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I ANTI-HIV AGENTS

A. The changing picture of HIV

In the mid-to-late 1970s, a small but growing number of relatively young men and women sought care at leading hospitals in Brussels, Cologne, Kinshasa, New York, Oslo, Port-au-Prince, Paris and San Francisco. They were experiencing many of the following symptoms:

- persistently swollen lymph nodes
- fever
- unintentional weight loss
- fatigue
- repeated episodes of diarrhea
- an increasing number of skin lesions
- oral yeast infection (thrush)

The results of blood and other tests suggested that their immune systems were very weak. Subsequently, they all developed life-threatening infections and unusual cancers. Doctors were baffled that previously healthy young people would develop such a strange collection of symptoms and infections. We now call this AIDS.

By 1983, the mystery was partly solved when French scientists found the germ responsible for AIDS from samples of a patient's lymph nodes. We now call this HIV.

Tales of simplicity

Understanding exactly how HIV causes AIDS has proven elusive, even in the present era. Initial theories based on limited evidence suggested that HIV attacked a key cell of the immune system—CD4+ T-cells (or simply, CD4+ cells). Researchers thought that by wiping out these cells HIV paved the way for immune deficiency.

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Information Exchange
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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
<http://www.catie.ca>
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The splendor of complexity

However, with the passage of time it has become clear that HIV does more than attack CD4+ T-cells. This virus also infects several other types of immune cells, such as dendritic cells (which help to amplify the immune response) and macrophages (which help to alert the immune system to invading germs and also attack those same germs and tumours). HIV-infected cells also spew out a range of proteins that confuse and increasingly disable the immune system, perhaps even turning this vital defense system against itself.

Emerging research suggests that HIV infection results in an additional problem—one that can affect many organs/systems—called inflammation.

A virus' touch

It seems that from as early on as the point of first contact—when HIV invades the wet tissue of the anus, penis or vagina—it begins the process of causing deep and lasting changes to the immune system. Increasingly, researchers are realizing that HIV infection triggers the release of high levels of chemical signals that put the immune system into a state of permanent activation. Over the short-term, this activation is generally helpful when mobilizing the immune system against invading germs. However, in the case of HIV, activation helps the virus infect cells.

Prolonged immune activation also has other unintended consequences: It reduces the life-span of vital T-cells and possibly other immune system cells. Beyond the immune system, inflammation, along with exposure to harmful proteins made by HIV-infected cells, probably does the following:

- weakens the kidneys
- accelerates liver injury caused by hepatitis B and C viruses
- damages and inflames blood vessels and hastens the onset of heart disease
- undermines the health of bones, causing them to become thinner

These are just some of the effects of continuous inflammation in the setting of long-term HIV infection. As scientists conduct further research, it is possible that there are other complications as well.

The role of therapy

In high-income countries, highly active antiretroviral therapy (HAART) is widely available. Combination anti-HIV therapy has greatly

reduced deaths from AIDS-related infections and has greatly prolonged survival, at least in people who are engaged in their care and treatment.

HAART works by reducing the production of HIV. In turn, lower levels of HIV allow the immune system to begin repairing itself. Since it suppresses HIV levels, an added benefit of HAART is that inflammation is also reduced. But because HAART does not eliminate inflammation, this problem persists. Researchers are now trying to understand the roots of this inflammation and how to suppress it.

Lurking in the shadows

One possibility is that even in HAART users whose virus levels in the blood are so low that they cannot accurately be counted (so-called undetectable levels) HIV is slowly infecting immune cells deep inside lymph tissues or perhaps places where HAART cannot concentrate—the brain and spinal cord, ovaries and testicles.

Another possible cause of inflammation is this: In an attempt to rid the body of HIV-infected cells, the immune system inadvertently turns against itself, attacking immune cells and trying to reduce the hyper-activation by suppressing its own activity.

Whatever the cause of the continuing inflammation, research teams in North America and Western Europe are studying HIV infection and inflammation and trying to find ways of dampening inflammation without harming the immune system.

