Telomere/telomerase dynamics within the human immune system: effect of chronic infection and stress. *Experimental Gerontology*. 2011 Feb-Mar;46(2-3):135-40.

8. van Baarle D, Nanlohy NM, Otto S, et al. Progressive telomere shortening of Epstein-Barr virus-specific memory T cells during HIV infection: contributor to exhaustion? *Journal of Infectious Diseases*. 2008 Nov 1;198(9):1353-7.

9. Mirabello L, Huang WY, Wong JY, et al. The association between leukocyte telomere length and cigarette smoking, dietary and physical variables, and risk of prostate cancer. *Aging Cell*. 2009 Aug;8(4):405-13.

10. Alder JK, Guo N, Kembou F, et al. Telomere length is a determinant of emphysema susceptibility. *American Journal of Respiratory and Critical Care Medicine*. 2011 Oct 15;184(8):904-12.

11. Choi J, Fauce SR, Effros RB. Reduced telomerase activity in human T lymphocytes exposed to cortisol. *Brain, Behavior and Immunity*. 2008 May;22(4):600-5.

12. Smith RL, de Boer R, Brul S, et al. Premature and accelerated aging: HIV or HAART? *Frontiers in Genetics*. 2012;3:328.

13. Cohen S, Janicki-Deverts D, Turner RB, et al. Association between telomere length and experimentally induced upper respiratory viral infection in healthy adults. *JAMA*. 2013 Feb 20;309(7):699-705.

14. Willeit P, Willeit J, Mayr A, et al. Fifteen-year follow-up of association between telomere length and incident cancer and cancer mortality. *JAMA*. 2011 Jul 6;306(1):42-4.

C. Research on reducing the impact of aging

It is true that as people age, their immune systems (and other organs) decline. HIV infection itself does apparently prematurely age the immune system. However, potent combination anti-HIV therapy (commonly called ART or HAART) is able to help the immune system partially correct defects caused by HIV infection. This partial correction is sufficient, at least in people who respond to ART, to make many AIDS-related infections now a relatively rare occurrence in high-income countries. It may be that if ART is started very soon after HIV infection occurs, it

could help prevent some of HIV's detrimental effects on the immune system. Specifically, it may be able to prevent HIV-associated aging (shortening telomeres) of the immune system. This is something that needs to be explored in clinical trials.

Staying healthy

One team of scientists that studies aging and telomere length in HIV-negative people notes that "a number of physiologic and/or psychological factors have an impact on overall health as well as effect on telomere length [in cells of the immune system]."

Several studies have found an association between shortened telomeres and the following:

- sustained stress
- major depression
- obesity

A team of Canadian researchers has found that substance use—tobacco smoking and exposure to street drugs—appears to age the immune systems of HIV-positive women.

Observational studies have found that the following factors may lengthen telomeres in HIV-negative people:

- regular exercise
- maintaining a healthy weight
- eating more fruit and vegetables
- quitting smoking
- engaging in activities to help reduce the negative effects of stress, such as meditation and yoga

Emerging research suggests the possibility that eating a diet rich in omega-3 fatty acids (found in relatively large amounts in wild salmon, anchovies and sardines) may play a role in reducing inflammation and maintaining telomere length.

Until studies in HIV-positive people are done, the impact of these activities on their telomeres is not clear. What is clear is that taking ART, engaging in healthy activities (see above list), practising safer sex to reduce exposure to herpes viruses (some studies suggest that such viruses play a role in aging) and, where necessary, getting help and support for recovery from depression and addiction(s) are likely to enable HIV-positive people to stay healthy, reduce their risks for many illnesses and improve their quality of life.

REFERENCES:

1. Weng NP. Telomeres and immune competency. *Current Opinion in Immunology*. 2012 Aug;24(4):470-5.

2. Imam T, Jitratkosol MH, Soudeyns H, et al. Leukocyte telomere length in HIV-infected pregnant women treated with antiretroviral drugs during pregnancy and their uninfected infants. *Journal of Acquired Immune Deficiency Syndromes*. 2012 Aug 15;60(5):495-502.

3. Pawelec G, McElhaney JE, Aiello AE, et al. The impact of CMV infection on survival in older humans. *Current Opinion in Immunology*. 2012 Aug;24(4):507-11.

4. Derhovanessian E, Theeten H, Hähnel K, et al. Cytomegalovirus-associated accumulation of late-differentiated CD4 T-cells correlates with poor humoral response to influenza vaccination. *Vaccine*. 2013 Jan 11; 31(4):685-90.

