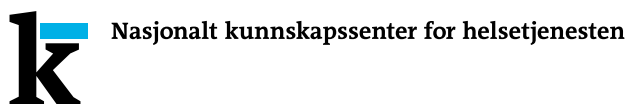


Antiretroviral drugs, genotoxicity, and adverse effects

Notat fra Kunnskapssenteret
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Background: Antiretroviral drugs (ARVs) are used for treating HIV-infected patients and also specifically for reducing the risk of mother-to-child transmission of HIV in relation to pregnancy and childbirth. In this report we review the consequences that have been demonstrated for children following in utero exposure of these drugs. We focus mainly on the groups of drugs that are known to be potentially genotoxic (NRTIs). The risk of cancer-development is the concern that is most commonly related to genotoxicity, however we also review other outcomes we believe to be important. **Methods:** This is a summary of relevant research reports identified through searches in several databases and reference lists in relevant papers. **Main results:** • The research findings currently available do not indicate an increased risk of adverse health outcomes related to in utero exposure of ARVs. • Zidovudine for preventing mother-to-child transmission has not been associated with premature delivery, still birth, low birth weight, birth defects or any other major adverse health outcomes in the first years of life.

(fortsetter på baksiden)

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• Also, for ARV-treatment during pregnancy, no serious adverse effects have been demonstrated in the young children. Despite this, some uncertainty remains regarding the risk of short term adverse effects:

- The use of some drugs (NRTIs) may lead to a slightly increased risk of mitochondrial disease
- Protease inhibitors may increase the risk of premature birth.
- Exposure to the drug efavirenz during the first trimester may increase the risk of malformations.

Other aspects: The long-term safety of the drugs, e.g. the risk of cancer-development, is not known due to the limited period of time the drugs have been used. Studies are ongoing to monitor the long term consequences of in utero exposure to ARVs. It is also too early to establish whether genotoxic effects from these drugs may be transferred across generations. The possible risks linked to the use of ARVs in pregnancy need to be weighed against the established benefits. For every five HIV-positive pregnant women on ARVs, about one child less becomes infected. The report is commissioned by Norad.

Title Antiretroviral drugs, genotoxicity, and adverse effects

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Summary

The Norwegian Agency for Development Cooperation (Norad) requested a summary of research findings related to clinically important adverse effects from in utero exposure to antiretroviral (ARV) medication. The request was motivated by concerns that have been raised related to genotoxic properties of some ARVs.

In this report we review the consequences that have been demonstrated for children following in utero exposure of ARVs. We focus mainly on the groups of drugs that are known to be potentially genotoxic. The risk of cancer-development is the concern that is most commonly related to genotoxicity, however we also review other outcomes we believe to be important.

We identified two high quality systematically developed literature reviews and several traditional reviews of lower methodological quality.

The research findings currently available do not indicate an increased risk of adverse outcomes related to in utero exposure of ARVs. Zidovudine for preventing mother-to-child transmission has not been associated with premature delivery, still birth, low birth weight, birth defects or any other major adverse health outcomes in the first years of life after in utero exposure. Also, for ARV-treatment during pregnancy, no serious adverse effects have been demonstrated in the young children.

Despite this, some uncertainty remains, also regarding the risk of short term adverse effects after in utero exposure:

- The use of some drugs (nucleoside reverse transcriptase inhibitors) may lead to a slightly increased risk of mitochondrial disease
- Protease inhibitors may increase the risk of premature birth
- Exposure to the drug efavirenz during the first trimester may increase the risk of malformations

The long-term safety of the drugs, e.g. the risk of cancer-development, is not known due to the limited period of time the drugs have been used. Studies are ongoing to monitor the long term consequences of in utero exposure to ARVs. It is also too early to establish whether genotoxic effects from these drugs may be transferred across generations. However, as of today there are no documented examples in humans of any drug-induced genetic changes being transmitted to unexposed offspring.

The possible risks linked to the use of ARVs in pregnancy need to be weighed against the established benefits. For every five HIV-positive pregnant women on ARVs, about one child less becomes infected.

Background

Antiretroviral drugs (ARVs) are used for treating HIV-infected patients and also specifically for reducing the risk of mother-to-child transmission of HIV in relation to pregnancy and childbirth. The effectiveness of the drugs in extending and improving quality of life in HIV-infected patients is firmly established [1]. Likewise, the drugs have been shown to substantially reduce the risk of mother-to-child transmission [2]. Mother-to-child transmission (MTCT) of HIV can occur during pregnancy, during labour or after birth. Transmission during pregnancy is thought to account for 25-40% of MTCT, the remaining cases occurring during delivery or due to breastfeeding after birth.

Globally, a large proportion of HIV-infected have no access to this treatment. In an attempt to make ARVs more widely available, the World Health Organization (WHO) launched the "3 by 5"-campaign, with the aim of having 3 million patients on ARVs by the end of 2005. Several other international initiatives have been introduced aimed at increasing access to ARVs.

