Potent combination anti-HIV therapy (commonly called ART or HAART) has produced tremendous benefits for HIV-positive people, improving their survival and health. The benefits from ART are so powerful that researchers increasingly expect that some ART users will have a near normal life-expectancy. Specifically, researchers have forecasted that a young adult who becomes infected today and is diagnosed and begins treatment shortly thereafter, and who is able to take ART every day exactly as directed, and is engaged in their health care, and who does not have addiction or mental health issues, co-infections and other pre-existing conditions, should live into their 80th year.

Faced with such promising prospects, some HIV-positive people are starting families. Today, it is extremely rare for infants in Canada to be born with HIV or to become infected after birth when the following measures are taken:

- counselling with a doctor about pregnancy planning
- HIV testing and counselling before pregnancy
- the use of ART during pregnancy so that the mother’s viral load is less than 50 copies/ml
- regular visits to a clinic for care and advice during pregnancy
• use of intravenous AZT and, if medically necessary, sometimes the use of additional medicines for the mother during the birthing process as recommended by Canadian guidelines
• giving birth via Caesarean section (if medically necessary)
• giving the newborn a short course of anti-HIV medicines for further protection
• using formula and not breastfeeding, as HIV can be spread via breast milk
• not pre-chewing food for the baby when solids are introduced. Adults who have both HIV and oral infections can inadvertently cause a small amount of blood to leak and be present in the food that they chew. This blood can contain HIV, and if the pre-chewed food is fed to the infant, it could transmit HIV.

Monitoring after birth
Researchers in high-income countries have established databases that collect health-related information from HIV-positive women and their children. The purpose of these databases is to help researchers monitor trends in health and any birth defects that may occur.

The vast majority of analyses of these databases have been reassuring about the general safety of ART on the fetus. However, signals of a possibly increased risk for birth defects have emerged from some analyses in the past decade:

• An increased risk for male genital abnormalities (the most common are called hypospadias) was found in some babies born to women who used the anti-HIV drug AZT (Retrovir, zidovudine and in Combivir and Trizivir) during the first three months of pregnancy. However, a sophisticated analysis subsequently determined that exposure to AZT was not the cause of this problem (more information about hypospadias appears later in this issue of TreatmentUpdate).
• An overall increased risk for birth defects has been found among some infants who were exposed to the anti-HIV drug efavirenz (Sustiva, Stocrin and in Atripla) during the first three months in the womb.

Newer drugs
As more drugs have been licensed for the treatment of HIV, there is a need for further monitoring of their safety on the fetus.

Scientists at 22 clinics in the U.S. as well as at the National Institutes of Health (NIH) and Harvard University have collaborated on an analysis of the potential impact of anti-HIV drugs and possible associations with birth defects. The scientists found that overall the risk of potential birth defects was very low. However, they did find an association between an increased risk for birth defects and exposure to the following combination of anti-HIV medicines:

• atazanavir (Reyataz) and ritonavir (Norvir)

There are more details on this and other findings below.

Study details
Researchers reviewed health-related data collected from 1995 to mid-2012 from two groups of HIV-positive mothers and their HIV-negative children. This broad time span is useful for examining possible trends, particularly as different anti-HIV medicines became licensed. The scientists focused on data collected from 2,580 children and their mothers.

Results—Overall
Of 2,580 children, 175 (nearly 7%) had a confirmed birth defect. The vast majority of these were major birth defects.

The most common abnormalities involved muscle and/or bone, followed by the cardiovascular system.

Checking prescription medicines
The use of certain other prescription medicines (other than anti-HIV drugs) was reviewed by the doctors because there have been reports of birth defects in some children born to mothers who took these drugs during pregnancy.

The first trimester of pregnancy—the first 12 weeks—is a time when the fetus is rapidly developing. As a result, the fetus is very susceptible
to developmental problems that could be caused by certain drugs (mentioned below) and other factors. The U.S. study team focused on the following prescription medicines:

- common antidepressants, including Celexa, Prozac, Paxil, Zoloft, Luvox and Lexapro. The researchers found that use of these medicines during the first trimester of pregnancy was rare; about 1% of infants in the study were exposed to these drugs while in the womb. Of the 30 infants whose mothers used these drugs during pregnancy, one infant was born with a birth defect.

