AZT: Unsafe at Any Dose?

AZT, also known as Zidovudine, ZDV and Retrovir, is one of the most commonly prescribed anti-HIV drugs, and the main drug prescribed to prevent transmission of HIV from mother to child. However, there are serious concerns about its toxicity and effectiveness. Read the referenced quotes below, and decide for yourself.

The quotes are categorized as:

- Warnings from Experiments with Animals
- Harmful Effects on Blood and Bone Marrow
- AZT and Cancer
- Harmful Side Effects, General
- Lack of Effectiveness…and Toxicity
- AZT and Mitochondria
- Muscle Disorders (including Heart)
- AZT and Pregnant Women, Fetuses and Children
- Increased Risk of Sickness and Death with AZT

Harmful Effects on Blood and Bone Marrow

AZT is known to suppress the ability of the body to produce red blood cells (anemia) and white blood cells (*-penia, e.g. neutropenia -- deficiency of neutrophils or pancytopenia -- deficiency of all types of cells).

"Reversible pure red cell aplasia is a recognized complication of both zidovudine and lamivudine, typically occurring within the first 3 months of therapy *[1,2]*. We report the case of a 29-year-old man with HIV, severe haemophilia A and hepatitis C, who developed reversible pure red cell aplasia 4 years after commencing zidovudine."

Weinkove R et al. Zidovudine-induced pure red cell aplasia presenting after 4 years of therapy. AIDS. 2005 Nov 18;19(17):2046-2047.

"For this study, 1278 patient charts were screened, and 758 were included in the study…Of *[these]*, 30.3% (230) were anemic (Hb *[hemoglobin]* level of 12.5 g/dL or less) at some time during the study…The majority of the ever-anemic patients (67%; 154 of 230) had a nadir *[lowest]* Hb level of 12.0 to 12.5 g/dL, which was considered mild to moderate

anemia…Anemia was significantly more prevalent in patients who were currently being treated with HAART regimens containing zidovudine *[AZT]*…The presence of an AIDS diagnosis was not an independent risk factor for anemia in multivariate logistic regression analysis, although markers of disease progression, such as decreasing CD4+ cell count and increasing viral load, remain independent predictors of risk. ”

Wills TS et al. Anemia prevalence and associated risk factors in a single-center ambulatory HIV clinical cohort. AIDS Read. 2004 Jul 12.

“Zidovudine *[AZT]* was generally well tolerated in this high-risk population…*[from Table II: 32%-Anemia grade >=2; 11%-Neutropenia; 13%-Thrombocytopenia; 45%-Received transfusion; 26%-Received erythropoetin; 11%-HIV infection; 8%-Died]*…Slightly more than half of the subjects had anemia severe enough to require a transfusion *[giving new meaning to the term 'well tolerated']*”

Capparelli E et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. J Pediatr. 2003 Jan;142(1):47-52
http://www2.us.elsevierhealth.com/scripts/om.dll/serve?action=searchDB&searchDBfor=pub&id=pd.

“Recent epidemiologic studies of HIV-related anemia have strongly and repeatedly associated low hemoglobin level with disease progression and mortality. Patients who are at greater risk for anemia may include those of African-American ancestry, and those with low CD4 cell counts, high virus load, and low mean corpuscular volume and those receiving zidovudine *[AZT]*…*[in one study]* for patients without anemia, 3.1% died by 12 months. In contrast, for patients with mild anemia, 15.9% had died, and for patients with severe anemia, 40.8% had died *[this association remained even after controlling for CD4/viral load measurements]* ”

Sullivan P. Associations of Anemia, Treatments for Anemia, and Survival in Patients with Human Immunodeficiency Virus Infection. J Infect Dis. 2002;185: S138-42.

“We conducted a longitudinal study of 797 human immunodeficiency virus (HIV) positive women (7732 visits) and 389 HIV-negative women (3651 visits) to characterize anemia... Risk factors for anemia *[included]* zidovudine use *[1.14 times more likely]*. Anemia was common and associated with an increased risk of death (hazards ratio, 1.64; 95% CI, 1.21 2.23) among HIV-positive women...the mortality rate during the follow-up period was 37% in those who were anemic at enrollment and 22% in those who were not anemic at enrollment ”

Semba RD et al. Prevalence and Cumulative Incidence of and Risk Factors for Anemia in a Multicenter Cohort Study of Human Immunodeficiency Virus Infected and Uninfected Women. Clin Infect Dis. 2002 Jan 15;34:260-6
www.journals.uchicago.edu/CID/journal/issues/v34n2/010718/brief/010718.abstract.html.

"1 patient *[out of a grand total of 10 in this clinical trial]* suffered from severe anemia resulting from ZDV *[AZT]* therapy"

Lafeuillade A et al. Pilot study of a combination of highly active antiretroviral therapy and cytokines to induce HIV-1 remission. J Acquir Immune Defic Syndr. 2001 Jan 1;26(1):44-55.

"In a retrospective evaluation of medical records of 32,867 HIV-infected persons followed in nine cities in the United States, the 1-year incidence of anemia, defined as a hemoglobin level <10 g/dl or a physician's diagnosis of anemia, was approximately 37% for patients with a clinical AIDS-defining condition; 12% for those with immunologic AIDS, defined as a CD4 count <200; and 3% for persons without either of these conditions…Use of ZDV either currently or in the past 6 months was associated with anemia…A total of 41.5% of those with a history of ZDV in the past 6 months and 27.7% of those without such history were anemic at baseline…The strong statistical associations between worsening parameters of HIV disease and increased likelihood of anemia…suggest that effective antiretroviral therapy may be associated with improvement in Hb *[hemoglobin]* levels *[!]* "

Levine AM et al. Prevalence and correlates of anemia in a large cohort of HIV-infected women: Women's Interagency HIV Study. J Acquir Immune Defic Syndr. 2001 Jan 1;26(1):28-35

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"Of variables related to HIV infection, low CD4+ cell count, AIDS diagnosis and receiving zidovudine *[AZT]* therapy were predictive for prevalent anemia "

van der Werf MJ et al. Prevalence, incidence and risk factors of anaemia in HIV-positive and HIV-negative drug users. Addiction. 2000 Mar;95(3):383-92.

"We found that 78.2% of the patients with mild or severe anaemia at baseline had received zidovudine *[AZT]* "

Mocroft A et al. Anaemia is an independent predictive marker for clinical prognosis of HIV-infected patients from across Europe. AIDS. 1999 May 28;13 (8):943-50.

"While effective drug therapy is continued in zidovudine*[AZT]*-treated HIV-infected patients…PROCRIT Reduces Transfusion Requirements and Helps Lift the Burden of Anemia. "

Advertisement for PROCRIT. 1997.

"the drug *[AZT]* has some serious side effects, the most important of which is myelosuppression *[damage to the ability of the bone marrow to produce new white blood cells]* "

Moore RD et al. Long-term safety and efficacy of zidovudine in patients with

advanced human immunodeficiency virus disease. Zidovudine Epidemiology Study Group. Arch Intern Med. 1991 May;151(5):981-6.

"178 subjects (34%) had a hemoglobin concentration below 5 mmol per liter *[anemia]*...A greater proportion of subjects in the standard-treatment *[high dose AZT]* group had a first episode of severe anemia earlier in the study, as compared with the proportion in the low-dose group. 134 subjects (26%) received red-cell transfusions (65 in the standard-treatment group and 69 in the low-dose group)...230 subjects(44%) had a *[low]* neutrophil *[infection fighting white blood cells]* count...134 (51%) in the standard-treatment group and 96 (37%) in the low-dose group...22 subjects (4%) had a *[low]* platelet *[blood clotting cells]* count. "

Fischl MA et al. A randomized controlled trial of a reduced daily dose of Zidovudine in patients with the Acquired Immunodeficiency Syndrome. N Engl J Med. 1990;323(15):1009-14.