Some concerns have been raised related to an increase in the use of ARVs. A major worry is linked to the fact that some ARVs are genotoxic, i.e. causing changes to genetic material. The fetus is exposed to this potential influence when ARVs are taken during pregnancy. Damaged DNA may, for instance, lead to cancer. The possibility that detrimental drug-induced DNA-damage may be transferred from one generation to another has also been proposed.

In January 2006 The Norwegian Development Agency (Norad) asked the Norwegian Knowledge Centre for the Health Services to summarise the research findings that are related to this subject. Primarily, an overview of existing systematic reviews or other reviews of acceptable quality was requested, focusing mainly on important outcomes for the offspring of women that have been taking ARVs during pregnancy.

ARVs have only been widely used since the early 1990s. Consequently, the chances of detecting long-term adverse effects are limited. However, a large number of children have been exposed to ARVs in utero, making it possible to detect adverse effects in the shorter term.

Concerns related to genotoxicity are mainly related to one specific subgroup of ARVs, the nucleoside reverse transcriptase inhibitors (NRTIs), e.g. zidovudine (AZT) and lamivudin (3TC). This is because these drugs act by incorporating into the DNA of the HIV-virus, thereby inhibiting further DNA-replication.

Assessing risk of in utero exposure of drugs is commonly done by using animal models, and several experiments have been conducted where pregnant rodents (mice and rats) have been given NRTIs. It has been shown that such exposure may lead to increased risk of cancer-development in mice, but the risk is dosage-dependant [3]. At dosages comparable with what is used in human medicine, the risk of cancer-development seems not to be increased in mice [3,4]. There are major biological differences between rodents and humans, which makes interpretation of these findings difficult. Studies of pregnant monkeys have demonstrated that traces of zidovudine can be found in cells in several organs taken from the offspring [3].

Drugs from two of the major groups of ARVs, the NRTIs and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) readily cross the placenta and enter the blood stream of the fetus. The third group of ARVs, the protease inhibitors (PIs), does not. Zidovudine has been found in the DNA of white blood cells from cord blood of babies exposed to the drug in utero [3].

These findings put together give reasons to be concerned that genotoxic effects from ARVs may lead to adverse health outcomes for children that have been exposed in utero.

Several regimens of ARVs during pregnancy have been employed, involving various drugs and for various lengths of time. Thus, there is considerable variation in terms of ARV exposure depending on the regimen given.

In this report we review the consequences that have been demonstrated for children following in utero exposure of ARVs. We focus mainly on the groups of drugs that are known to be potentially genotoxic (NRTIs). The risk of cancer-development is the concern that is most commonly related to genotoxicity, however we also review other outcomes we believe to be important.

There is an association between ARV-treatment in HIV-infected individuals and increased risk of disease related to mitochondrial dysfunction [5]. This is thought to be mediated by drug-effects on mitochondrial DNA. In this report we only review the effects on offspring. Consequently, adverse effects that are seen in individuals taking ARVs, are beyond the scope of our assignment, and will not be addressed here.

Methods

We searched several databases (The Cochrane Library, PubMed and Embase) for research reports. Reference-lists in relevant papers were also used as a source.

The search strategy was developed in cooperation between two persons (AF and INN). AF refined the strategy, conducted the searches, and assessed the search-results. Potentially relevant articles were assessed in full-text by AF and INN.

The findings were summarised qualitatively by AF and INN.

Further details on the literature-search are available from the authors.

Results

Literature-search

We identified two high quality reviews that we considered relevant:

1. A systematic review (Cochrane) reporting outcomes for children of women that had participated in clinical trials of ARVs to prevent mother-to-child transmission of HIV [2], and
2. A systematically developed overview of research relevant to prenatal screening for HIV, prepared for the U.S. Preventive Services Task Force. This document covered systemic reviews as well as primary studies [6]

We also identified nine traditional review articles addressing our subject [4,7-14]. The difference between the systematically developed reviews and the traditional ones is that the authors of the former conducted thorough searches for relevant research papers, and that their methods of identifying, summarising and interpreting data are well described. For instance, none of the traditional review authors have reported their strategy for identifying relevant literature. However, the traditional reviews varied considerably in terms of quality, and some of them are comprehensive literature reviews despite their methodological weaknesses.

Premature delivery

There is no evidence from clinical trials that zidovudine increases the risk of premature delivery [2]. However, there are mixed findings on a possible association between combination ARV-therapy and premature delivery. Findings from some studies indicate that the use of PIs during pregnancy may confer an increased risk [6]. It is however difficult to assess the risk of ARV therapy in isolation from other risk factors that mothers receiving ARV therapy may be exposed to.

All the literature reviews we have identified conclude similarly [4,7-14].

Still birth

No increase in stillbirths has been observed in clinical trials comparing zidovudine and placebo for preventing mother-to-child transmission of HIV [2].

All literature reviews we have identified conclude that there is no evidence of an increased risk of still birth following in utero exposure to ARVs [10,13].