- certain antimicrobial drugs, such as the antibiotics Bactrim/Septra (trimethoprim-sulfamethoxazole) and the anti-parasite drug pyrimethamine. These drugs were used by 107 pregnant women, six of whom gave birth to infants with birth defects.

**Focus on ART**

The research team was able to find detailed medical records concerning the potential exposure to ART while in the womb on 2,517 infants. The rest of this report is focused on this group.

**Specific classes of drugs**

**Nucleoside analogues**

*commonly called nukes*

Researchers generally did not find any data linking individual nukes to an increased risk for birth defects except for the use of the following drugs when taken in the first trimester:

- AZT – associated with an increased risk for defects in male genitals (including hypospadias)
- 3TC – associated with an increased risk for defects in male genitals (including hypospadias)

The combination of the following two nukes at any time during pregnancy was an issue:

- ddI (didanosine, Videx EC) + d4T (stavudine, Zerit)

Although the use of this combination was rare (less than 1% of women used it), it was associated with an eight-fold increased risk of birth defects.

**Non-nukes**

No association between the use of efavirenz or nevirapine (Viramune) and birth defects was found. However, bear in mind that only about 4% of pregnant women in the study used efavirenz and 5% used nevirapine.

**Protease inhibitors—during the first trimester**

In Canada and other high-income countries today, low doses (between 100 and 200 mg/day) of ritonavir are used to raise or maintain levels of another protease inhibitor in the blood for the treatment of HIV. When used in this way, ritonavir is commonly referred to as a booster.

The use of atazanavir during the first trimester of pregnancy in the following combinations was associated with a statistically significant increased risk of birth defects:

- atazanavir + ritonavir
- atazanavir + ritonavir + tenofovir
- atazanavir + ritonavir + FTC (Emtriva, emtricitabine)

In general, when the above-listed combinations were used during the first trimester, they were associated with a two-fold increased risk of birth defects.

In contrast, when combinations such as the following were used in the first trimester of pregnancy, they were not significantly associated with an increased risk of birth defects:

- atazanavir + AZT
- atazanavir + 3TC

Researchers stated that while the use of low-dose ritonavir with atazanavir was linked to an increased risk for birth defects, when low-dose ritonavir was used with a different protease inhibitor, such as lopinavir (in Kaletra), it was not linked to any significantly increased risk for birth defects.

Furthermore, researchers found that the use of the protease inhibitor darunavir (Prezista) seemed to be protective against the development of birth defects. However, only 54 women used darunavir in this study. During the study, women who used darunavir would have taken it with a low dose of ritonavir.
Bear in mind

1. ART is extremely useful when it comes to helping HIV-positive women deliver healthy, HIV-negative infants who generally have normal development as children. As new HIV drugs are introduced and treatment guidelines and clinical practice shift, more research is needed to find the best regimens for fetal safety.

2. In the present study, the overall risk of birth defects in children born to women who used ART was nearly 7%. This is higher than seen in some other studies of children born to HIV-positive mothers in the U.S. and UK, where rates between 3% and 6% were found. A recent Italian study focusing on the period between 2001 and 2011 reported a rate of 3.2% of children of HIV-positive mothers born with birth defects.

The precise reason(s) for the overall higher rates of birth defects in the present study is not clear and deserves further scrutiny both by the researchers involved with the study as well as outside investigators.

3. Atazanavir has been in widespread use for nearly a decade in high-income countries. Yet during that time no other study has reported a statistically significant association between the use of atazanavir + ritonavir during pregnancy and birth defects, so this finding requires confirmation with other studies and databases. Until such confirmation takes place, the study’s findings should be treated as a signal of possible importance.

4. The association found with male genital birth defects and the use of AZT or 3TC in the first trimester of pregnancy is interesting. However, there are many potential factors that have been associated with an increased risk for hypospadias in newborns (regardless of the mother’s HIV status) and a larger study has not found any link between exposure to AZT or 3TC in the first trimester and subsequent development of hypospadias. We explore this larger study in the next article.

5. It is important to keep in mind that the present study is observational in design. Such studies are good at finding associations but cannot prove cause and effect. In other words, such studies cannot prove that boosted atazanavir indeed causes birth defects in some infants.