"The occurrence of severe anemia, although more common in the 500-mg*[per day]* zidovudine *[AZT]* group than the placebo groiup (5 cases vs. 1 case), was rare in both grouips. The subjects in the 1500-mg group, however, had higher rates of anemia (6.3%) and neutropenia (6.3%)."

Volberding PA et al. Zidovudine in asymptomatic human immunodeficiency virus infection: a controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. N Engl J Med. 1990 Apr 5;322(14):941-9.

"One or more transfusions were reported for 19.7% of patients *[taking AZT]*, but anemia was reported as a serious adverse event in only 11.4% of patients. The mean time to first transfusion was 98 days after beginning therapy. "

Creagh-Kirk T et al. Survival experience among patients with AIDS receiving zidovudine. Follow-up of patients in a compassionate plea program. JAMA. 1988 Nov 25;260(20):3009-15.

"Zidovudine is well known to produce haematological toxicity in vitro and in some patients...It is worrying that bone marrow changes in patients on zidovudine seem not to be readily reversed when the drug is withdrawn…These findings have serious implications for the use of zidovudine in HIV positive but symptom-free individuals. "

Mir N, Costello C. Zidovudine and Bone Marrow. Lancet. 1988 Nov 19;2 (8621):1195-6.

"Between 10% and 25% of patients experienced decreases in granulocyte counts to less than 750/cubic-mm during each month of therapy…The incidence of anemia remained relatively constant over time. Approximately 10% of patients per month reported with hemoglobin levels less than 7.5 g/dl, and fewer than 5% were reported with levels less than 6.5 g/dl…At the physicians' discretion, transfusions with packed red blood cells were used to manage hemoglobin levels in patients with anemia *[Figure 4 shows that 20-25% of patients*

required transfusions during the main portion of the trial (12-52 weeks)]…Anemia and granulocytopenia remained the major reasons for dose reductions or discontinuation of zidovudine treatment. ”

Richman DD, Andrews J. Results of continued monitoring of participants in the placebo-controlled trial of zidovudine for serious human immunodeficiency virus infection. Am J Med. 1988 Aug 29;85(2A):208-13.

“nearly one half of patients treated with AZT for *[HIV]*-associated disease develop transfusion-dependent anaemia due to bone marrow depression ”

Dainiak N et al. 3’-Azido-3’-deoxythymidine (AZT) inhibits proliferation in vitro of human haematopoietic progenitor cells. British Journal of Haematology. 1988 Jul;69(3):299-304.

“Blood transfusion is often necessary in patients with AIDS, especially in those receiving AZT, a drug which produces severe anaemia in a proportion of recipients. Forty nine (36%) of 138 patients treated with AZT … required blood transfusion at least once. ”

Costello C. Haematological abnormalities in human immunodeficiency virus (HIV) disease. J Clin Pathol. 1988 Jul;41(7):711-5.

“In the current study, transfusion-dependent anemia occurred in 6 of 15 patients with AIDS and Kaposi sarcoma who were receiving zidovudine therapy. All 6 affected patients required their first blood transfusion between 3 and 9 weeks after starting zidovudine therapy, and each required 4 to 14 units of packed erythrocytes to maintain a hemoglobin level above 100 g/L over a 12-week study. ”

Walker RE et al. Anemia and erythropoiesis in patients with the acquired immunodeficiency syndrome (AIDS) and Kaposi sarcoma treated with zidovudine. Ann Intern Med. 1988;108:372-6.

“The hematocrit *[red blood cell count]* decreased in the same patients...with three of eight patients requiring red-cell transfusion by the fourth week of treatment. ”

Hymes KB et al. The Effect of Azidothymidine on HIV-related Thrombocytopenia. N Engl J Med. 1988 Feb 25;318(8):516-7.

“Four patients with *[AIDS]*, and a history of Pneumocystis carinii pneumonia developed severe pancytopenia *[marked decrease in all types of blood cells]*…12 to 17 weeks after the initiation of azidothymidine (AZT) therapy…Partial bone marrow recovery was documented within 4 to 5 weeks in three patients, but no marrow recovery has yet occurred in one patient during the more than 6 months since AZT treatment was discontinued. ”

Gill PS et al. Azidothymidine Associated with Bone Marrow Failure in the Acquired Immunodeficiency Syndrome (AIDS). Ann Intern Med. 1987 Oct;107 (4):502-505

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"Anemia…developed in 24% of AZT recipients and 4% of placebo recipients (P<0.001). 21% of AZT recipients and 4% of placebo recipients required multiple red-cell transfusions (P<0.001). Neutropenia (<500 cells per cubic millimeter) occurred in 16% of AZT recipients, as compared with 2% of placebo recipients (P<0.001). "

Richman DD et al. The Toxicity of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex. N Engl J Med. 1987 Jul 23;317 (4):192-197.

"more than half of all AIDS patients may not benefit from the drug because it is more toxic for them than their AIDS infection. The most serious side effect of AZT is to suppress the bone marrow, leaving patients highly vulnerable to bacterial infections "

Kolata G. Imminent marketing of AZT raises problems; marrow suppression hampers AZT use in AIDS victims. Science. 1987 Mar 20;235:1462-3.

Harmful Side Effects, General

AZT has a wide range of side effects. Those that have not been reported widely enough to deserve their own section are reported here.

"Perinatal treatment with 3'-azido-3'-deoxythymidine (AZT) has been found to reduce the rate of maternal-infant transmission of HIV; however, AZT is clastogenic at therapeutic doses in adult patients and induces cancers in the offspring of mice treated in utero. The purpose of the present study was to investigate the mutagenicity of AZT at the hypoxanthine-guanine phosphoribosyltransferase (hprt) locus of the human lymphoblastoid cell line, TK6, following in vitro exposures. ..There was a significant increase over background in hprt Mfs *[mutation frequencies]* in TK6 cells exposed to 300mM AZT for 3 days (1.8-fold increase). In cells exposed for 6 days, there was a decrease in...cell survival. .. These preliminary results indicate that AZT treatment is mutagenic and produces large deletions in human cells. "

Sussman HE et al. Mutagenicity of AZT in the human lymphoblastoid cell line, TK6. 2nd National AIDS Malignancy Conference. 1998 Apr;94.

"AZT … induces significant toxic effects in humans exposed to therapeutic doses... Cytogenetic observations on H9-AZT cells showed an increase in chromosomal aberrations and nuclear fragmentation when compared with unexposed H9 cells...The toxicities explored here suggest that the mechanisms of AZT induced cytotoxicity in bone marrow of the patients chronically exposed to the drug in vivo may involve both chromosomal and mitochondrial DNA damage. "

Agarwal RP, Olivero OA. Genotoxicity and mitochondrial damage in human lymphocytic cells chronically exposed to 3'-azido-2',3'-dideoxythymidine. Mutat

Res. 1997 May 23;390(3):223-231.

"Clinical manifestations of ANA *[Antiviral Nucleoside Analogs, such as AZT]* toxicity: It is self-evident that ANAs, like all drugs, have side-effects. However, the prevalent and at times serious ANA mitochondrial toxic side-effects are particularly broad ranging with respect to their tissue target and mechanisms of toxicity: … Haematalogical toxicity *[anemia, and other blood disorders]* … Myopathy *[muscle disorders]* … Cardiotoxicity *[heart disorders]* … Hepatic toxicity *[liver disorders]* … Peripheral neuropathy *[nerve damage]* "

Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. Nat Med. 1995 May;1(5):417-22.

"During the maintenance phase after completion of the study, 2 additional patients showed signs of severe hematologic toxicity, and one patient had severe myopathy. These toxicities were attributed to ZDV *[AZT]*…Patients with previous ZDV exposure had a higher incidence of advanced HIV disease and tended to have lower, but not *[statistically]* significant, pretreatment CD4 lymphocyte counts "

Meng TC et al. Combination therapy with recombinant human soluble CD4-immunoglobulin G and zidovudine in patients with HIV infection: a phase I study. J Acquir Immune Defic Syndr. 1995 Feb 1;8(2):152-60.