5. Chen S, Jm de Craen A, Raz Y, et al. Cytomegalovirus seropositivity is associated with glucose regulation in the oldest old. Results from the Leiden 85-plus Study. I*mmunity & Ageing*. 2012 Aug 28;9(1):18.

6. Lichtfuss GF, Cheng WJ, Farsakoglu Y, et al. Virologically suppressed HIV patients show activation of NK cells and persistent innate immune activation. *Journal of Immunology*. 2012 Aug 1;189(3):1491-9.

7. Deeks SG, Verdin E, McCune JM. Immunosenescence and HIV. *Current Opinion in Immunology*. 2012 Aug; 24(4):501-6.

8. Cavanagh MM, Weyand CM, Goronzy JJ. Chronic inflammation and aging: DNA damage tips the balance. *Current Opinion in Immunology*. 2012 Aug;24(4):488-93.

9. Hearps AC, Maisa A, Cheng WJ, et al. HIV infection induces age-related changes to monocytes and innate immune activation in young men that persist despite combination antiretroviral therapy. *AIDS*. 2012 Apr 24;26(7):843-53.

10. Choi J, Fauce SR, Effros RB. Reduced telomerase activity in human T lymphocytes exposed to cortisol. *Brain, Behavior and Immunity*. 2008 May;22(4):600-5.

11. Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences USA*. 2004 Dec 7;101(49):17312-5.

12. Weng NP, Akbar AN, Goronzy J. CD28(-) T cells: their role in the age-associated decline of immune function. *Trends in Immunology*. 2009 Jul;30(7):306-12.

13. Brydon L, Lin J, Butcher L, et al. Hostility and cellular aging in men from the Whitehall II cohort. *Biological Psychiatry*. 2012 May 1;71(9):767-73.

14. Steptoe A, Hamer M, Butcher L, et al. Educational attainment but not measures of current socioeconomic circumstances are associated with leukocyte telomere length in healthy older men and women. *Brain, Behaviour and Immunity*. 2011 Oct;25(7):1292-8.

15. Dowd JB, Bosch JA, Steptoe A, et al. Cytomegalovirus is associated with reduced telomerase activity in the Whitehall II cohort. *Experimental Gerontology*. 2013; *in press*.

16. Lavretsky H, Epel ES, Siddarth P, et al. A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition,

and telomerase activity. International *Journal of Geriatric Psychiatry*. 2013 Jan;28(1):57-65.

17. Farzaneh-Far R, Lin J, Epel ES, et al. Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. *JAMA*. 2010 Jan 20;303(3):250-7.

18. Kiecolt-Glaser JK, Epel ES, Belury MA, et al. Omega-3 fatty acids, oxidative stress, and leukocyte telomere length: A randomized controlled trial. *Brain, Behaviour and Immunity*. 2013 Feb;28:16-24.

D. Risk factors for kidney dysfunction

The immune system is located in an organ called the spleen, the thymus gland, and in small clusters—lymph nodes and lymph tissues—throughout the body. Furthermore, cells of the immune system take up residence in key organ-systems, such as the brain, heart, liver, lungs, kidneys and bones, to help protect them from infection. This widespread distribution of the immune system can have its disadvantages. In the case of germs that attack the immune system, unless the germs are quickly controlled, they inadvertently are spread by cells of the immune system to many parts of the body. This is the case with HIV.

The importance of the kidneys

The kidneys are a pair of bean-shaped, fist-sized organs in the region of the lower back. These vital organs filter waste products from blood, help to produce vitamin D and regulate the level of oxygen-carrying red blood cells.

The kidneys receive a large proportion of the blood (about 20%) pumped by the heart. This flow of blood brings oxygen and nutrients but also waste products to the kidneys. Waste products concentrate in the cells of the kidneys that specialize in filtering blood and reabsorbing nutrients and important substances from the filtered material. As a result of reabsorbing substances from the filtered material, drugs may become concentrated in some parts of the kidney, causing damage. As the amount of drug in the kidney rises, this could also trigger the formation of crystals of the drug. Crystals can act as seeds, attracting more particles of drugs and eventually leading to the formation of stones.