6. The NIH recently released limited information about a robustly designed study called PROMISE. This trial took place in several countries in Southern Africa and is relatively large (3,500 HIV-positive mothers). Participants were randomly assigned to one of several regimens. The interim results from this study are indeed promising for mothers given combinations of three anti-HIV drugs. However, only when the full data set is released can researchers compare findings from PROMISE (focusing on the rate of major birth defects) to the present American observational study.

Acknowledgement

We thank infectious disease specialist Jason Brophy, MD, for his helpful comments, expert review and research assistance.

REFERENCES:


B. Good news about HIV drug safety from an even larger study

The largest database that has captured information on the safety of ART used during pregnancy is the Antiretroviral Pregnancy Registry (herein after called the Registry). This database conducts observational, or cohort, analyses. The Registry is located in the U.S. and although about 78% of its cases are from the U.S., it also collects information from 67 other countries, including Canada, Brazil and countries in Europe and Southern Africa. Scientists with the Registry have analysed information collected between 1989 and 2014. Out of 16,646 evaluable reports sent to the Registry, 7,135 were cases in which the fetus was exposed to ART during the first trimester of pregnancy.

Researchers with the Registry made the following statement:

“For the overall population exposed to antiretroviral drugs in this Registry, no increases in risk of overall birth defects or specific defects have been detected to date.”

This is very reassuring news for HIV-positive mothers and their healthcare providers.

Focus on two older drugs

The Registry has data on so many pregnancies and infants that it has the statistical power to detect the potential association of many individual drugs used in HIV regimens with birth defects. The vast majority of drugs used by HIV-positive women were not found to have any association with an increased risk for birth defects. However, there were two notable exceptions, as follows:

- ddI (didanosine, Videx EC)
- nelfinavir (Viracept)

The rate of infants with birth defects possibly due to exposure to these drugs was approximately 2.9%. This is in comparison to a rate of 2.7% in another database. Researchers with the Registry described this increase (from 2.7% to 2.9%) in birth defects among mothers who used these drugs to be “modest.” They stated that “no pattern of birth defects has been detected” with fetal exposure to ddI and nelfinavir, and they are not certain that the “modest” increase in birth defect rates with these drugs has any clinical relevance.

Today in Canada and other high-income countries, doctors do not routinely prescribe ddI and/or nelfinavir, as there are safer and more effective drugs from which they can choose when caring for all HIV-positive people, including pregnant women.

Screening many drugs

Due to the high number of participants enrolled, the Registry has the ability to detect the possibility of “at least a two-fold increase in the risk of overall birth defects” associated with exposure in the
womb during the first trimester of pregnancy to the following drugs:

- abacavir (Ziagen, and in Kivexa, Trizivir and Triumeq)
- atazanavir (Reyataz)
- darunavir (Prezista and in Prezobix)
- didanosine (ddI, Videx)
- efavirenz (Sustiva, Stocrin and in Atripla)
- indinavir (Crixivan)
- stavudine (d4T, Zerit)

However, no increased signal of risk was detected.

The Registry is also able to detect the possibility of “at least a 1.5-fold increased risk” of overall birth defects associated with exposure in the womb during the first trimester to the following drugs:

- FTC (emtricitabine and in Emtriva, Atripla, Complera and Stibild)
- 3TC (lamivudine and in Combivir, Trizivir, Ziagen and Triumeq)
- tenofovir (Viread and in Truvada, Atripla, Complera and Stibild)
- lopinavir (in Kaletra)
- AZT (zidovudine, Retrovir and in Combivir and Trizivir)

With the exception of AZT, the Registry did not find any possible signal of increased risk for birth defects.

**Regarding AZT**

Given this initial safety signal with AZT, the Registry then further investigated the possible association of exposure to AZT in the womb with defects in the male genitals of infants. Here is their statement about this:

“The Registry concludes that the data do not support a causal relationship between Zidovudine and/or lamivudine exposure and [birth defects affecting male genitals]. The disappearance of the [increased risk] in more sophisticated analyses suggests that the increase may be related to other factors.”

Researchers with the Registry are continuing to be vigilant about the impact of AZT and other drugs on the health of the fetus, and, as data accumulates, will issue additional reports. Our next story deals with other factors that may play a role in hypospadias.

**Acknowledgement**

We thank infectious disease specialist Jason Brophy, MD, for his helpful comments, expert review and research assistance.

