U.S. analysis of the safety of ART during pregnancy

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-cotrimoxazole) and the antiparasite 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.

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—Sean R. Hosein

REFERENCES:

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