There are many compounds that have anti-inflammatory activity, including the following:

- aspirin or related compounds
- fish oil
- statins – this is the name given to a group of cholesterol-lowering medications, such as atorvastatin (Lipitor) and rosuvastatin (Crestor)
- drugs used to treat arthritis and other inflammatory conditions

Researchers now have to perform lab experiments using HIV-infected cells, monkeys infected with the AIDS-causing simian immunodeficiency virus (SIV) and the above-listed or other compounds. Such experiments are necessary, as some anti-inflammatory compounds can severely weaken the immune system (excessive doses of aspirin or fish oil can cause bleeding, and so on).

In this issue of *TreatmentUpdate*, we report on several developments in the field of inflammation and HIV.

REFERENCES:

1. Jonassen TO, Stene-Johansen K, Berg ES, et al. Sequence analysis of HIV-1 group O from Norwegian patients infected in the 1960s. *Virology*. 1997 Apr 28;231(1):43-7.
2. Vandepitte J, Verwilghen R and Zachee P. AIDS and cryptococcosis (Zaire, 1977). *Lancet*. 1983 Apr 23;1(8330):925-6.
3. Sterry W, Marmor M, Konrads A, et al. Kaposi's sarcoma, aplastic pancytopenia, and multiple infections in a homosexual (Cologne, 1976). *Lancet*. 1983 Apr 23;1(8330):924-5.
4. Bygbjerg IC. AIDS in a Danish surgeon (Zaire, 1976). *Lancet*. 1983 Apr 23;1(8330):925.
5. Friedman-Kein A. Disseminated Kaposi's sarcoma syndrome in young homosexual men. *Journal of the American Academy of Dermatology*. 1981 Oct;5(4):468-71.
6. Saimot AG, Coulaud JP, Mechali D, et al. HIV-2/LAV-2 in Portuguese man with AIDS (Paris, 1978) who had served in Angola in 1968-74. *Lancet*. 1987 Mar 21;1(8534):688.
7. Appay V, Sauce D. Immune activation and inflammation in HIV-1 infection: cause and consequences. *Journal of Pathology*. 2008 Jan;214(2):231-41.
8. Grossman Z, Meier-Schellersheim M, Paul WE, et al. Pathogenesis of HIV infection: what the virus spares is as important as what it destroys. *Nature Medicine*. 2006 Mar;12(3):289-95.
9. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Medicine*. 2008 Oct 21;5(10):e203.
10. Cadogan M, Dalgleish AG. HIV immunopathogenesis and strategies for intervention. *Lancet Infect Diseases*. 2008 Nov;8(11):675-84.
11. 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.
12. Boasso A, Hardy AW, Anderson SA, et al. HIV-induced type I interferon and tryptophan catabolism drive T cell dysfunction despite phenotypic activation. *PLoS One*. 2008 Aug 13;3(8):e2961.
13. Perlmutter A, Mittal A, Menter A. Tuberculosis and tumour necrosis factor-alpha inhibitor therapy: a report of three cases in patients with psoriasis. Comprehensive screening and therapeutic guidelines for clinicians. *British Journal of Dermatology*. 2009 Jan;160(1):8-15.

B. HAART reduces inflammation in the blood but...

HAART generally reduces the production of HIV, allowing the immune system to begin repairing itself. As a result, the number of important CD4+ T-cells in the blood increases and these and other

cells of the immune system regain their ability to detect and fight infections. However, HAART does not cure HIV infection and the immune system's repair is partial.

Red alert

In HIV infection, it appears that the immune system becomes activated shortly after the virus has entered and begins to spread throughout the body. In the case of most germs, this activation and subsequent inflammation is useful because it helps alert and marshal the immune response to control an infection. But in the case of HIV, this activation may not be helpful because the virus appears to take advantage of activation in order to help it infect more cells and to turn the immune system against itself.