**REFERENCES:**


**C. Understanding the risks for hypospadias**

In the previous articles in this issue of *TreatmentUpdate*, we mentioned that some studies have found a possible link between the use of certain medicines in pregnancy and a risk of male genital birth defects, or hypospadias. In this article, we discuss hypospadias and research findings from pregnant HIV-negative women. This information puts the risk for hypospadias in context.

**What is hypospadias?**

In males, the opening of the urethra, through which urine leaves the body, is on the tip of the penis. However, with hypospadias, this opening can form on other parts of the shaft of the penis, on the scrotum or even close to the anus. This can be corrected in infancy with surgery.
Points to consider

1. Hypospadias incidence
Hypospadias can occur in about one in every 300 boys born to HIV-negative mothers. Reports from East Asia, Western Europe and the U.S. suggest that in the past two decades hypospadias may have become more common.

The reasons for this trend are not clear but may be due to better monitoring of infants as well as better reporting and collection of data about birth defects. There are also studies that suggest that there are several factors that may affect the potential risk for hypospadias, including the following:

- certain medicines
- some chemicals and pesticides
- certain health issues encountered by pregnant women and the fetus
- genes

We explore some of these issues next.

2. Pregnancy-related complications and issues
As a result of pregnancy, some women develop temporarily higher-than-normal blood pressure (hypertension) and kidney dysfunction. These are part of a syndrome called preeclampsia and require monitoring and in some cases treatment. Elevated blood pressure during pregnancy can affect the blood supply to the fetus and potentially restrict its growth.

A British study explored the issue of birth defects in 12,821 infants born to HIV-negative women between the years 1998 to 2010. It found that the use of medicines during the first trimester of pregnancy to lower blood pressure in women with hypertension was associated with an increased risk for hypospadias. It also found that women diagnosed with preeclampsia, whether or not they were treated for this condition, were at heightened risk for giving birth to children with birth defects, including hypospadias.

Another study from the U.S. also found an increased risk for hypospadias among infants of HIV-negative women with higher-than-normal blood pressure, regardless of whether they received treatment.

Taken together, the results from these two studies point to the fact that changes in the environment that surrounds the fetus can affect its development.

Research has also found that male babies who are born prematurely and/or who are born underweight are at increased risk for having hypospadias. This may be related to a condition whereby the placenta (the physical connection between the mother and fetus), which supplies oxygen and nutrients to the fetus and helps to remove wastes, is not working properly. Researchers are not certain why this might cause hypospadias.

3. Seizure medication
Researchers in Australia reviewed reports of birth defects collected between 1999 and 2012 among women who took anti-seizure drugs. They found that women who took, on average, higher doses of the drug valproate (valproic acid) during the first trimester of pregnancy were at increased risk for giving birth to infants with birth defects, particularly hypospadias. Women whose physicians decreased their dose of valproate had a reduced risk for infants being born with birth defects. Valproic acid can interfere with male hormones.

4. Obesity
Several studies have found that very overweight women were at increased risk for giving birth to male infants with hypospadias. However, not all researchers agree about the impact of obesity on the risk of hypospadias.

5. Genes and the environment
Hypospadias can occur in infants whose parents have a family history of this condition, suggesting that there is a genetic link.

In some cases, the genes in question have to do with receptors for the hormone estrogen or sensitivity to the hormone testosterone. Some researchers suspect that there are possible interactions between genes in the fetus and chemicals or hormone-like compounds in the environment.

One theory is that certain pollutants in the environment, called endocrine disruptors or hormone disruptors, interact with the fetus. Examples of these pollutants are:

- PCBs (polychlorinated biphenyls)
- PCDFs (polychlorinated dibenzofurans)
- dioxins (polychlorinated dibenzo-p-dioxins, or PCDD)
- some pesticides
The hormone testosterone is essential for the formation of male genitals. But it is possible that some of these pollutants or other chemicals could mimic the effect of estrogen and affect the development and formation of the penis. This theory about the impact of environmental contaminants is controversial. Indeed, while results of some experiments in animals may support the link between some pollutants and genital malformation, there is no clear proof of this link in humans.

**Note well**

As mentioned earlier in this issue of TreatmentUpdate, ART is very valuable when it comes to helping HIV-positive women deliver healthy, HIV-negative infants who generally have normal development as children.

**Acknowledgement**

We thank infectious disease specialist Jason Brophy, MD, for his helpful comments, expert review and research assistance.

