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Safety and Tolerability of Zidovudine

WHO

Zidovudine (ZDV) is the "oldest" antiretroviral agent in clinical use, approved over 10 years ago, and therefore the most extensively evaluated.

Current Reccomendations for the use of Zidovudine

In combination therapy for treatment of adult and paediatric HIV Infection.[1-4,44]
In combination therapy for the prevention of Post Exposure Prophylaxis (PEP) [1-4,44]
As monotherapy for the prevention of Mother to Child Transmission of HIV (MTCT) [5]

Zidovudine, for the indication of prevention of mother to child transmission (MTCT) of HIV infection , is included in the 1998 World Health Organisation's Model List of Essential Drugs . [6]

Frequently Reported adverse effects

	Frequency [7]
Headache	42%-62.5%
Gastrointestinal Intolerance	
nausea	46% - 61%
anorexia	11%-20.1%
vomiting	6%-25%
Bone Marrow Toxicity	
granulocytopenia	1.8%-37%
anaemia	1.1% - 29%

Headache and gastro-intestinal intolerance tend to occur soon after initiation of treatment with Zidovudine and often subside with continued treatment.

Bone marrow toxicity

This is the major dose-limiting toxic effect of Zidovudine.[3]
It manifests clinically as **anaemia** , **neutropenia** and sometimes as **platelet deficits** with onset after several weeks of treatment. Anaemia has been reported in all the clinical situations where Zidovudine is used and in patients of all ages , including infants born to mothers who had received Zidovudine during pregnancy.[8,9,10]
Haematological indices must be monitored before and during therapy with Zidovudine.
In the context of MTCT prevention, the occurrence of anaemia seems to be related to the duration of therapy with Zidovudine. The "short course" regimens of Zidovudine adapted for this indication in developing countries [26] may therefore carry a lower risk of producing anaemia in the mothers. Anaemia in infants , following perinatal exposure to Zidovudine, has generally been reported as mild and often does not require treatment.

Nevertheless, in pregnancy , there are separate co-factors contributing to the development of anaemia and women should only be offered Zidovudine after correction of any pre-existing deficiency anaemia.
The World Health Organisation recommends that Zidovudine be withheld from pregnant women with Hb < 8 g / L . [5]

The toxic potential of Zidovudine on the bone marrow is greater in advanced disease with a "more damaged " immune system. [3,11]
When Zidovudine is used in a short course, as in PEP for example,[12] or when longer term treatment is discontinued, the haematological abnormalities revert to normal .[3]

Less frequently reported adverse effects

Less frequently reported adverse effects , that are not life threatening , include insomnia and hyperpigmentation of the skin and nails.[7]
Muscle inflammation (myopathy) causing muscle pain and weakness; fatty enlargement of the liver and lactic acidosis are rare but potentially serious adverse effects.[3]

Mitochondrial Toxicity

Mitochondrial toxicity is a rare *class toxic effect* shared by the **nucleoside analogues.**[16,17,18] Zidovudine belongs to this class of drugs.

Fatty enlargement of the liver and lactic acidosis , which have long been acknowledged as rare toxicities of Zidovudine; [13,14,21] along with the myopathy that has been linked to Zidovudine treatment, [15] are attributed to this toxic effect on cellular mitochondria. There are several anecdotal reports of this phenomenon .[19,20]

Recently, a group of French researchers reported some cases of fatal mitochondrial toxicity, manifesting as neurological dysfunction , in children exposed , before birth , to a combination of Zidovudine + Lamivudine. From this study, mitochondrial toxicity is not clearly attributable to a single drug in the combination.
The French authors go on to state that further analysis of the toxic effects of these drugs is necessary and that the current recommendations for the use of Zidovudine in the prevention of MTCT should be maintained.[22]
In response to this report from France, a team of investigators in the United States (US) was formed , with the purpose of analysing records from available US cohorts , to look for evidence of fatal mitochondrial toxicity. From an initial retrospective review of deaths among 15,000 children exposed to a nucleoside analogue during the perinatal period, they report no death attributable to mitochondrial toxicity.[23]
This **Perinatal Safety Review Working Group** in the US has made available to us a pre-publication manuscript with results of the now expanded analysis which includes records on over 20,000 children. They also conclude that current recommendations on the use of Zidovudine for the prevention of MTCT should be maintained.

Effects of Zidovudine on the new born.

The most convincing arguments for the comparative safety of Zidovudine are from observational studies on children exposed to Zidovudine *in utero* in the context of MTCT. This is the only instance where Zidovudine is recommended for use on its own and the recipients - the fetus and the new born , are delicate creatures relatively vulnerable to toxicity .
The longest follow up data is published from the American Paediatric Aids Clinical Trial Group (PACTG) - Protocol 076. A cohort of HIV negative children, exposed to Zidovudine before and after birth , is prospectively observed for physical and mental growth and development , for the occurrence of tumours and for the integrity of the immune system . At up to 5.6 years follow up no major adverse effects are reported.[24]
Other studies, albeit with shorter periods of follow-up, have similarly reported on the safety of Zidovudine used in this context.[25,26,27]
A study done in India , between 1990 and 1993, reported multiple minor congenital abnormalities observed in babies whose mothers had been exposed to Zidovudine.
The indication for Zidovudine in these study subjects was therapy of HIV infection and not MTCT prevention. In analysing the results of this study, the researchers take into account that there are multiple factors which contribute to an increased likelihood of birth defects in the HIV infected population and argue that the observed frequency of birth defects , from their study , was not much higher than baseline risk in the general population reported from similarly designed studies. They conclude that from this study population , no particular pattern of fetal abnormality was directly attributable to Zidovudine toxicity.[28]
Continued observations for the long term adverse effects of Zidovudine used in this context are still required. [29]