Location is everything

Only 2% of the immune system's cells are in the blood. The majority of these cells are in lymph nodes and tissues. And most of the lymph nodes and tissues are found around the intestines. Since HIV infects cells of the immune system, most HIV is also found where those cells are, in lymph nodes and tissues. Lymph nodes and tissues are bustling hives of activity as the immune system battles germs. Historically, much HIV research has been done only on the cells of the immune system that can be found in the blood.

Back to the lymph nodes

In the late 1970s, when a small number of people with AIDS sought help, researchers studying the immune systems of these mysteriously ill patients noticed that they had persistently swollen lymph nodes. Biopsy and examination of the lymph nodes in those days also revealed inflammation and, in some cases, tumours.

Now researchers are once again revisiting the lymph nodes to find out what's going on there. Researchers from the United States' National Institutes of Health (NIH) and Sweden's Karolinska Institute are collaborating on obtaining a better understanding of how HIV damages the immune system, looking at lymph nodes in people infected with HIV and monkeys infected with the AIDS-causing virus SIV. Their findings reveal "an underlying immunologic condition" that may prevent the complete recovery of the immune system, even in HAART users.

The NIH-Karolinska's findings may also help other scientists to gain a better grasp of how HIV damages the immune system and to find ways to prevent and reverse this damage.

Study details

The research team collected blood samples from the following volunteers:

- 45 untreated HIV positive people whose average viral load was about 160,000 copies and average CD4+ count was 340 cells
- 45 HIV positive people who had been using HAART for at least two years whose average CD4+ count was 750 cells and average viral load was less than 50 copies

Doctors removed tonsils from the following volunteers:

- 5 healthy HIV negative people
- 6 untreated HIV positive people
- 4 HIV positive people taking HAART

Blood and lymphatic tissue were taken from five SIV positive monkeys before and after they received anti-HIV therapy.

Results—blood

HIV positive people who were not taking HAART had high levels of certain proteins, called TRAIL and FasL, that can cause cells of the immune system to commit suicide. In cells, this process of self-death triggered by those proteins is called apoptosis. In contrast, HAART users had near-normal levels of the death-inducing proteins TRAIL and FasL.

Death's friends

In order for TRAIL and FasL to work (cause apoptosis), they have to find their corresponding receptors on a cell and bind to those receptors. In the case of TRAIL, its receptor is called DR5 (death receptor 5) and FasL's receptor is called Fas.

In general, CD4+ cells in the blood of people not using HAART had high levels of these two receptors.

Results—in the lymph tissues (tonsils)

Levels of TRAIL and FasL that can trigger cell suicide were elevated in the lymph tissue of HIV positive people who were not taking HAART. The same was true for the death receptors DR5 and Fas in people not taking HAART.

However, in the lymph nodes and tissues of HAART users researchers were surprised to find that levels of death receptors—DR5 and Fas—were at least twice as high as in HIV negative people. Their surprise occurred because in the blood of

HAART users, levels of these receptors were near normal.

Stunned by these findings, the research team duplicated its work in SIV positive monkeys. They obtained the same results.

A note on HIV

During HIV infection, the virus spreads to lymph nodes and tissues, where it infects and directly kills cells of the immune system. However, HIV can indirectly cause death and immunologic mayhem. It can hyper-activate the immune system, making it more susceptible to damage, and it can turn the immune system on itself, causing T- and other cells to unnecessarily undergo self-destruction, or apoptosis.

A hyper-activated immune system, despite the use of HAART, in which CD4+ cells have excessive levels of death receptors, is susceptible to further damage by invading germs. For instance, co-infection with members of the herpes virus family (HSV-1, HSV-2, CMV, EBV, HHV-8 and so on), hepatitis C virus and syphilis germs could result in increased levels of the death proteins TRAIL and FasL. Since many immune cells in a hyper-activated immune system are already primed for death by displaying DR5 and Fas, exposure to TRAIL and FasL because of co-infection could further weaken the immune system.

The findings from the Swedish-American team may help to explain why the immune system is only partially repaired despite years of HAART.

Now further research needs to be done to find out why, even with the use of HAART, CD4+ cells are so ready to die.