**REFERENCES:**


D. ART during pregnancy found safe for babies’ hearts

As mentioned before in this issue of *TreatmentUpdate*, the use of potent combination anti-HIV therapy (commonly called ART or HAART) along with other measures can significantly help pregnant HIV-positive women give birth to healthy, HIV-negative babies. Researchers are continuing to monitor the health of babies born to HIV-positive mothers to assess the safety of ART. In one such study, researchers at Wayne State University in Detroit collaborated with scientists in other parts of the U.S. to assess any potential ART-related injury or birth defects in infants. Reassuringly, they found no evidence of toxicity to the heart in children born to HIV-positive mothers who used ART during pregnancy. However, they appear to have found a possible signal of subtle changes to the thickness of the heart’s pumping chambers in some of these children. This latter finding needs to be treated with caution and we explain why in this report.

Study details

Researchers from 22 clinics across the U.S. that cared for infants born to HIV-positive mothers pooled their data and analysed it, seeking statistical relationships between any potential signals of birth defects or injury to the heart and potential factors that may have caused such problems. They assessed the heart health of the infants by using ultrasound scans. One ultrasound scan was done per child.

For their study, researchers gathered and compared data between 2007 and 2012 from the following two groups of infants:

- 411 HIV-negative infants born to ART-using women
- 98 HIV-negative infants whose mothers were also HIV negative

**Results**

The researchers found a statistical signal that suggested that fetal exposure to the drug AZT (zidovudine, Retrovir and in Combivir and Trizivir) may have resulted in a very subtle change to the shape of part of the heart. The net result of this would be that slightly more physical stress would be applied to the walls of the heart by the flow of blood.

**Points to consider**

1. Perhaps the most important finding is that researchers did not find any clinically significant injury of the hearts of HIV-negative children born to HIV-positive mothers; that is, the hearts were functioning normally.

   The researchers did appear to find some very subtle changes to the hearts of children, which, in their words, “could be at least partially explained by [exposure to ART in the womb].” Readers should note that the researchers’ statement contains uncertainty; that is, they are not sure what role ART played in their findings. Furthermore, the present study is observational in nature; such studies are good at finding associations between a drug and an outcome but cannot prove cause and effect.

   In other words, the present study cannot discriminate between the potential effect of ART in the womb and the effect of HIV in the womb. Thus this study’s findings must be treated with caution and require verification in another study.

2. Several factors are associated with very subtle changes to the shape of the heart’s pumping chambers. For instance, in the present study, researchers found that the use of tobacco and/or alcohol during pregnancy resulted in changes in the hearts of infants as follows:

   - the pumping ability of the heart was weakened
   - the walls of the heart became thicker

   These effects were independent of the use of ART.

   Also, in the time before ART was available in high-income countries (before 1996), researchers found that HIV-infected children
commonly developed enlarged hearts. Complications arising from enlarged hearts and cardiac dysfunction were reported in HIV-positive children before 1996.

It is possible that there are other causes for the subtle cardiac issue seen in the current study. For instance, the U.S. researchers suggested that chronic low-level inflammation in the womb, triggered by the mother’s HIV infection, might be a culprit. Previous research with HIV-negative children born to HIV-positive mothers suggests that some of these children may have elevated levels of inflammation in their cardiovascular system despite being born HIV negative.

3. To cast some clarity on the issue, robustly designed studies are needed. Such studies take time to create and operate and are relatively expensive.

REFERENCES:

E. General risk factors for premature births

One of the reports in this issue of TreatmentUpdate deals with a hormonal issue that appears to cause some HIV-positive women to give birth prematurely. Before delving into this report, we first provide some background about prematurity.

Most pregnancies in high-income countries are successful, with healthy babies being born. However, in some cases women may go into labour prematurely. In general, babies born prematurely need a high degree of care in specialized centres in hospitals so they can finish developing and be ready for life outside the womb without constant medical assistance. All of the factors that cause women to deliver babies prematurely are not known, but here are some that can increase the risk for giving birth prematurely:

- diabetes
- heart disease
- kidney disease

Other risk factors include some of the following:

- a premature widening of the cervix (called cervical insufficiency)
- having a history of giving birth prematurely
- urinary tract infections or an infection that affects the membranes surrounding the fetus
- preeclampsia – a syndrome of higher-than-normal blood pressure and excess protein in the urine that can develop during pregnancy
- poor nutrition
- substance use, including tobacco and street drugs
- reduced production of the hormone progesterone

It is important to know that in some cases doctors may not be able to find a cause for premature birth.