"among the subjects with CD4+ *[immune system]* cell counts < 200/mm3, the risk of developing HIV dementia among those reporting any antiretroviral use (AZT, ddI, ddC, or d4T) was 97% higher than among those not using this antiretroviral therapy...In addition, the findings of our analysis seem to confirm previous observation of a neurotoxic effect of antiretroviral agents. Numerous studies have linked the use of ddI, ddC, and d4T *[nucleoside analogs]* to the development of toxic sensory neuropathies, usually in a dose-dependent manner "

Bacellar A et al. Temporal trends in the incidence of HIV-1 related neurological diseases: Multicenter AIDS cohort study. Neurology. 1994 Oct;44:1892-1900.

"*[this study included US health care workers exposed]* to blood from a patient with documented HIV infection *[81% had AIDS]* as a result of percutaneous injury (for example, a needlestick or a cut from a sharp object), contamination of mucous membranes, or contamination of nonintact skin…From October 1988 to Jun 1992, the period when use of zidovudine *[AZT]* was studied, 848 workers were enrolled. Postexposure zidovudine was used by 265 (31%) of these workers…in doses range from 200 to 1800 mg/day and for periods of 1 to 180 days…The proportion of enrolled workers using zidovudine increased from 5% in the fourth quarter of 1988 to 50% in the third quarter of 1990 and has been stable subsequently…no seroconversions occurred among 301 workers not using zidovudine, and 1 seroconversion occurred among 143 workers using zidovudine…176 (75%) reported one or more symptoms, most commonly nausea, malaise or fatigue, or

headache. Symptoms were reported less frequently among workers who did not use zidovudine…Of 175 workers who completed 21 or more days of *[AZT]* prophylaxis, 51 (29%) had paired hemograms at least 21 days apart…7 (14%) had a 10% or greater reduction in hemoglobin or hematocrit values…74 (31%) of workers did not complete their planned regmine of zidovudine because of adverse symptoms (73) or reduction in hemoglobin level (1)…28 (12%) of workers were absent from work for periods ranging from 1 to 49 days because of adverse events attributed to zidovudine…because of uncertainty about efficacy and safety, the Public Health Service concluded in January 1990 that a recommendation for or against the use of posexposure zidovudine could not be made. "

Tokars JI et al. Surveillance of HIV infection and zidovudine use among health care workers after occupational exposure to HIV-infected blood. The CDC Cooperative Needlestick Surveillance Group. Ann Intern Med. 1993 Jun 15;118 (12):913-9.

"Long-term tolerance of zidovudine *[AZT]* treatment was retrospectively analysed in 97 patients with AIDS or AIDS-related complex. After one year of treatment 68% and after two years 87% of the patients had had at least one dose adjustment during their course of therapy. Myelotoxicity *[damage to the blood forming tissues]* was the most common cause (58% of all cases) of dose reductions and therapy interruptions (dose adjustments). At the time of the first dose adjustment 33 patients (34%) were suffering from anaemia (*[hemoglobin]* less than 6.0 g/dl), 20 patients (21%) from leukopenia (leukocytes less than 1.5 x 10^9], and 10 patients (10%) from thrombocytopenia (thrombocytes less than 75 x 10^9]. 56 patients (57%) needed one or more blood transfusions during therapy. The median time from the start of therapy to the time of the first dose adjustment was 14 weeks in patients who had a first dose adjustment because of anaemia without co-existing leukopenia or thrombocytopenia "

Van Leeuwen R et al. Failure to maintain high-dose treatment regimens during long-term use of zidovudine in patients with symptomatic Human Immunodeficiency Virus type 1 infection. Genitourin Med. 1990 Dec;66(6):418-22.

"16 of 38 patients developed nail discoloration after zidovudine therapy was begun. Dyschromia was usually apparent within 4 to 8 weeks but also occurred as late as 1 year "

Don PC et al. Nail dyschromia associated with zidovudine. Ann Intern Med. 1990;112(2):145-6.

"Zidovudine was reasonably well tolerated in this study...27% *[remained]* on full dose at the end of the first year of therapy. The full daily (1.2 g) was received by 68 patients (24%) for the entire duration of their time on therapy. Of these full-dose patients, six died within 6 weeks of commencing therapy...172 patients (56%) developed a new AIDS-defining condition during therapy; 130 patients *[42%]* developed the condition more than 6 weeks after commencing zidovudine therapy...Anemia was the most frequently reported adverse

experience during zidovudine therapy. Transfusions were reported necessary for 155 patients (50%) while on zidovudine, 91 patients (representing 29% of the total) required transfusions on more than one occasion. ”

Swanson CE, Cooper DA. Factors influencing outcome of treatment with zidovudine of patients with AIDS in Australia. AIDS. 1990;4(8):749-57.

“Of the 524 subjects enrolled *[in this study of people in the early stages of AIDS and HIV antibodies]*, 4 never received zidovudine *[AZT]*, 41 completed the study, and 479 were withdrawn from zidovudine treatment *[i.e. virtually everyone]*. The reasons for withdrawal from zidovudine were the development of an opportunistic infection or a neoplasm *[cancer]*...(54 subjects); death (43); toxic reactions (183); withdrawal by the subject (169) and other reasons (30)...*[of the]* 183 subjects withdrawn...because of toxic reactions, zidovudine was discontinued earlier in more subjects in the standard-treatment group than in the low-dose group *[40% vs. 29%]*. Among the symptoms only headache was noted more frequently in the low-dose group...22 subjects (8%) in the standard-treatment group and 27 (10%) in the low-dose group had elevated levels of hepatic *[liver]* enzyme...178 subjects (34%) had a hemoglobin concentration below 5 mmol per liter *[anemia]*...134 subjects (26%) received red-cell transfusions (65 in the standard-treatment group and 69 in the low-dose group)...230 subjects(44%) had a *[low]* neutrophil *[infection fighting white blood cells]* count...134 (51%) in the standard-treatment group and 96 (37%) in the low-dose group...22 subjects (4%) had a *[low]* platelet *[blood clotting cells]* count”

Fischl MA et al. A randomized controlled trial of a reduced daily dose of Zidovudine in patients with the Acquired Immunodeficiency Syndrome. N Engl J Med. 1990;323(15):1009-14.

“Of the 265 patients who withdrew from study treatment voluntarily, 44 listed medical symptoms as the primary reason. Of these 44 withdrawals, 8 occurred in the placebo group, 13 in the 500-mg*[per day]* zidovudine *[AZT]* group and 23 in the 1500-mg zidovudine group…the most common *[symptoms reported by these people]* were gastrointestinal upset, confusion and malaise…The overall benefits of the treatment of early HIV disease with zidovudine must be weighted against potential toxicity and the costs associated with therapy, as well as the uncertainty that it will confer a long-term benefit in survival.”

Volberding PA et al. Zidovudine in asymptomatic human immunodeficiency virus infection: a controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. N Engl J Med. 1990 Apr 5;322(14):941-9.

“AZT inhibition of DNA synthesis in 3 hr bone marrow cultures is relatively consistent in a variety of hematologic disorders. As approximately two-thirds of AIDS patients appear to be *[deficient in]* folate and/or vitamin B12, the fact that AZT-induced inhibition of pyrimidine incorporation into DNA *[required for DNA elongation]* is occurring in cells which may be megaloblastic, i.e., in a state of impaired DNA synthesis, suggests that these cells may be more susceptible to AZT toxicity. The data also support the notion that AZT

inhibition results predominantly from termination of DNA chain elongation. ”

Herzlich BC et al. Synergy of inhibition of DNA synthesis in human bone marrow by azidothymidine plus deficiency of folate and/or vitamin B12?. Am J Hematol. 1990 Mar;33(3):177-83.