REFERENCES:

1. Appay V, Sauce D. Immune activation and inflammation in HIV-1 infection: cause and consequences. *Journal of Pathology*. 2008 Jan;214(2):231-41.
2. Grossman Z, Meier-Schellersheim M, Paul WE, et al. Pathogenesis of HIV infection: what the virus spares is as important as what it destroys. *Nature Medicine*. 2006 Mar;12(3):289-95.
3. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Medicine*. 2008 Oct 21;5(10):e203.
4. Cadogan M, Dalgleish AG. HIV immunopathogenesis and strategies for intervention. *Lancet Infect Diseases*. 2008 Nov;8(11):675-84.
5. 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.

6. Boasso A, Hardy AW, Anderson SA, et al. HIV-induced type I interferon and tryptophan catabolism drive T cell dysfunction despite phenotypic activation. *PLoS One*. 2008 Aug 13;3(8):e2961.

C. Treatment interruption uncovers HIV's attack on the kidneys

At the turn of the 21st century, several clinical trials were held to try to assess the impact of treatment interruption in people with HIV/AIDS. The largest and best-designed of these studies was called SMART. Many analyses of SMART appear in *TreatmentUpdate* 170. In SMART, the risks of specific events among people who interrupted therapy compared to people who remained on HAART were as follows:

- death – twice as high
- life-threatening infections – seven times as high
- cancer – six times as high
- major cardiovascular (heart attack or stroke), kidney or liver damage – two times as high
- life-threatening reaction(s) as a result of medication-related side effects – 20% higher

Some of these problems were linked to excessive inflammation. The SMART data set is still being analysed. But what has become clear is that HIV infection transforms the immune system, causing prolonged and high levels of inflammation deep within the body. This inflammation not only affects the immune system but also degrades the heart and circulatory system, the liver and kidneys. This last organ is particularly vulnerable to HIV-related damage because parts of the kidney can be infected by HIV. Because of the relatively high rate of kidney damage seen during SMART, researchers were interested in finding out more about this outcome.

Study details

Researchers who study the kidneys sometimes use assessments of a protein called cystatin C. This protein is made by most cells and is filtered by the kidneys. Measuring levels of cystatin C in the blood can provide doctors with a fairly accurate picture of kidney health, particularly before serious damage has developed.

An international team of researchers associated with SMART decided to check cystatin C levels in stored blood samples from participants in SMART.

The entire SMART study enrolled more than 5,000 HIV positive volunteers between 2002 and 2006. The kidney sub-study used data collected from 249 people who did not interrupt their use of HAART and 250 people who did interrupt therapy.

People who interrupted HAART did so whenever their CD4+ count rose above the 350-cell mark and resumed therapy whenever it fell below 250 cells. This practice continued throughout the study.

The average profile of participants in the kidney sub-study at the time they entered SMART was as follows:

- 30% female, 70% male
- age – 44 years
- CD4+ count – 540 cells
- lowest-ever CD4+ count – 250 cells
- cystatin C levels – 0.99 mg/dl

SMART participants were randomly assigned to one of the following two groups:

- viral suppression group (continued HAART)
- drug conservation group (treatment interruption according to CD4+ count levels)

Blood samples were regularly collected for analysis. None of the participants in the kidney sub-study had a history of cardiovascular disease (which could affect the kidneys).

The reference range of cystatin C in young, healthy people is between 0.52 and 0.92 mg/dl.

Results

After the first month of SMART, cystatin C levels rose slightly in the drug conservation group and fell slightly in the viral suppression group. Still, the difference between the two groups became statistically significant; that is, not likely due to chance alone. Moreover, in the people interrupting HAART, cystatin C levels remained higher for the rest of the study. And if large increases of cystatin C occurred during the study, they tended to occur in people who had interrupted HAART.

Medicines to lower blood pressure tend to affect the kidneys. In SMART, participants in both groups who used these medications had, on average, a 91% increase in cystatin C levels.

Other factors, such as race/ethnicity or the use of nukes (nucleoside analogues), did not affect cystatin C levels.