Progesterone

The ovaries produce the hormone progesterone. It helps prepare the uterus for hosting a fertilized egg. Once this occurs and the physical connection between the fetus and mother—the placenta—develops, the placenta produces the bulk of progesterone during the remainder of pregnancy. Progesterone helps the fetus to grow and protects it from the mother’s immune system. This protection is necessary because the developing fetus contains a mix of proteins, some from the mother and some from a foreign source—the father. Ordinarily the mother’s immune system would attack material it senses as foreign or non-maternal. However, progesterone and other hormones produced by the placenta cause the mother’s immune system to tolerate the fetus.

Research with HIV-negative women has found that in some cases supplementation with progesterone can help reduce the risk of pre-term birth by as much as 45%.

The next report focuses on Canadian research on progesterone and premature birth among HIV-positive women.
REFERENCES:

F. Premature births, protease inhibitors and progesterone

As mentioned earlier in this issue of *TreatmentUpdate*, in Canada and other high-income countries the use of potent anti-HIV therapy (commonly called ART or HAART) during pregnancy along with other steps can greatly reduce the risk of mother-to-child transmission of HIV.

Protease inhibitors are a commonly prescribed class of anti-HIV drugs for pregnant women in high-income countries. Examples of protease inhibitors in common use today include the following:

- a fixed-dose combination of lopinavir + ritonavir (Kaletra)
- darunavir (Prezista) + ritonavir (Norvir)
- atazanavir (Reyataz) + ritonavir

Researchers in Toronto and elsewhere in Canada have found that “the benefits of ART far outweigh the potential adverse effects” for both the mother and the fetus. However, in recent years, as treatment guidelines in high-income countries shift toward encouraging all HIV-positive people, regardless of CD4+ count, to initiate ART, and new drugs have become available, more research is needed to help doctors better understand the safety of ART during pregnancy.

Some studies have found an increased risk for the following problems in HIV-positive pregnancies:

- preeclampsia – a syndrome of higher-than-normal blood pressure and excess protein in the urine that can develop during pregnancy
- premature birth
- infants with less-than-ideal birth weight

The cause of these problems is not clear.

Canadian research

Researchers in Toronto have been investigating the potential impact of protease inhibitors on pregnancy. In a series of complex experiments, researchers studied the impact of ART on cells, mice and pregnant women. Their findings suggest that a particular component of ART—the class of anti-HIV drugs called protease inhibitors—reduces levels of the hormone progesterone. This hormone is important for the growth and survival of the fetus. The researchers are planning a pilot study of a progesterone cream with pregnant HIV-positive women who use protease inhibitors.

Lab studies with cells

In experiments in the lab with cells that can develop and form the placenta, researchers studied the impact of anti-HIV drugs, either singly or in combinations commonly used in pregnancy. The researchers tested three main classes of anti-HIV drugs as follows:

**Nukes (nucleoside analogues)**
- AZT (Retrovir, zidovudine and in Combivir and Trizivir)
- 3TC (lamivudine and in Combivir, Kivexa, Trizivir and Triumeq)

**Non-nukes**
- nevirapine (Viramune)

**Protease inhibitors**
- atazanavir
- darunavir
- lopinavir
- ritonavir

The three main protease inhibitors—atazanavir, darunavir and lopinavir—are generally taken with a small dose of another protease inhibitor, ritonavir.
The purpose of the small dose of ritonavir is to raise the concentration of the main protease inhibitor in the blood and keep it elevated for about 24 hours. In this way, many regimens containing protease inhibitors can be taken just once daily. Ritonavir has this effect in a large part because it impairs the activity of enzymes in the intestine and liver that can break down protease inhibitors. It also impairs the activity of tiny pumps inside of cells that attempt to flush foreign substances out of a cell. Ritonavir and other drugs that have a similar effect are commonly called boosters.

As protease inhibitors are generally used with a booster, researchers tested combinations of protease inhibitors with low-dose ritonavir.

**Experiments with cells**

The researchers used cells that develop into the placenta. They found that, in general, exposure to protease inhibitors (singly) reduced the cells’ production of progesterone. The strongest effect was seen with exposure to ritonavir. However, atazanavir and lopinavir also reduced progesterone production. Exposure to darunavir did not reduce progesterone production.