HIV and the kidneys

HIV can infect cells and structures of the kidney. Such infection of kidney cells can occur even in people who are taking anti-HIV therapy and whose viral load in the blood is low. Furthermore, some cells and structures of the kidney appear to act as a reservoir for HIV, allowing this virus to infect cells that produce more HIV. This can happens even when viral load in the blood may be less than 50 copies/ml due to treatment.

Continuous low-level production of HIV in the kidneys likely causes inflammation, which can, over time, slowly degrade the functioning of these vital organs.

In addition to HIV, other conditions or activities can cause kidney dysfunction, including the following:

- higher-than-normal blood pressure
- abnormal lipid levels
- diabetes
- obesity
- tobacco smoking
- hepatitis C virus (HCV)
- injection of street drugs

Additionally, there are medicines that have been associated with kidney dysfunction, such as the following:

- chronic use of NSAIDS (non-steroidal anti-inflammatory drugs) commonly used to treat pain and inflammation – Aspirin, ibuprofen (Advil, Motrin), naproxen (Aleve), celecoxib (Celebrex)
- certain antibiotics – vancomycin and a class of antibiotics called aminoglycosides (such as gentamicin)
- antifungal drugs – amphotericin B
- anticancer drugs – doxorubicin, cis-platinum
- antidepressants – lithium
- transplant drugs – cyclosporine, tacrolimus
- antiviral drugs – intravenous acyclovir, foscarnet, cidofovir (Vistide)
- antiparasite drugs – pentamidine

HIV-positive people who use the drugs listed above and/or have the aforementioned conditions may be at increased risk for kidney dysfunction.

Tenofovir

The drug tenofovir has activity against HIV and hepatitis B virus (HBV). Tenofovir is sold under the brand name Viread and in fixed-dose formulations with other drugs under the following names:

- Truvada – tenofovir + FTC
- Atripla – tenofovir + FTC + efavirenz
- Complera – tenofovir + FTC + rilpivirine
- Stribild – tenofovir + FTC + cobicistat + elvitegravir

Different types of studies

Tenofovir is an effective part of many HIV treatment regimens. In randomized, controlled clinical trials, tenofovir has been found to be generally safe and reports of serious kidney dysfunction were uncommon. However, participants in such trials likely have little or no pre-existing health conditions that place them at increased risk for kidney dysfunction. Once a drug is approved by regulatory authorities, it gets prescribed to a wide variety of patients, some of whom likely have pre-existing health issues. To help doctors understand how effective and safe a drug is outside of a randomized clinical trial, observational studies are generally used. Such studies enroll thousands of participants and monitor them for several years.

Caution needed

A major drawback of observational studies is that while they are good at finding associations between a drug and an effect, they cannot prove that a drug *caused* a particular side effect. Therefore, the results of observational studies, while often headline-grabbing, need to be treated cautiously. Such studies are bedeviled by confounding factors that can cause researchers to inadvertently arrive at incorrect conclusions. Scientists who conduct observational studies are well intentioned and do their utmost to take into account possible confounding factors. Unfortunately, no matter how large an observational study, the research team analysing the data can never be certain that every possible confounding factor has been taken into account.

Observational studies are important but can only serve as a guide to developing further studies of a more robust statistical design to explore important issues.

Our next report examines an observational study that sought to link the use of specific anti-HIV drugs with kidney dysfunction.

REFERENCES:

1. Fierer DS, Klotman ME. Kidney and central nervous system as reservoirs of HIV infection. *Current Opinion in HIV/AIDS*. 2006 Mar;1(2):115-20.

2. Marras D, Bruggeman LA, Gao F, et al. Replication and compartmentalization of HIV-1 in kidney epithelium of patients with HIV-associated nephropathy. *Nature Medicine*. 2002 May;8(5):522-6.

3. Winston JA, Bruggeman LA, Ross MD, et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *New England Journal of Medicine*. 2001 Jun 28;344(26):1979-84.

4. Harris RC, Neilson EG. Chapter 278. Adaption of the Kidney to Renal Injury. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012.

5. Bargman JM, Skorecki K. Chapter 280. Chronic Kidney Disease. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012.

6. Waikar SS, Bonventre JV. Chapter 279. Acute Kidney Injury. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012.

7. Ryom L, Mocroft A, Kirk O, et al. Exposure to antiretrovirals (ARVs) and risk of renal Impairment among HIV-positive Persons with normal baseline renal function: the D:A:D study. *Journal of Infectious Diseases*. 2013; *in press*.