Regular tests

Routine assessments of kidney health to estimate GFR (glomerular filtration rate) using formulae such as the MDRD (modification of diet in renal disease) and Cockcroft-Gault were done. But these tests did not detect kidney damage. Perhaps this is because cystatin C can sometimes detect subtle kidney damage.

The increase in cystatin C levels was also linked to increased levels of D-dimer, suggesting an increased risk for blood clots. And, as cystatin C levels rose, levels of “good” cholesterol (HDL) fell. These changes in cystatin C and D-dimer levels suggest that uncontrolled HIV infection increases inflammation, which leads to kidney damage and an increased risk of serious cardiovascular disease.

The kidney sub-study of SMART suggests the following:

- HIV infection affects the functioning of the kidneys.
- In particular, uncontrolled HIV infection weakens the kidneys and increases the risk for cardiovascular disease.
- Regular assessment of cystatin C levels is an emerging method of determining kidney health.
- Cystatin C levels offer an advantage over other assessments of kidney health because they may be able to detect subtle kidney damage.
- Large clinical trials with HIV positive people are now needed to find out just how useful cystatin C is in this population.

REFERENCES:

1. Mocroft A, Wyatt C, Szczech L, Neuhaus J, El-Sadr W, Tracy R, Kuller L, Shlipak M, Angus B, Klinker H, Ross M; INSIGHT SMART Study Group. Interruption of antiretroviral therapy is associated with increased plasma cystatin C. *AIDS*. 2009 Jan 2;23(1):71-82.
2. Odden MC, Scherzer R, Bacchetti P, et al. Cystatin C level as a marker of kidney function in human immunodeficiency virus infection: the FRAM study. *Archives of Internal Medicine*. 2007 Nov 12;167(20):2213-9.

II SIDE EFFECTS AND COMPLICATIONS

A. HAART and the safety of the fetus

In high-income countries, the widespread availability of highly active antiretroviral therapy (HAART) has dramatically decreased deaths from AIDS-related infections. As a result, HIV positive people in these countries are generally living longer, and some are thinking about having children.

Fortunately, HIV positive women can increase their chances of giving birth to a healthy, HIV negative baby, with several steps as follows:

- getting counselling before becoming pregnant
- receiving prenatal counselling and care
- taking HAART while pregnant so that viral load is as low as possible
- receiving intravenous AZT shortly before delivery
- having a C-section (Cesarean section)
- giving the infant six consecutive weeks of AZT after birth
- not breast-feeding, as breast milk contains HIV and can infect the baby

As a result of these steps, in high-income countries the risk of giving birth to an HIV positive baby is now less than 2%.

Drug safety

Ever since the very unfortunate episode of birth defects as a result of the use of the tranquilizer thalidomide, pregnant women have been especially careful about protecting the fetus from the toxicity of medicines. Some pregnant HIV positive women may be concerned about the potential effect of HAART on the safety of the fetus. These concerns are reasonable because the results of experiments on mice and monkeys revealed that some anti-HIV drugs, particularly nukes (nucleoside analogues), can affect the genetic material (DNA) of the offspring of these animals. And if this effect holds true in human infants, there is the possibility of a long-term risk for cancer.

But it is important to bear in mind that humans are neither mice nor monkeys; that is, results of animal experiments are merely a guide and do not always accurately predict what will happen when people are given the same drugs. The wonderful news is that two large studies, one in the United Kingdom and the other in France, have found no increased risk of cancer or birth defects in children

born to HIV positive women who used anti-HIV drugs during pregnancy.

In the following reports we review research on the effects of exposing the fetus to anti-HIV medicines. Overall, many years of research show that the immense benefit of HAART in pregnant HIV positive women continues to outweigh any theoretical risks to the fetus.