Similar effects were seen when protease inhibitors were used in combination with ritonavir. Neither nukes nor non-nukes affected progesterone levels.

**Experiments with pregnant mice**

Researchers gave pregnant mice doses of protease inhibitors that resulted in drug concentrations similar to those seen in pregnant women who use such drugs. The researchers found that protease inhibitor–based regimens significantly reduced progesterone concentrations in mice. Furthermore, by reducing the level of progesterone in the pregnant mice, protease inhibitors indirectly affected fetal health by reducing the chances of survival. A mouse’s body can absorb a dead fetus in a process called resorption. Among the fetuses that did not undergo resorption, most did not achieve a normal weight while in the wombs of pregnant mice.

It is important to bear in mind that mice in this experiment received very high concentrations (for mice) of protease inhibitors. As such, it should not be surprising that they experienced adverse reactions, both biochemically and physically. However, such concentrations of protease inhibitors are within the normal and safe range for humans and there have not been any reports of fetal resorption in HIV-positive pregnant women treated with protease inhibitors.

In contrast, pregnant mice given a combination of ATZ + 3TC did not develop problems with progesterone and their fetuses were of normal weight. However, the survival of the fetuses was affected as resorption still occurred for some reason.

Researchers gave some pregnant mice protease inhibitors supplements of progesterone. As a result, the weights of their fetuses increased but did not reach the normal range. Furthermore, some fetuses continued to die and undergo resorption by the mother.

**Studies in women**

Researchers collected blood samples from 27 HIV-positive pregnant women, most of whom (22 of 27 women, or 82%) were taking protease inhibitor–based ART. Among these 22 women, a majority (55%) was taking Kaletra (lopinavir + ritonavir). None of the women smoked tobacco or used street drugs.

For general purposes of comparison, researchers also observed the pregnancies of 17 HIV-negative women.

On average, all the women in the study were in their 26th week of pregnancy and were of similar age (33 years) and ethno-racial background. In general, babies born to HIV-positive women weighed less than those born to HIV-negative women. Rates of premature delivery were not different between the two groups of women.

However, HIV-positive women tended to have statistically significantly less progesterone in their blood (132 ng/mL) than HIV-negative women (180 ng/mL).

Among HIV-positive women, progesterone levels were lower in users of protease inhibitors than in women who used other components of ART.
Points to consider

1. The Toronto research consists of a series of complex experiments with cells, mice and pregnant women. The data from the experiments strongly suggest that the use of certain protease inhibitors during pregnancy is linked to lower progesterone levels and lower birth weight.

2. ART improves the overall health of HIV-positive women and greatly reduces the risk of transmitting HIV to the fetus and to the baby during birth. However, protease inhibitor–based ART may, in some cases, cause the placenta to produce less progesterone and possibly increase the risk of the mother giving birth prematurely.

3. The present study in pregnant women was small, observational in design and not a randomized controlled clinical trial (RCT). Bear in mind that an RCT would require a large number of women, likely from many countries, would be complex and take several years to complete, and therefore would be an expensive and labour-intensive undertaking. Due to the limitations with observational studies, the researchers cannot be certain that protease inhibitors were responsible for the low birth weights noted in the offspring of HIV-positive women.

4. It is also possible that there were immunological issues that have not been fully explored that could have played a role in the pregnancy results that the Toronto researchers found in HIV-positive women. For instance, the placenta produces hormones, including progesterone, that somewhat weaken the immune system of the mother so that the fetus (which contains genetic material from both its mother and father) can survive. It is possible that protease inhibitors could have an effect on the immunological balance between the mother and fetus. This could, in theory, affect fetal health and outcomes, such as low birth weight.

5. The Canadian researchers with the help of the Canadian HIV Trials Network (CTN) are going to be exploring a pilot study—code-named CTNPT 025—of progesterone supplementation in pregnant HIV-positive women. In part, researchers will assess if it is possible to recruit women for such a study in Canada. For further details about this, contact the CTN.

6. The apparent lack of effect of darunavir on progesterone levels is intriguing and needs to be assessed in further studies.