8. Fine DM, Gallant JE. Nephrotoxicity of antiretroviral agents: Is the list getting longer? *Journal of Infectious Diseases*. 2013; *in press*.

9. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS*. 2012 Apr 24;26(7):867-75.

10. Jaffe JA, Kimmel PL. Chronic nephropathies of cocaine and heroin abuse: a critical review. *Clinical Journal of the American Society of Nephrology*. 2006 Jul;1(4):655-67.

E. Kidney injury and anti-HIV drugs – the latest from the DAD study

The DAD study is a very large observational study that has recruited nearly 50,000 HIV-positive participants from Australia, Europe and the U.S. From time to time, DAD researchers undertake analyses of their findings and publish them.

In its latest report, the DAD team analysed data from about 22,000 HIV-positive participants, some of whom saw their kidney health decline

over time. DAD researchers found that, over time, participants who used the following drugs had an increased risk for kidney dysfunction:

- tenofovir (Viread)
- atazanavir (Reyataz) + ritonavir (Norvir)
- lopinavir-ritonavir (Kaletra)

The study's findings are discussed below.

Study details

Researchers scoured the DAD database (currently containing information on about 50,000 HIV-positive people) for participants who initially had normal kidney function when they entered DAD. Normal kidney function was defined as having an estimated glomerular filtration rate (eGFR) of 90 ml/minute or greater. Also, participants had to have at least three subsequent eGFRs in the database so that researchers could see how this assessment changed over time. Using this screening, the research team found 22,603 eligible HIV-positive participants on whom they focused their analyses.

The average profile of participants upon entering the study was as follows:

- gender – 73% men, 27% women
- age – 39 years
- CD4+ count – 440 cells
- HIV viral load – 126 copies/ml
- duration of HIV infection – 5 years
- co-infected with hepatitis B virus – 12%
- co-infected with hepatitis C virus – 12%
- used tobacco – 44%
- higher-than-normal blood pressure – 8%
- diabetes – 3%

Participants were monitored for about five years.

Results—Declining kidney health

About 468 participants (2%) had worsening kidney health over the course of the study. These participants entered the study with an eGFR greater than 90 ml/min but by the end of the study had an eGFR of 70 ml/min or less.

The DAD researchers also found that among participants whose kidney health was declining (as assessed by decreased eGFR results) and whose doctors stopped prescribing the offending treatment, the eGFRs were less likely to continue to fall. Unfortunately, the study was not designed to explore the reversibility of kidney dysfunction; that will need to be done in another study. Still, this finding is a positive sign that perhaps kidney damage caused by some HIV treatments is not permanent.

Reduced kidney function

Taking many factors into account, the length of time that participants spent on treatment with the following drugs was associated with decreased kidney health:

- tenofovir
- atazanavir + ritonavir
- lopinavir-ritonavir

These associations were statistically significant.

Other factors associated with a declining eGFR were as follows:

- increasing age
- being female
- injecting street drugs
- a history of AIDS

Bear in mind

Among healthy HIV-negative people, researchers expect to see a decline in eGFR of about 1.0 ml/min per year. However, in the present study a substantial decrease (about 20 ml/min) was seen in about 2% of participants.

The good news is that the vast majority (98%) of participants did not have a significant decline in the health of their kidneys.

Our next report puts the latest results from DAD into context.

REFERENCES:

1. Ryom L, Mocroft A, Kirk O, et al. Exposure to antiretrovirals (ARVs) and risk of renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *Journal of Infectious Diseases.* 2014; *in press.*

2. Fine DM, Gallant JE. Nephrotoxicity of antiretroviral agents: Is the list getting longer? *Journal of Infectious Diseases.* 2014; *in press.*

F. Putting reports of kidney injury into perspective

The most recent analysis by the DAD team found that declining kidney function was found in about 2% of 22,000 HIV-positive participants who were monitored for five years. This decline, assessed by eGFR (estimated glomerular filtration rate), was linked to use of the following drugs:

- tenofovir
- atazanavir-ritonavir
- lopinavir-ritonavir

What do these findings mean?

It is important to bear in mind that the DAD study had several shortcomings, as follows:

- As mentioned earlier in this issue of *TreatmentUpdate*, DAD is an observational study. Observational studies are good at finding associations but due to built-in design limitations cannot prove that exposure to a particular drug did indeed cause a particular outcome.
- DAD researchers used an older formula (called Cockcroft-Gault) rather than the more modern CKD-Epi formula to calculate eGFR. This may have underestimated the decline in kidney health. Furthermore, researchers were unable to use other, more specific means of assessing kidney health such as levels of phosphorus in the blood or the concentration of protein in the urine.
- Insufficient information on the race-ethnicity of participants was available. This is important, as some HIV-positive people of African descent are at increased risk for kidney dysfunction.