“58% of all subjects with AIDS and AIDS-related complex receiving zidovudine experienced granulocytopenia of grade 3 or higher...Serious anemia occurred in 32% of all subjects receiving zidovudine...and could be typically managed by dose attenuation, temporary dose interruption of zidovudine therapy and/or red blood cell transfusions...12% of subjects...had an episode of thrombocytopenia *[low platelet count]* after the initiation of zidovudine therapy...Ten patients had liver enzyme levels elevated...and were managed with dose attenuations or interruptions of zidovudine therapy...One report of a grand mal seizure, two events associated with cardiac dysfunction, and five reports of myopathy were the only new serious potentially drug-related adverse events reported during extended periods of zidovudine administration. ”

Fischl MA et al. Prolonged zidovudine therapy in patients with AIDS and advanced AIDS-related complex. JAMA. 1989 Nov 3;262(17):2405-10.

“We report a patient who experienced acute cholestatic hepatitis on initial exposure to and rechallenge with zidovudine and, as a result, was unable to receive further therapy with the drug...Seven days *[after starting AZT therapy]* the patient presented with a 2-day history of intermittent fevers and abdominal discomfort...Seven days *[after re-starting AZT therapy once the initial symptoms resolved]* the patient again experienced fever, right upper quadrant pain, nausea, and headache...One month later *[after discontinuing AZT]* the liver function tests had almost completely returned to normal and remained without significant abnormalities. ”

Dubin G, Braffmann MN. Zidovudine-induced hepatotixicity. Ann Intern Med. 1989;110(1):85-6.

“AZT was started at full dose in 260 patients, 64 with ARC and 196 with AIDS. In 58 of these patients, AZT had to be stopped at least once for a minimum of 7 days. In 142 other patients, dosage was reduced by half because of leucopenia (79), leucopenia and anaemia (32), anaemia (20), rash (3), vomiting (3), headaches and insomnia (2), myalgia (2), or hepatitis (1). 3 patients reduced the dose with no medical reason. Later on, progression of toxicity led to suspension of AZT (for at least 7 days) in 85 of the 142 patients whose treatment had been reduced to half dose. Thus AZT was stopped at least once in 143 (55%) patients who began the full-dose regimen. Because of their initial haematological status 105 (28.8%) patients were treated from the start with half-dose AZT - toxicity led to cessation of treatment in 71 (67.6%) cases ”

Dournon E et al. Effects of zidovudine in 365 consecutive patients with AIDS or AIDS-related complex. Lancet. 1988 Dec 3;2:1297-1302.

"*[adverse reactions]* reported were one case of Stevens-Johnson syndrome in a severely atopic *[allergic]* patient and 32 reports of seizures. "

Creagh-Kirk T et al. Survival experience among patients with AIDS receiving zidovudine. Follow-up of patients in a compassionate plea program. JAMA. 1988 Nov 25;260(20):3009-15.

"In a cytogenetics study performed in cultured human lymphocytes, dose-related structural (but not numerical) chromosomal alterations were noted at concentrations of 3 micrograms/ml and higher "

Ayers KM. Preclinical toxicology of zidovudine. An overview. Am J Med. 1988 Aug 29;85(2A):186-8.

Muscle Disorders (including Heart)

AZT causes muscle damage, which often shows up as muscle wasting or pain. It is believed that this is largely through damage to mitochondria, the energy regulating organelles in every animal cell. AZT may interfere with the replication of mitochondria (which have their own DNA) or with their supply of phosphates, the energy currency of cells.

"antiretroviral treatment with AZT amplified cardiac dysfunction and worsened ultrastructural features of AIDS CM *[cardiomyopathy - damage to heart muscle]* in TG *[transgenic mice, including some genetic material believed to be from HIV]*...AZT damaged cardiac mitochondria in WT *[wild-type mice (not genetically engineered)]*, with destruction, swelling, cristae dissolution, and fragmentation. Similarly, hearts from AZT-treated TG showed increased mitochondrial damage, but with greater intensity "

Lewis W et al. Cardiac Dysfunction occurs in the HIV-1 transgenic mouse treated with Zidovudine. Lab Invest. 2000 Feb;80(2):187-97.

"Myopathy *[muscle damage]* in long-term therapy with ZDV *[AZT]* due to mitochondrial damage has been described by several investigators"

Brinkman K et al. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as a common pathway. AIDS. 1998 Oct 1;12(14):1735-44.

"AZT seemed to be the most potent inhibitor of cell proliferation *[cell killer]*…AZT, ddi and ddC *[all nuceloside analogs]* all exert cytotoxic *[cell killing]* effects on human muscle cells and induce functional alterations of mitochondria due to mechanisms other than the sole mtDNA *[mitochondrial DNA]* depletion. Our results provide only a partial explanation of the fact that AZT, but not ddI and ddC, can induce a myopathy *[muscle damage]* in HIV-infected patients."

Benbrik E et al. Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddl) and zalcitabine (ddC) on cultured human muscle cells. J Neurol Sci. 1997 Jul;149(1):19-25.

"Although the association of AZT with decreased cardiac contractility *[cardiomyopathy=heart muscle damage]* has been debated, our data indicates a strong correlation between treatment with AZT and the development of a decrease in left ventricular performance in children with HIV infection. The fact that 17 of the 19 patients in the study in whom cardiomyopathy developed had received AZT suggests that the observed decreases in left ventricular performance could have had clinical consequences…AZT withdrawal should be considered in any child in whom cardiomyopathy develops"

Domanski MJ et al. Effect of zidovudine and didanosine treatment on heart function in children infected with human immunodeficiency virus. J Pediatr. 1995 Jul;127(1):137-46

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"Long term therapy with *[AZT]* can induce a toxic myopathy associated with mitochondrial changes "

Chariot P, Gherardi R. Partial cytochrome c oxidase deficiency and cytoplasmic bodies in patients with zidovudine myopathy. Neuro Muscul Disorders. 1991;1:357-363.

"typical mitochondrial myopathy *[muscle damage]* has been reported to be expressed among many patients with AIDS treated with long-term azidothymidine (AZT) therapy…for AIDS patients, it is urgently necessary to develop a remedy substituting this toxic substance, AZT "

Hayakawa M et al. Massive conversion of guanosine to 8-hydroxy-guanosine in mouse liver mitochondrial DNA by administration of azidothymidine. Biochem Biophys Res Commun. 1991;176:87-93.

"A clinically significant myopathy that precedes the development of zidovudine associated mitochondrial myopathy has been a rarity in our experience. "

Coker R et al. Exacerbation of HIV-associated myopathy by zidovudine. AIDS. 1991;5(2):229-31.

"Before 1986, when zidovudine (formerly called azidothymidine *[AZT]*) was introduced…the number of patients with HIV-associated myopathy was small, and myopathy *[muscle disorders]* was considered a rare complication of HIV infection. During the past two years *[1988-1989]*, an increasing number of patients receiving long-term zidovudine therapy have had myopathic symptoms such as myalgia (in up to 8% of patients), elevated serum creatine kinase levels (in up to 15%), and muscle weakness. These

symptoms generally improve when zidovudine is discontinued...We conclude that long-term therapy with Zidovudine can cause a toxic mitochondrial myopathy, which... is indistinguishable from the myopathy associated with primary HIV infection. ”

Dalakas MC et al. Mitochondrial myopathy caused by long-term zidovudine therapy. N Engl J Med. 1990;322(16):1098-1105.