REFERENCES:

G. Attitudes toward rapid HIV testing during labour

In Canada and other high-income countries researchers estimate that a sizeable fraction of HIV-positive people (about 25% in Canada, according to the Public Health Agency of Canada) are not aware of their infection status. If the spread of HIV is to be reduced and the benefits of ART brought to more people, health authorities need to place more emphasis on reducing barriers to the offer of an HIV test accompanied by counselling and swift referral to care and treatment.
As mentioned earlier in this issue of TreatmentUpdate, HIV testing, counselling and the use of potent combination therapy (commonly called ART or HAART), along with other measures, can improve an HIV-positive mother’s health and greatly reduce the risk that she will give birth to a baby with HIV.

However, for an HIV-positive mother and her fetus to benefit from ART, she must first know her HIV status. Hospitals have encountered visits from women very late in pregnancy or who were in labour and who had no idea of their HIV status. In such cases, HIV testing must be done with rapid testing to help doctors decide if measures are necessary to protect the fetus during and after the birthing process.

In the summer of 2011, as part of a study, researchers at St. Michael's Hospital in Toronto surveyed 152 pregnant women about the acceptability and attitudes that they have toward receiving the possibility of an HIV testing during labour. The researchers reported that nearly 60% of women would accept such testing. If the test came back positive, 94% of women would accept taking ART and would use formula to feed their infants (HIV can be spread via breast milk).

Results

A total of 92 women completed the questionnaires. They were an average of 30 years old, most had more than a high school education and, according to the researchers, “all were HIV-negative.”

In total, 80% of the women disclosed that they had previously been tested for HIV (and were negative). Seventy-one percent of the women “were aware of having been tested [for HIV] during their current pregnancy.”

The main reasons that some women gave for refusing a potential HIV test included the following:

- 39% did not want to know their test result
- 29% felt that they would be in too much pain during labour

The researchers found that barriers to HIV testing centred around the following concerns raised by the women:

- disapproval of their HIV status in the community
- a negative reaction from their partner to a possible positive test result

Women who stated that they were not likely to consent to HIV testing had the following concerns:

- they wanted to “know more of the benefits of early [HIV] diagnosis”
- they wanted to know how long they had to wait for the test result
- they were concerned about the testing process
- they were concerned about the confidentiality of the test result

Women who were willing to undergo HIV testing compared to women who did not wish to undergo such testing were significantly more interested in the following:

- learning about HIV treatment options
- learning about access to health services
- getting help and advice for how to tell a partner about a possible positive HIV test result

The researchers asked women about issues that would make the offer of an HIV test more acceptable and some of their responses were as follows:

- if information was made available about the testing process
- if they received individualized counselling
- if they could participate in a discussion to learn more about how to prevent mother-to-child transmission of HIV

The majority of women said that they would like to discuss the test results with a doctor, preferably in a setting that offered privacy.

The study’s findings underscore the type of information and counselling that would make pregnant women comfortable when the offer of an HIV test is made.
Bear in mind

As the researchers asked women for their responses to the idea of an HIV test, they are not certain how these women might respond to the offer of an actual test during labour.

The researchers admit that their study “did not include many women who would be considered high risk for HIV such as [those who use street drugs, sex trade workers] and refugees from [regions where HIV is relatively common].”

The findings from the present study are useful because they can be used, together with the help of pregnant women, to develop sensitive HIV testing programs for this population.

REFERENCE:


H. Pregnancy-related resources

If you are pregnant or want to have a baby and are concerned about having a healthy baby, speak to your doctor and nurse.

Resources

Society of Obstetricians and Gynaecologists of Canada

*Canadian HIV Pregnancy Planning Guidelines*

*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*

*Information for Women who are Diagnosed with HIV during Pregnancy*

*Pregnancy Planning Information for HIV+ Women and Their Partners*

*Information for HIV+ New Moms*
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 provides information resources to help people living with HIV 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.

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© CATIE, Vol. 27, No. 1
January 2015

ISSN 1181-7186 (print)
ISSN 1927-8918 (online)
CATIE Ordering Centre Catalogue Number ATI-60225E
(Aussi disponible en français, ATI-60225F)

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

What CATIE Does

CATIE is Canada's source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life. For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

CATIE Publications

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

CATIE News
CATIE's bite-sized HIV and hepatitis C news bulletins.

HepCInfo Updates
CATIE's bi-weekly electronic newsletter highlighting key hepatitis C prevention, treatment and epidemiology information.

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 Positive Side magazine
Holistic health information and views written by and for people living with HIV.

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

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