Despite this, there is generally good news for HIV-positive people and their healthcare providers: Only 2% of participants in the DAD study developed kidney dysfunction over five years. This is very reassuring that anti-HIV treatment is safe for the kidneys of most people.

Among the 2% of participants with significantly declining eGFR, here are some issues related to the drugs that DAD identified as possible culprits:

Atazanavir

This drug is similar in structure to an older anti-HIV drug called indinavir (Crixivan). This protease inhibitor was known to increase the risk for kidney stones. In the present study, atazanavir was taken with the drug ritonavir (Norvir), which increases and prolongs the concentration of atazanavir in the blood. Other studies have found that in rare cases atazanavir has been linked to an increased risk of kidney stones and also inflammation of the kidney, so perhaps the DAD findings should not be surprising. It is possible that crystals of atazanavir may have formed in the kidneys of some participants, causing kidney dysfunction. However, further investigation is needed in order to understand why some people develop atazanavir-related kidney problems.

Tenofovir

Previous reports suggest that varying degrees of kidney dysfunction can occur in some HIV-positive people who use this drug. The precise reason(s) for this is not clear. As mentioned previously in this issue of *TreatmentUpdate*, parts of the kidney involved in filtering blood and reabsorbing substances that are later used to form urine may inadvertently build up high levels of tenofovir, causing damage. However, this was not specifically investigated in the DAD study. The research team did note that when doctors detected declining eGFRs in their patients on tenofovir, they replaced this drug with another anti-HIV medicine and kidney health improved. As this particular DAD study was not designed to assess recovery from kidney dysfunction, this finding should be treated as preliminary but encouraging and worthy of further study by the DAD team.

Kaletra (lopinavir-ritonavir)

Researchers outside of DAD who reviewed the study's findings were surprised to find any association between declining kidney function and Kaletra. This medicine has been in use for over a decade in most high-income countries and has been well studied. In its heyday, Kaletra was the most widely used protease inhibitor for HIV treatment with excellent efficacy and "little suggestion of renal toxicity," according to kidney specialist Dr. Derek Fine and infectious disease specialist Dr. Joel Gallant (both are at the Johns Hopkins School of Medicine in the U.S.), writing in an editorial about the DAD study.

Given that this particular DAD analysis used data from participants enrolled in 2004, it is likely that they were prescribed lopinavir-ritonavir because

they had been HIV positive for a prolonged period and were exposed to previous treatment longer than other participants. As a result, prior to starting lopinavir-ritonavir, they likely had weaker kidneys. Untreated HIV infection degrades the kidneys and they may have had fewer cells in the kidneys to filter blood despite having a normal eGFR.

The results of DAD's kidney analysis, particularly with atazanavir and lopinavir-ritonavir, are intriguing but require further investigation with different studies before firm conclusions can be drawn about the impact of these drugs on the kidneys.

What to do?

Both Drs. Fine and Gallant sum up the implications from the DAD report in this way:

- Monitor kidney function in tenofovir users and discontinue tenofovir when possible in patients who "may be experiencing nephrotoxicity."
- Monitoring of kidney health should include not only levels of creatinine in the blood but from time to time assessment of the functioning of the kidney tubules (which concentrate wastes)—including levels of phosphorus in the blood and levels of protein and sugar in the urine. These tests are more focused than mere eGFR and give a better picture of kidney health in users of HIV treatments.
- Monitor kidney function in patients taking atazanavir-ritonavir and "consider switching to an alternative [drug] in those experiencing a decline in eGFR."
- The data in DAD linking the use of lopinavir-ritonavir to kidney dysfunction are very limited so at this time the doctors cannot make firm recommendations.

Perhaps most importantly, the doctors state:

> "We must remember that decline in kidney function can occur over time in HIV-[positive] patients taking other antiretroviral agents, those not being treated with ART at all and in HIV-negative patients. The assumption that such declines are due to drug toxicity is not always correct. An evaluation for other causes is appropriate."