“In our review of our clinic patients who have received zidovudine therapy for more than 6 months, 16% (14 of 86 patients) have had persistently elevated creatine kinase values. Six percent of these patients (5 of 86) developed symptomatic myalgia and objective proximal muscle weakness. These 5 symptomatic patients had received zidovudine for an average of 45 weeks and had had creatine kinase elevations for several weeks before onset of symptoms. Of these 5 patients, 4 had creatine kinase values return to normal and symptoms resolve after zidovudine was withdrawn...Three patients were rechallenged with zidovudine: each had recurrent creatine kinase elevations at a dose of 600 mg/d. The zidovudine dose was increased to 1200 mg/d in 2 patients: after a few days, both developed recurrent muscle symptoms that again responded to dose reduction. ...Results of quadriceps muscle biopsies done on our patients who responded to zidovudine withdrawal showed severe myopathic changes without evidence of inflammatory infiltrates. Electron microscopy revealed many ultrastructural changes, including destruction of the sarcomere profile with z-band change in the form of streaming and rod bodies. Muscle mitochondria showed wide variation in size, swelling, degeneration and laminar bodies. ...There have been 40 case reports *[to 1990]* of patients who have developed myopathy while taking zidovudine (including our 5 symptomatic patients). Zidovudine therapy was discontinued in 34 of these patients and 26 improved. ”

Till M, MacDonnell KB. Myopathy with Human Immunodeficiency Virus type 1 (HIV-1) infection: HIV-1 or zidovudine?. Ann Intern Med. 1990;113(7):492-4.

“A severe proximal myopathy, predominantly affecting the legs, seems to be a significant complication of long-term zidovudine therapy, even at reduced doses; it affected 18% of our patients who had received treatment for more than 200 days. Other drugs could not be implicated. The pathogenesis is obscure; the myopathy resolves on cessation of zidovudine, but not on dose-reduction, though there is then a risk of rebound encephalitis. ”

Helbert M et al. Zidovudine-associated myopathy. Lancet. 1988 Sep 17;2:689-90.

“A 24-year-old woman presented in January, 1988, with a 2-week history of progressive leg weakness and difficulty in walking. She had been found to be HIV antibody positive in April 1986, and in October, 1986, Pneumocystis carinii pneumonia developed. After the pneumonia she had been on zidovudine 200 mg 4-hourly and had required three blood transfusion for consequent myelosuppression *[white blood cell deficiency]*. On examination there was proximal weakness but no wasting of the upper and lower limbs, tenderness of the shoulders and thighs, and preserved deep tendon reflexes. Her gait was waddling and she was unable to rise out of a chair without using her arms...7 days after zidovudine

withdrawal, her proximal weakness and muscle tenderness had improved significantly, and muscle force was clinically normal at follow-up 2 months later. ”

Gorard DA, Henry K, Guilodd RJ. Necrotising myopathy and zidovudine. Lancet. 1988 May 7;1:1050.

“All *[four]* patients had an insidious onset of myalgias, muscle tenderness, weakness, and severe muscle atrophy favouring the proximal muscle groups. Physical examinations revealed varying degrees of muscle weakness and grossly apparent atrophy. Weight loss due to muscle loss was uniformly noted; in one patient, the loss was a striking 18 kg... Zidovudine was discontinued in three patients, who subsequently had symptomatic improvement...The patient who continued to receive the drug had persistent ”

Bessen L. Severe Polymyositis-like Syndrome Associated with Zidovudine Therapy of AIDS and ARC. N Engl J Med. 1988 Mar 17;708.

Warnings from Experiments with Animals

Experiments have been performed on animals that would be unethical in humans (whether they are really ethical on animals is another question). The information that they have produced about AZT is very worrying. It is generally ignored by AIDS doctors and researchers.

“Antiretroviral nucleoside analogue drugs are a major constituent of highly active antiretroviral therapy (HAART), the most advanced form of treatment for HIV-1 infection. Currently, HAART combinations that include zidovudine (ZDV *[AZT]*) and lamivudine (3TC) are highly effective in preventing HIV-1 vertical transmission; most children are born with no evident adverse clinical effects. However, ZDV is a moderately strong transplacental carcinogen in mice, and potential long-term consequences of fetal exposure to most HAART combinations remain unknown. To model human transplacental ZDV and 3TC exposures, experiments were performed in Erythrocebus patas monkeys given human-equivalent drug exposure protocols. Pregnant monkeys were dosed with either no drug (n = 2), 40.0 mg ZDV/d (about 6 mg/kg body weight/d) for the last 50% (10 weeks) of gestation (n = 3), or with the same regimen of ZDV plus 24.0 mg 3TC/d (about 3.6 mg/kg body weight/d) for the last 20% (4 weeks) of gestation (n = 3). Multiple fetal organs were examined at term for DNA incorporation of ZDV and 3TC using two separate radioimmunoassays (RIAs). Values for ZDV-DNA incorporation were similar in fetuses exposed to ZDV alone and those exposed to ZDV plus 3TC. Values for 3TC-DNA in fetal organs were greater than or equal to values for ZDV-DNA, indicating that the total DNA damage sustained by fetuses exposed to both drugs was at least double that observed in fetuses exposed to ZDV alone. Telomere shortening, determined by Southern blot with a telomeric probe, was observed in most organs of the three animals exposed in utero to ZDV

plus 3TC. No telomere shortening was evident in the unexposed fetuses, and occasional telomere shortening was found in fetuses exposed to ZDV alone. Overall, these studies demonstrate that monkey fetuses exposed in utero to the combination ZDV plus 3TC sustain a higher level of drug-DNA incorporation and show evidence of more telomere damage than monkey fetuses exposed to ZDV alone. ”

Olivero OA et al. Transplacental Genotoxicity of Combined Antiretroviral Nucleoside Analogue Therapy in Erythrocebus patas Monkeys. J Acquir Immune Defic Syndr. 2002 Apr 1;29(4):323-9.

“3'-azido-3'-deoxythymidine (AZT) is given to pregnant women positive for the human immunodeficiency virus type 1 (HIV-1) to reduce maternal-fetal viral transmission. To explore fetal mitochondrial consequences of this exposure, pregnant Erythrocebus patas monkeys were given daily doses of 1.5 mg (21% of the human daily dose) and 6.0 mg (86% of the human daily dose) of AZT/kg body weight (bw), for the second half of gestation. At term, electron microscopy of fetal cardiac and skeletal muscle showed abnormal and disrupted sarcomeres with myofibrillar loss. Some abnormally shaped mitochondria with disrupted cristae were observed in skeletal muscle myocytes. Oxidative phosphorylation (OXPHOS) enzyme assays showed dose-dependent alterations. At the human-equivalent dose of AZT (6 mg of AZT/kg bw), there was an approximately 85% decrease in the specific activity of NADH dehydrogenase (complex I) and three- to six-fold increases in specific activities of succinate dehydrogenase (complex II) and cytochrome-c oxidase (complex IV). Furthermore, a dose-dependent depletion of mitochondrial DNA levels was observed in both tissues. The data demonstrate that transplacental AZT exposure causes cardiac and skeletal muscle mitochondrial myopathy in the patas monkey fetus. ”

Gerschenson M et al. Fetal mitochondrial heart and skeletal muscle damage in Erythrocebus patas monkeys exposed in utero to 3'-azido-3'-deoxythymidine.. AIDS Res Hum Retro. 2000 May 1;16(7):645-44.

“CD-1 mice exposed prenatally to 12.5 and 25.0 mg of AZT...had statistically significant increases in numbers of liver, lung and female reproductive tract tumors. These observations have been extended to offspring at 2 years of age...there was a 2- to 3-fold increase in the incidence (from 20% in controls to 55-60% in AZT groups) and multiplicities of lung tumors in AZT-exposed mice. The incidence of hepatocellular adenomas in the female mice exposed to prenatal AZT increase from 0 in the control group to 20% in the high dose AZT group, and hepatocellular carcinomas metastasizing to lungs were observed only in AZT-treated mice. Prenatal administration of AZT also increased the incidence of neoplasms of reproductive tract, female mammary gland epithelium and squamous cell epithelium of forestomach. AZT...significantly reduced the incidence of hematopoietic tumors ”

Diwan BA et al. Transplacental carcinogenicity of 3'-azido-3'-deoxythmidine (AZT) in mice. Proc Am Assoc Cancer Res. 1998;39:21.