REFERENCES:

1. Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. *AIDS*. 2008 May 11;22(8):973-81.
2. Anderson BL, Cu-Uvin S. Pregnancy and optimal care of HIV-infected patients. *Clinical Infectious Diseases*. 2009; *in press*.
3. Olivero OA. Mechanisms of genotoxicity of nucleoside reverse transcriptase inhibitors. *Environmental and Molecular Mutagenesis*. 2007 Apr-May;48(3-4):215-23.
4. Poirier MC, Olivero OA, Walker DM, et al. Perinatal genotoxicity and carcinogenicity of anti-retroviral nucleoside analog drugs. *Toxicology and Applied Pharmacology*. 2004 Sep 1;199(2):151-61.
5. Wogan GN. Does perinatal antiretroviral therapy create an iatrogenic cancer risk? *Environmental and Molecular Mutagenesis*. 2007 Apr-May;48(3-4):210-4.
6. Thorne C, Newell ML. Safety of agents used to prevent mother-to-child transmission of HIV: is there any cause for concern? *Drug Safety*. 2007;30(3):203-13.
7. Benhammou V, Warszawski J, Bellec S, et al. Incidence of cancer in children perinatally exposed to nucleoside reverse transcriptase inhibitors. *AIDS*. 2008 Oct 18;22(16):2165-77.
8. Townsend CL, Willey BA, Cortina-Borja M, et al. Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990–2007. *AIDS*. 2009; *in press*.

B. French study clears HAART of cancer link in kids

There is no evidence that anti-HIV drugs cause cancer in adults. However, these medicines are taken by pregnant HIV positive women, and therefore could, in theory, have a negative effect on the fetus and, later, infant. This possibility arises for a number of reasons, including that of rapid growth and development in the fetus and child. During the time in the womb and later in early childhood, human genetic material (DNA) is extremely active as many genes are activated. Exposure to potentially cancer-causing substances such as nukes during this time could interfere with the fetus' or child's genetic material, sowing the seeds for cancer later in life.

Recognizing this, French scientists have been collecting health information on children born to HIV positive mothers. Their most recent analysis of their data suggests that there is no overall cancer risk to children born to mothers who used anti-HIV drugs during pregnancy. However, the effect of certain combinations of anti-HIV drugs has raised concern, so further investigation of these combinations is required.

Study details

Researchers sought information on 8,853 children born to HIV positive mothers in France between 1990 and May 2007. All the children were exposed to nukes and other anti-HIV agents during their time in the womb and/or after birth. About 65% of the women began taking treatment during their second trimester of pregnancy.

Results

By May 1, 2007, a total of 10 cases of cancer (four girls, six boys) had been diagnosed in children as follows:

- leukemia – three children
- cancer of the pineal gland (in the brain) or pineoblastoma – two children
- eye cancer (retinoblastoma) – two children
- cancers arising in the supportive tissue of the brain (gliomas) – three children

These 10 cancers were detected, on average, when the children were four years old.

Making sense of the data

In general, researchers would have expected about 9 cases of cancer among this number of children if they had been born to HIV negative mothers in France. So the difference in expected and observed numbers of children with cancer born to HIV positive and HIV negative mothers was not statistically meaningful.

Of the 10 children born to HIV positive mothers, five children had tumours in the brain or spinal cord (these constitute the central nervous system, or CNS). Among children born to HIV negative mothers in the same period in France, only two cases of tumours in the CNS would be expected. However, this difference in tumours between the children was not statistically significant.

The researchers did note that four cases of cancer affecting the nerves outside the CNS, the kidneys or other organs/systems occurred in children born to HIV negative mothers during the same period. None of these cancers occurred in children born

to HIV positive mothers and researchers do not know why this was the case.

Risk factors

The risk of children developing cancer in the French study was not linked to any of the following features of the mother:

- geographic origin
- drug addiction
- viral load
- CD4+ count

However, being born severely premature (having spent less than 33 weeks in the womb) increased the risk of a child developing cancer 10-fold.

Compared to children who were exposed to AZT (zidovudine, Retrovir) in the womb, children who were exposed to the following two drugs had an unexpected 12-fold increased risk of cancer:

- ddI (didanosine, Videx)
- 3TC (lamivudine)

The findings about prematurity, and the combination of 3TC and ddI were unexpected.