Zidovudine and tumours

Much attention has been given to reports, from animal experiments, that Zidovudine causes tumours. There are 2 contradictory reports. In one study, published in 1997, Olivero and colleagues demonstrated that Zidovudine could be incorporated into the genetic material (DNA) of mice and monkeys following pre-natal exposure to the drug. After 1 year , they recorded an increased incidence of certain tumours in the mice.[30]
These authors concluded at the time , that Zidovudine was toxic to genes and that this was a factor in the subsequent development of tumours observed in the mice.
They called for similar experiments to be carried out on humans and recently it has indeed been demonstrated that Zidovudine can be incorporated into the DNA of infants following exposure *in utero*. [32]
The clinical significance of these findings is not yet clear.

The other study, published at about the same time , contradicts the first.
Ayers and colleagues concluded that under the conditions of their study on mice, there is no evidence that Zidovudine is a transplacental carcinogen. [31]
From the PACTG – 076 cohort , no increased incidence of tumours in children has been observed at up to five and a half years of follow up. [24,27]
There are other reports of Zidovudine toxicity from animal experiments,[33,34]
which are not substantiated by evidence from studies on humans.
Clinical experience at present provides no evidence that Zidovudine causes tumours.

Effect of AZT on the immune system

There is no direct evidence for a deleterious effect of Zidovudine on the immune system. A paper from the Italian Register for HIV Infection in Children reports a more rapid progression of HIV disease in children exposed to Zidovudine perinatally.[35]
These researchers caution against using their results as a reason to forbid Zidovudine use. They propose that maternal to child transmission of drug resistant HIV virus may be a contributing factor and call for further studies to clarify this.
From the PACTG – 076 observational cohort, there is no association found between perinatal exposure to Zidovudine and more rapid disease progression among the HIV infected sub-group of children.[10]

Drug Resistance

Strains of HIV with reduced susceptibility to Zidovudine were isolated as early as 10 years ago. With increasing use, the occurrence of drug resistance has increased to an estimated 10 % of the current transmission seen in some developing countries. [36,43]
Drug resistant HIV can be transmitted from one person to another [37] and from mother to child .[38] Infection with drug resistant strains of HIV may predict a more rapid progression of disease; [35,39] and resistance to one drug in a class confers cross resistance to other drugs of the same class thereby limiting the patient's future treatment options.[40,41]
Incompletely suppressive drug regimens (for example, prolonged monotherapy) which allow for continued viral replication , favour natural selection for drug resistant HIV strains.[42,43] In order to delay the emergence of drug resistance, combination therapy with highly active antiretroviral agents is recommended. [44]

In the prevention of MTCT, Zidovudine is used as monotherapy in short courses.
Few studies have addressed the clinical implications of selecting for drug resistance with this regimen. Eastman and colleagues have investigated vertical transmission of Zidovudine resistant HIV in the PACTG cohort .[45] This study is mainly designed to examine the relationship between transmission of Zidovudine resistant HIV and the success of MTCT prophylaxis. They find no strong association between the occurrence of genotypic Zidovudine resistance and failure of prevention of MTCT.
They also report , however , that as long as the mother has well preserved immune function (CD_4 count > 200 /μL) and limited or no prior experience of Zidovudine , the chances of resistance developing by the time of delivery are low. This may be partly explained by the fact that resistance to Zidovudine takes several months to develop. [43]
Two other groups , studying prevention of MTCT, report similarly on low rates of transmission to infants of Zidovudine resistant HIV virus .[46,47]

Important drug interactions [7]

Several medications are likely to cause additive bone marrow toxicity when used concurrently with Zidovudine and among these are agents likely to be used for the treatment of opportunistic infections in HIV / AIDS e.g: *Pyrimethamine; Sulfadiazine; Co-trimoxazole; Ganciclovir; Amphotericin B; Flucytosine.*
Haematological evaluation is advised .

Fluconazole interferes with the metabolism of Zidovudine making toxicity more likely at normal treatment doses. Dosage adjustments are advised.

The anti-tuberculosis medications – *Rifampicin* and *Rifabutin* induce the metabolism of Zidovudine , thereby lowering the therapeutic levels of the latter.
The clinical effect of Zidovudine should be monitored and the dosage adjusted if necessary.

In one **animal** experiment ,[48] concurrent use of Zidovudine and the anti-tuberculosis drugs *rifampicin* and / or *isoniazid* increases the potential for haematologic toxicity. This interaction has not been studied in humans.

Evidence for safety of Zidovudine in developing country settings

The bulk of the literature on clinical tolerability of Zidovudine originates from studies in industrialised countries where the experience in its therapeutic use is much broader. However, for the specific indication of short course Zidovudine monotherapy in the prevention of MTCT, the clinical trials were carried out and are on going in developing countries.[25,26] From the currently available reports of these trials, it is noted that the safety and tolerability profile of Zidovudine does not differ significantly in developing countries.

Conclusion

In conclusion, WHO considers Zidovudine to have an acceptable clinical safety profile. For the specific indication of the prevention of MTCT, WHO considers Zidovudine to be an essential drug that should be made available at all times , in adequate amounts and in the appropriate dosage formulations.
Zidovudine should be used under careful medical supervision , paying due attention to the relative clinical contraindications and monitoring for potential toxicities.

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