"The AZT animals *[Macaques given AZT during pregnancy]* developed an asymptomatic macrocytic anemia, but hematologic parameters returned to normal when AZT was discontinued. Total leukocyte count decreased during pregnancy and was further affected by AZT administration. AZT-exposed infants were mildly anemic at birth. AZT caused deficits in growth, rooting and snouting reflexes, and the ability to fixate and follow near stimuli visually "

Ha JC et al. Fetal, infant, and maternal toxicity of zidovudine (azidothymidine) administered throughout pregnancy in Macaca nemestrina. J Acquir Immune Defic Syndr. 1998 May 1;18(1):27-38.

"At 1 year of age, the offspring of AZT-treated mice exhibited statistically significant, dose-dependent increases in tumor incidence and tumor multiplicity in the lungs, liver and female reproductive organs. AZT incorporation into nuclear and mitochondrial DNA was detected in multiple organs of transplacentally exposed mice and monkeys...AZT is genotoxic in fetal mice and monkeys and is a moderately strong transplacental carcinogen in mice examined at 1 year of age "

Olivero OA et al. Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys. J Natl Cancer Inst. 1997 Nov 5;89(21):1602-8.

"At 1 year of age, the offspring of AZT-treated mice exhibited statistically significant, dose-dependent increases in tumor incidence and tumor multiplicity in the lungs, liver, and female reproductive organs. AZT incorporation into nuclear and mitochondrial DNA was detected in multiple organs of transplacentally exposed mice and monkeys. Shorter chromosomal telomeres were detected in liver and brain tissues from most AZT-exposed newborn mice but not in tissues from fetal monkeys. Conclusions: AZT is genotoxic in fetal mice and monkeys and is a moderately strong transplacental carcinogen in mice examined at 1 year of age. "

Olivero OA et al. Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys. J Natl Cancer Inst. 1997 Nov 5;89(21):1602-8.

"…in adult mice, lifetime AZT administration induces vaginal tumors at a 10-20% incidence...In newborn monkeys and mice, AZT was incorporated into DNA of many fetal tissues...AZT appears to be a moderately-strong transplacental carcinogen *[i.e. it crosses the placenta and may cause cancer in the fetus]* "

Olivero OA et al. AZT is a Genotoxic Transplacental Carcinogen in Animal Models. J Acquir Immune Defic Syndr. 1997 Apr 1;14(4):A29.

"Hemoglobin dropped significantly in the AZT-treated animals *[Macaques]* after treatment began and remained low until the end of the study...Postnatal weight increase was significantly lower in AZT-exposed infants...Infant hematocrits taken at time of birth were

lower in the AZT-exposed group...AZT-exposed infants took three times as many sessions as controls to meet criterion on Black-White Learning, a simple discrimination task...It took significantly more matings to achieve the six AZT pregnancies than the six control pregnancies ”

Ha JC et al. Fetal toxicity of zidovudine (azidothymidine) in Macaca nemestrina: preliminary observations. J Acquir Immune Defic Syndr. 1994;7(2):154-7.

“we have found positive correlations between the dose of AZT administered to female CD-1 mice, the incorporation of AZT into vaginal DNA, the hyperproliferation of the vaginal epithelial basal layer, and the aberrant expression of alpha-6 integrin toward the epithelial suprabasal strata of the vagina, a target organ for carcinogenesis in mice. These results suggest that there is an ordered progression of abnormal events leading to tumorigenesis in vaginal epithelial tissues. ”

Olivero OA et al. Vaginal epithelial DNA damage and expression of preneoplastic markers in mice during chronic dosing with tumorigenic levels of 3'-azido-2',3'-dideoxythymidine (AZT). Cancer Res. 1994;54:6235-42.

“It previously has been demonstrated that zidovudine (AZT) is lethal to early murine *[mouse]* embryos. The effect of the drug on pre- and postimplantation embryos was examined to delineate the timing of this toxicity and to investigate its possible mechanisms. Embryos exposed in the whole mouse during preblastocyst development were unable to proceed beyond the blastocyst stage *[i.e. failed to implant in the uterine wall]*. Similarly, when two-cell embryos harvested from unexposed females were exposed to low-concentration (1 microMole) AZT in vitro over 24 h, development beyond the blastocyst stage was inhibited. In contrast, drug exposure during in vitro blastocyst and postblastocyst development resulted in little or no morphologic toxicity. Further investigation revealed that preblastocyst AZT exposure resulted in the development of blastocysts with significantly lower cell numbers than control embryos. While embryonic exposure to AZT at the blastocyst and postblastocyst stages also resulted in retarded cell division, the effects were milder than those recorded after preblastocyst exposure. These data demonstrate that the critical period of AZT toxicity toward murine embryos is between ovulation and implantation and indicate that AZT directly suppresses cell division in the preimplantation embryo. ”

Toltzis P et al. Effect of zidovudine on preimplantation murine embryos. Antimicrob Agents Chemother. 1993 Aug;37(8):1610-3.

“Mice receiving AZT during gestation yielded fewer fetuses…and greater numbers of resorptions…Exposure to AZT was highly correlated with failure to develop to the blastocyst stage…These data indicate that AZT has a direct toxic effect on the developing mouse embryo. ”

Toltzis P et al. Zidovudine-associated embryonic toxicity in mice. J Infect Dis. 1991;163:1212-8.

"The most consistent hematologic effect from treatment with AZT *[in mice]* was a poorly regenerative, macrocytic anemia "

Luster MI et al. Experimental studies of the hematologic and immune system toxicity of nucleoside derivatives used against HIV infection. Int J Immunopharmacol. 1991;13 Suppl 1(Suppl 1):99-107.

"*[in mice]* AZT had a profound effect on the number of erythrocytes *[mature red blood cells]* and a small effect on the number of leukocytes *[white blood cells]*…anemia was seen in all the mice tested at 1,000 mg/kg per day "

Mansuri MM et al. Comparison of In Vitro Biological Properties and Mouse Toxicities of Three Thymidine Analogs Active against Human Immunodeficiency Virus. Antimicrob Agents Chemother. 1990 Apr;34(4):637-641.

"Male and female cynomolgus monkeys were given zidovudine *[AZT]*, 35 to 300 mg/kg per day orally, in studies of 3 and 6 months' duration…the only treatment-related alteration noted was a reversible, mild to moderate, dose-related, macocytic anemia…In the 6-month study, bone marrow cytology…revealed a retardation in the maturation of all cell lines, with the ertythroid elements *[red blood cells]* being affected to the greatest degree…Dams *[pregnant female rabbits]* given 500 mg/kg per day gained less weight during the dosing period, developed anemia, and showed an increased incidence of late fetal resorptions. No evidence of teratogenicity *[birth defects]* was seen, even though it was shown that zidovudine crossed the placenta…Zidovudine was also studied for its ability to morphologically transform cultured BALB/c-3T3 mouse cells and was found to be positive at concentrations of 0.5 micrograms/ml and higher…From the Department of Toxicology and Experimental Pathology. Burroughs Wellcom Co. *[the manufacturer of AZT]* "

Ayers KM. Preclinical toxicology of zidovudine. An overview. Am J Med. 1988 Aug 29;85(2A):186-8.

AZT and Cancer

AZT has a strong association with cancer, not surprising for a drug that interferes with DNA replication, and therefore cell division. Note that uncontrolled cell division is the definition of cancer.