Birth defects

No increase in any specific fetal abnormality has been identified for the use of ARVs during pregnancy [6]. However the use of the NNRTI efavirenz is generally discouraged during pregnancy due to a high rate of deformities in exposed monkeys [4].

All literature reviews we have identified conclude similarly [4,7-14].

Weight and height

The rate of children with birth-weights below 2,500 g was not increased among those exposed to zidovudine compared to children of women receiving placebo, in clinical trials [2]. No increase in the rate of low birth weight has been identified with currently recommended ARV-regimens [6]. Longer term studies (up to 4 years) are only available for zidovudine, and these findings do not indicate that exposed infants are at risk in terms of growth or development [6].

All literature reviews we have identified conclude similarly [7,9,10,13].

Mitochondrial disease

There is evidence of mitochondrial dysfunction in children exposed to ARVs in utero based on biochemical and molecular studies. However, the clinical meaning of this is unclear [6]. An association between clinical symptoms or deaths due to mitochondrial dysfunction has not been found among uninfected infants exposed to ARVs [6].

The review articles we have identified put varying emphasis on the findings from a French study of 1,754 infants that had been exposed to zidovudine or a zidovudine-lamivudine combination in utero [4,7-14]. The French researchers reported possible mitochondrial disease among eight of these infants, including two deaths. A review of 16,000 children in the U.S. did not find any increased mortality among children exposed to NRTIs, and no deaths among the children were found to be clearly linked to mitochondrial disease.

All literature reviews we have identified conclude that a slight increased risk of mitochondrial disease among infants exposed to NRTIs in utero can not be dismissed.

Cancer-risk

The reviews we have identified base their assessment of cancer-risk on a study-report from 1999 where children had been followed up for up to six years after in utero exposure to zidovudine [4,6-13]. There were no cases of tumours or deaths from cancers reported at that time.

There is broad consensus among the literature reviews that the currently available data do not indicate an increased risk of cancer, however several of the authors point out that longer term data are needed to rule out this possibility.

Some of the children from the 1999-report are still followed up with regards to cancer risk, and younger children exposed to ARVs in utero are included in this cohort. An updated report of cancer-incidence in these children has been prepared, and no cases were found among 1,859 children exposed to ARV-treatment in utero (Susan Brogly, personal communication). The children in the study were now up to 15 years old (median: 3 years).

In The European Collaborative Study a cohort of uninfected children born by HIV-positive mothers is being followed up. By the end of 2001 2,414 had been included in the study, of which 906 had been exposed to ARVs in utero. One case of lymphoma and one brain tumor was diagnosed, both occurring in unexposed children. No malignancies were reported among children that had been exposed to ARVs in utero. The median length of follow-up was 2.2 years (range: 0 to 15.9 years) [15].

Other diseases

One of the few adverse effects clearly demonstrated to be associated with in utero exposure to zidovudine is a mild, transient anaemia, usually not requiring any treatment [8-11,13].

Discussion

We have identified a series of review articles on adverse effects in children exposed to ARVs in utero. The conclusions are similar in all the reviews: Very few adverse effects have been demonstrated so far, and none of them are considered serious. This is reassuring given the fact that some of the drugs have been shown to cause changes in DNA. ARVs have only been widely used since the early 1990s and the oldest children that are being followed up after in utero exposure are now in their teens. Thus, it is still too early to rule out a risk of adverse effects in the longer term, such as cancer.

The possibility that in utero exposure to ARVs may cause genetic change affecting future generations has been proposed. Obviously there are no observations in humans that can help us to quantify this risk. We have not identified any animal-experiments where this has been tested. As a general rule, the risk of transferring DNA-change caused by drugs to the following generation seems very small: “In man, there is as yet no documented transmission to the offspring of drug- or chemical-induced heritable changes” [16].

This brief report is based on the findings from literature reviews conducted by others. We find it highly unlikely that we would have concluded differently if we had conducted our own systematic review of relevant research findings.

The WHO has published guidelines for prevention of MTCT of HIV in resource-constrained settings, and their summary of what is currently known about the risk for mutagenic and cancerogenic effects corresponds well with our findings [17].

Conclusion

In the shorter term, in utero exposure to ARVs appears not to be associated with serious adverse effects. However, whether there is a risk involved in the longer term, remains to be seen. The potential risk must be weighed against the benefits associated with such treatment. Without ARV-treatment, approximately 30 % of children of HIV-positive mothers become infected (estimates range from 13 % to 42 %) [6]. This risk is more than halved with treatment [2]. Thus, for every five HIV-positive pregnant women taking ARVs, about one child escapes infection.

Systematic follow-up of exposed children is required in order to establish whether the use of ARVs in pregnancy leads to adverse health outcomes in the long term. This is a challenging task, but cohorts of children in Europe and in the U.S. are being monitored with this specific purpose in mind [18]. WHO has proposed to launch similar studies in African countries [19].

Potential conflicts of interest

AF is a board member of MSF-Norway and has previously, in that capacity, lobbied for increased availability of antiretroviral drugs.

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