Key points

1. Overall, the rates of cancer seen in children born to HIV positive mothers in this study are similar to those seen in children born to HIV positive mothers in Germany and the United States.
2. The overall rate of cancers in these children is very, very low—less than 0.01%. This is the same rate as seen in children born to HIV negative mothers.
3. The results of the French study underscore the importance of continued monitoring of children born to HIV positive mothers.
4. The benefits of HAART used during pregnancy clearly continue to outweigh any potential risks to the fetus and subsequent child, at least for the first five years of life. Longer-term monitoring is necessary to find out the cancer risk of these children as they grown into adolescents and young adults.

REFERENCES:

1. Anderson BL, Cu-Uvin S. Pregnancy and optimal care of HIV-infected patients. *Clinical Infectious Diseases*. 2009; *in press*.
2. Benhammou V, Warszawski J, Bellec S, et al. Incidence of cancer in children perinatally exposed to nucleoside reverse transcriptase inhibitors. *AIDS*. 2008 Oct 18;22(16):2165-77.

C. Risk of deformities very low in infants exposed to HAART

Like their counterparts in France, researchers in the United Kingdom have been monitoring the health of children born to HIV positive women. In particular, they have focused their analysis on birth defects. Their results suggest that birth defects are not increased because of exposure to HAART.

Study details

The study team reviewed data on 8, 242 infants, 232 of whom had at least one birth defect.

Results—Timing

In the first three months after conception, moving from fertilized egg to fetus, development and growth is extremely rapid. During this time, because of such rapid growth the fetus is exquisitely sensitive to the effects of drugs. So British researchers focused on whether initiating HAART during the first trimester was associated with an increased risk of birth defects compared to other trimesters.

When they took into account maternal factors such as substance use, ethnicity, age and health, there was no significant difference in the risk of birth defects among women initiating HAART in different trimesters.

Different drug classes

No particular family or class of anti-HIV drugs was associated with an increased risk of birth defects.

Individual drugs

Based on studies in monkeys, efavirenz (Sustiva, and in Atripla) can cause severe birth defects. In the UK study, a total of 220 infants were exposed to efavirenz in the womb. Slightly more than 2% (five infants) developed birth defects, including the following:

- undescended testicles
- dislocated hips
- deformed intestines

But the rate of these birth defects was similar to that seen in children born to HIV negative women who did not take efavirenz.

A similar trend was seen with ddI in that whatever defects occurred were seen at the same rate in children born to HIV negative women.

In general

The most commonly reported birth defects affected the following body parts:

- muscle and skeleton
- limb
- heart and circulatory system
- genitals

AZT

In boys born to HIV negative mothers, a relatively common birth defect, occurring in 1 in 150 or 1 in 300 boys depending on where the study was done, is hypospadias. In this condition, the penis looks abnormal and the opening that is normally at the tip is located somewhere else, usually near the head of the penis. But in a small proportion of cases, this opening can occur on the underside of the penile shaft or even near the scrotum. Hypospadias can be corrected with surgery. There were 12 cases of hypospadias in the British study, all occurring in children exposed to AZT in the womb. However, this finding does not prove that AZT causes hypospadias. A formal clinical trial would be needed to resolve that issue.

Overall

The rate of birth defects was nearly 3% in the UK study. In children born to HIV negative women in the UK, the rate is between 2% and 3%. On the European continent, the rate is 2.2%. The results of the British study should reassure HIV positive women who are thinking of having a baby that the use of HAART does not pose a major risk for birth defects.

REFERENCES:

1. Anderson BL, Cu-Uvin S. Pregnancy and optimal care of HIV-infected patients. *Clinical Infectious Diseases*. 2009; *in press*.
 2. Townsend CL, Willey BA, Cortina-Borja M, et al. Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990–2007. *AIDS*. 2009; *in press*.
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Disclaimer

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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Writer
Editor

Sean Hosein
RonniLyn Pustil

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What CATIE Does

The Canadian AIDS Treatment Information Exchange (CATIE) 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 HAART

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 & Supplement 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: <http://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