"The anti-HIV drug 3'-azido-3'-deoxythymidine (AZT) is used successfully for reduction of perinatal viral transmission. However toxic side effects including carcinogenesis are possible. To test this, pregnant CD-1 Swiss mice were given 25.0 or 12.5 mg AZT on gestation days 12-18… Findings for all remaining offspring *[not killed for an earlier report]* up to 2 years old are reported here. AZT effects were most prominent in female offspring, with a significant threefold increase in lung tumors, a reduction in lymphoblastic

and follicle center cell lymphomas, and a significant increase in histiocytic sarcomas (0 in controls, 3% after low-dose AZT, and 8% after high-dose AZT, p = 0.022). Dose-dependent incidences of mammary gland, ovarian, and seminal vesicle tumors were low but significant: 0/106 controls, 3/105 low-dose, and 8/105 high-dose mice presented one of these neoplasms (p = 0.0025). Incidences of females showing any clearly AZT-related neoplasm, in lung, liver, ovary, or mammary gland or histiocytic sarcoma, in the second year, were 12/32 after the low dose and 14/27 after the high dose vs 3/23 controls (p = 0.0045). Also, the sensitivity of neonatal mice was assessed by administration of 25, 50, 100, or 200 mg/kg AZT on postnatal days 1 through 8. The effects at 2 years were similar to those seen after transplacental exposure, with significant increases in lung, liver, and mammary tumors in females…AZT had a much greater perinatal carcinogenic potency than it exhibited after administration to adult mice…the most worrisome new finding was the appearance, in the AZT exposure groups, of reproductive system tumors that were completely absent from untreated controls in this study, including mammary ademocarcinomas, ovarian tumors, seminal vesicle tumors, and testicular tumors."

Diwan BA et al. Multiorgan transplacental and neonatal carcinogenicity of 3'-azido-3'-deoxythymidine in mice. Toxicol Appl Pharmacol. 1999 Nov 15;161 (1):82-99.

"727 infants with known ZDV *[AZT]* exposure prospectively followed from birth between 1989 through May/June 1996 were included…115 (61%) of ZDV recipients in PACTG 076 *[a clinical trial giving AZT to mothers; 39% did not agree to continue with followup, a potential source of bias]*…Also included…are 612 infants enrolled into the WITS study…Mean infant follow-up was longer for PACTG 076/219 participants at 38.3 months…*[WITS participants had]* a shorter mean follow-up of 14.5 months…The longest reported follow-up for infants was just over 6 years…In the cited rodent study, mice with in utero *[in the womb]* ZDV exposure…*[had tumors]* documented only in mice sacrificed at or after the human equivalent of the second decade *[i.e. this study is worthless for determining whether there is a mid- to long-term risk of cancer from AZT exposure in the womb]*"

Hanson IC et al. Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine. J Acquir Immune Defic Syndr Hum Retrovirol. 1999 Apr 15;20(5):463-7.

"CD-1 mice exposed prenatally to 12.5 and 25.0 mg of AZT...had statistically significant increases in numbers of liver, lung and female reproductive tract tumors. These observations have been extended to offspring at 2 years of age...there was a 2- to 3-fold increase in the incidence (from 20% in controls to 55-60% in AZT groups) and multiplicities of lung tumors in AZT-exposed mice. The incidence of hepatocellular adenomas in the female mice exposed to prenatal AZT increase from 0 in the control group to 20% in the high dose AZT group, and hepatocellular carcinomas metastasizing to lungs were observed only in AZT-treated mice. Prenatal administration of AZT also increased the incidence of neoplasms of reproductive tract, female mammary gland epithelium and

squamous cell epithelium of forestomach. AZT...significantly reduced the incidence of hematopoietic tumors ”

Diwan BA et al. Transplacental carcinogenicity of 3'-azido-3'-deoxythmidine (AZT) in mice. Proc Am Assoc Cancer Res. 1998;39:21.

“Perinatal treatment with 3'-azido-3'-deoxythymidine (AZT) has been found to reduce the rate of maternal-infant transmission of HIV; however, AZT is clastogenic at therapeutic doses in adult patients and induces cancers in the offspring of mice treated in utero. The purpose of the present study was to investigate the mutagenicity of AZT at the hypoxanthine-guanine phosphoribosyltransferase (hprt) locus of the human lymphoblastoid cell line, TK6, following in vitro exposures. ..There was a significant increase over background in hprt Mfs *[mutation frequencies]* in TK6 cells exposed to 300mM AZT for 3 days (1.8-fold increase). In cells exposed for 6 days, there was a decrease in...cell survival. .. These preliminary results indicate that AZT treatment is mutagenic and produces large deletions in human cells. ”

Sussman HE et al. Mutagenicity of AZT in the human lymphoblastoid cell line, TK6. 2nd National AIDS Malignancy Conference. 1998 Apr;94.

“Similar levels of AZT-DNA incorporation were detected in peripheral blood from HIV-1-positive mothers and cord blood from their infants and tissues from newborn mice exposed to tumorigenic *[cancer-causing]* doses of AZT in utero. Therefore, the biologically effective dose (i.e. the amount of AZT that incorporated into DNA) was similar in both species even though the mouse daily dose of AZT was much higher than that received by humans. ”

Olivero AO et al. AZT, a genotoxic transplacental carcinogen in rodents, is incorporated into human fetal and maternal DNA. 2nd National AIDS Malignancy Conference. 1998 Apr 6;8.

“At 1 year of age, the offspring of AZT-treated mice exhibited statistically significant, dose-dependent increases in tumor incidence and tumor multiplicity in the lungs, liver and female reproductive organs. AZT incorporation into nuclear and mitochondrial DNA was detected in multiple organs of transplacentally exposed mice and monkeys...AZT is genotoxic in fetal mice and monkeys and is a moderately strong transplacental carcinogen in mice examined at 1 year of age ”

Olivero OA et al. Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys. J Natl Cancer Inst. 1997 Nov 5;89(21):1602-8.

“…in adult mice, lifetime AZT administration induces vaginal tumors at a 10-20% incidence...In newborn monkeys and mice, AZT was incorporated into DNA of many fetal tissues...AZT appears to be a moderately-strong transplacental carcinogen *[i.e. it crosses the placenta and may cause cancer in the fetus]* ”

Olivero OA et al. AZT is a Genotoxic Transplacental Carcinogen in Animal Models. J Acquir Immune Defic Syndr. 1997 Apr 1;14(4):A29.

"we have found positive correlations between the dose of AZT administered to female CD-1 mice, the incorporation of AZT into vaginal DNA, the hyperproliferation of the vaginal epithelial basal layer, and the aberrant expression of alpha-6 integrin toward the epithelial suprabasal strata of the vagina, a target organ for carcinogenesis in mice. These results suggest that there is an ordered progression of abnormal events leading to tumorigenesis in vaginal epithelial tissues. "

Olivero OA et al. Vaginal epithelial DNA damage and expression of preneoplastic markers in mice during chronic dosing with tumorigenic levels of 3'-azido-2',3'-dideoxythymidine (AZT). Cancer Res. 1994;54:6235-42.

"after starting antiretroviral treatment...the estimated probability of developing lymphoma ... by 36 months, *[was]* 46.4% (CI, 19.6% to 75.5%)...a direct role of therapy itself cannot be totally discounted...Zidovudine *[AZT]* can act as a mutagen"

Pluda JM et al. Development of non-Hodgkin lymphoma in a cohort of patients with severe human immunodeficiency virus (HIV) infection on long-term antiretroviral therapy. Ann Intern Med. 1990 Aug 15;113(4):276-82.

Increased Risk of Sickness and Death with AZT

AZT, the 'life saving' drug, may actually accelerate illness and death.

"participants of open-label ZDV *[AZT]* still had four to five times the incidence of ARC/AIDS/death of participants on blinded therapy *[of which approximately half were on AZT and half on placebo]*...The unadjusted hazard of ARC/AIDS/death was 4.6 times higher for participants *[in the deferred group]* who had received ZDV...after adjustment for latest CD4 this became 1.6...There was a suggestion of a benefit in terms of *[slower]* progression to ARC, AIDS or death *[with AZT]*, no effect on progression to AIDS or death, and a suggestion of an increase in mortality. "

White IR et al. Impact of treatment changes on the interpretation of the Concorde trial. AIDS. 1997;11:999-1006.