This is an important statement because many factors—including substance use and sexually transmitted infections—can affect kidney health. Indeed, it is noteworthy that participants who had decreasing eGFRs were generally more likely to have higher-than-normal blood pressure and diabetes and smoke tobacco. All three are known risk factors for poor kidney health.

REFERENCES:

1. Ryom L, Mocroft A, Kirk O, et al. Exposure to antiretrovirals (ARVs) and risk of renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *Journal of Infectious Diseases.* 2014; *in press.*

2. Fine DM, Gallant JE. Nephrotoxicity of antiretroviral agents: Is the list getting longer? *Journal of Infectious Diseases.* 2014; *in press.*

3. Rockwood N, Mandalia S, Bower M, et al. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. *AIDS.* 2011 Aug 24;25(13):1671-3.

4. Chan-Tack KM, Truffa MM, Struble KA, et al. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. *AIDS.* 2007 May 31;21(9):1215-8.

5. Lebrecht D, Venhoff AC, Kirschner J, et al. Mitochondrial tubulopathy in tenofovir disoproxil fumarate-treated rats. *Journal of Acquired Immune Deficiency Syndromes.* 2009 Jul 1;51(3):258-63.

6. Waikar SS, Bonventre JV. Chapter 279. Acute Kidney Injury. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine.* 18th ed. New York: McGraw-Hill; 2012.

7. Chen YM, Marcos LA, Liapis H, et al. An unusual cause of membranous glomerulonephritis in a patient with HIV. *International Urology and Nephrology.* 2012 Jun;44(3):983-6.

8. Bani-Hani S, Patel V, Larsen CP, et al. Renal disease in AIDS: it is not always HIVAN. *Clinical and Experimental Nephrology.* 2010 Jun;14(3):263-7.

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.

CATIE (Canadian AIDS Treatment Information Exchange) in good faith provides information resources to help people living with HIV/AIDS and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

We do not guarantee the accuracy or completeness of any information accessed through or published or provided by CATIE. Users relying on this information do so entirely at their own risk. Neither CATIE, nor the Public Health Agency of Canada, nor the Ontario Ministry of Health and Long-Term Care, nor any of their employees, directors, officers or volunteers may be held liable for damages of any kind that may result from the use or misuse of any such information. The views expressed herein or in any article or publication accessed or published or provided by CATIE are solely those of the authors and do not reflect the policies or opinions of CATIE or the views of the Public Health Agency of Canada, nor the Ontario Ministry of Health and Long-Term Care.

Permission to Reproduce

Credits

Writer **Sean Hosein**
Editor **RonniLyn Pustil**

© CATIE, Vol. 25, No. 1
February 2013

ISSN 1181-7186 (print)
ISSN 1927-8918 (online)
CATIE Ordering Centre Catalogue Number ATI-60205E
(*Aussi disponible en français, ATI-60205F*)

Production of this newsletter has been made possible through a financial contribution from the Public Health Agency of Canada.

What CATIE Does

CATIE, Canada's source for HIV and hepatitis C information, is committed to improving the health and quality of life of all people living with HIV/AIDS in Canada. CATIE serves people living with HIV/AIDS, and the people and organizations that support them, by providing accessible, accurate, unbiased and timely treatment information. CATIE provides such information through a comprehensive Web site, a bilingual toll-free phone service, electronic and print publications, a national reference library and workshops and exhibits at conferences across Canada.

CATIE Publications

TreatmentUpdate
CATIE's flagship treatment digest on cutting-edge developments in HIV/AIDS research and treatment. Subscribe to TreatmentUpdate and automatically receive an email notifying you the moment a new issue is available on-line or contact us at 1.800.263.1638 to receive a print subscription.

A Practical Guide to HIV Drug Treatment
The latest on what is known about the various aspects of treatment, including a description of the virus and the immune system, the stages of HIV disease, the tests used to assess health status, and anti-HIV medications.

A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

The Practical Guide series also includes:

- **A Practical Guide to Nutrition**
- **A Practical Guide to Complementary Therapies**
- **A Practical Guide to Herbal Therapies**

The Positive Side magazine
Holistic health information and views for PHAs.

Fact Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

pre*fix
A harm reduction booklet for HIV+ drug users.

Contact CATIE

by e-mail: info@catie.ca
on the Web: www.catie.ca
by telephone: 416.203.7122
1.800.263.1638 (toll-free)
by fax: 416.203.8284
by post: 505-555 Richmond Street W
Box 1104
Toronto, Ontario
M5V 3B1
Canada