"Extended follow-up of patients in one *[AZT]* trial, the Concorde study, has shown a significantly increased risk of death among the patients treated early...where is the evidence that for a patient with a CD4 count of 450 cells per cubic millimeter and a low plasma viral level, it would not be better to wait before initiating therapy?...In 1990...a patient with a CD4 count of 450 cells per cubic millimeter would have been advised to start monotherapy with zidovudine. We now tell such a patient that, in fact, follow-up data for up to 4.5 years

since that time have shown no survival benefit ”

Phillips AN, Smith GD et al. Viral load and combination therapy for Human Immunodeficiency Virus. N Engl J Med. 1997 Mar 27;336(13):958-9; author reply 960.

“The mortality rate was significantly higher among *[a group of 1372]* patients who had received antiretroviral therapy *[principally AZT]* before enrollment in the clinic ”

Chaisson RE, Keruly JC, Moore RD. Sex, race, drug use and progression of human immunodeficiency virus disease. N Engl J Med. 1995 Sep 21;333(12):751-6.

“None of the LTAs *[long term asymptomatics]* received any antiviral drugs during the study; however, 3 *[of 6]* rapid progressors…were treated with zidovudine…*[and]* a rapid progressor was treated with didanosine during the study. ”

Hogervorst E et al. Predictors for non- and slow progression in HIV type-1 infection: low viral RNA copy numbers in serum and maintenance of high HIV-1 p24-specific antibody levels. J Infect Dis. 1995;171:811-21.

“despite the evidence that purified *[blood clotting]* factor VIII is beneficial in maintaining or even increasing T-cell counts, several studies testing purified factor VIII *[as opposed to the older forms of Factor VIII which were 99% to 99.9% impurities]* are ambiguous about its effectiveness in preventing or treating AIDS. Some of these studies have only tested partially purified, i.e. 2-10 units/mg, instead of highly purified, i.e. 2000-3000 units/mg, factor VIII. But each of the studies that are ambiguous about the benefits have also treated their patients with toxic antiviral DNA chain terminators like AZT. Indeed the study by de Biasi et al. was the only one that has tested purified factor VIII in the absence of AZT. The study by Seremetis et al. initially called for no AZT, but later allowed it anyway. Thus in all but one study, the potential benefits of highly purified factor VIII have been obscured by the toxicity of AZT. ”

Duesberg PH. Foreign-protein-mediated immunodeficiency in hemophiliacs with and without HIV. Genetica. 1995;95:51-70.

“Adjusted for baseline CD4 *[immune cell counts]* and age *[correlated with lifetime exposure to clotting factor infusions]*, subjects *[hemophiliacs]* who had started on zidovudine *[AZT]* had increased risks, especially for AIDS *[4.46 times greater risk!]* and death *[2.37 times]* ”

Goedert JJ et al. Risks of immunodeficiency, AIDS, and death related to purity of factor VIII concentrate. Lancet. 1994 Sep 17;344(8925):791-2.

“Only 38% of the HLP *[Healthy long-term positives]* had ever used zidovudine *[AZT]* or other nucleoside analogues, compared with 94% of the progressors. ”

Buchbinder S et al. Long-term HIV-1 infection without immunologic progression.

AIDS. 1994 Aug;8(8):1123.

"A total of 172 (96 Imm, 76 Def) participants died *[169 who had taken some AZT, 3 who had only taken placebo]*...The results of Concorde do not encourage the early use of zidovudine in symptom-free HIV-infected adults. They also call into question the uncritical use of CD4 cell counts as a surrogate endpoint for assessment of benefit from long-term antiretroviral therapy...Representatives of the Wellcome Foundation *[Glaxo Wellcome manufactures AZT]* who were also members of the Coordinating Committee have declined to endorse this report."

Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. Lancet. 1994 Apr 9;343(8902):871-81.

"Leukopenia *[white blood cell deficiency]* occurred in 82% of the patients receiving early therapy and 77% of those receiving late therapy *[AZT only when AIDS occurred]*; 20% and 16%, respectively, had anemia. 14% and 10%, respectively, had severe leukopenia...and 5% and 2% had severe anemia requiring transfusion. Nausea (or vomiting) and diarrhea occurred more frequently in the early-therapy group than in the late-therapy group (40% vs. 23%, respectively; P <0.01)...The dosage of blinded study medication was reduced because of adverse reactions in 64 *[38%]* of the patients assigned to zidovudine (early therapy) and in 29 *[17%]* of those assigned to placebo (late therapy)...Once AIDS developed in patients receiving early therapy, more of them tended to have multiple AIDS diagnoses, a slightly higher proportion died, and the median survival time was slightly shorter than in similar patients who received late therapy "

Hamilton JD et al. A controlled trial of early versus late treatment with zidovudine in symptomatic human immunodeficiency virus infection. N Engl J Med. 1992;326 (7):437-43.

"None of the asymptomatic individuals was receiving zidovudine*[AZT]*. The CD4 count of patients receiving zidovudine was lower than that of those not receiving the antiviral (mean of 69 and 217/cubic-mm, respectively)…CD4 numbers were significantly lower in patients who developed HIV-related malignancies while receiving zidovudine "

Crowe SM et al. Predictive value of CD4 lymphocyte numbers for the development of opportunistic infections and malignancies in HIV-infected persons. J Acquir Immune Defic Syndr. 1991;4(8):770-6.

"after starting antiretroviral treatment...the estimated probability of developing lymphoma ... by 36 months, *[was]* 46.4% (CI, 19.6% to 75.5%)...a direct role of therapy itself cannot be totally discounted...Zidovudine can act as a mutagen "

Pluda JM et al. Development of non-Hodgkin lymphoma in a cohort of patients with severe human immunodeficiency virus (HIV) infection on long-term antiretroviral therapy. Ann Intern Med. 1990 Aug 15;113(4):276-82.

Lack of Effectiveness…and Toxicity

Although AZT is commonly described as a 'life saving' drug, there are some papers that show that it might be strikingly ineffective in at least some cases.

"At 6 weeks, the HIV-1 perinatal transmission rate was significantly lower among those who took nevirapine than zidovudine *[AZT]* (6.8% versus 30.3%) *[This contradicts the normal assumption that AZT reduces the risk from 25% to about 8%!]* "

Chung MH et al. Breast milk HIV-1 suppression and decreased transmission: a randomized trial comparing HIVNET 012 nevirapine versus short-course zidovudine. AIDS. 2005;19:1415-22.

"Median RNA viral load during the first week was not significantly different for children whose mothers had taken zidovudine *[AZT]*, compared with those in the placebo group. "

Rouet F et al. Early diagnosis of paediatric HIV-1 infection among African breast-fed children using a quantitative plasma HIV RNA assay. AIDS. 2001 Sep 28;15 (14):1849-56.

"The risk for developing AIDS among individuals in the ISS *[Italian Seroconversion Study]* cohort was less than 50% by 10 years after HIV seroconversion…The relative hazards of developing AIDS in patients who started treatment with zidovudine (AZT) monotherapy was 0.57 *[i.e. people starting AZT were only 57% as likely to have AIDS within the first year as others]* and 0.92 within the first year and after 1 year from AZT initiation *[indicating that the benefit of AZT was short term]* "

Rezza G. Determinants of progression to AIDS in HIV-infected individuals: an update from the Italian Seroconversion Study. J Acquir Immune Defic Syndr. 1998;17 Suppl 1:S13-6.

"for the most extensively used drug, *[AZT]*, whereas phosphorylation to the monophosphate is facile, the product is a very poor substrate for the next kinase in the cascade, thymidylate kinase. Because of this, although high concentrations of the monophosphate can be reached in the cell, the achievable concentration of the active triphosphate is several orders of magnitude lower. *[Note that triphosphorylation is necessary for AZT to be active against HIV]* "

Lavie A et al. The bottleneck in AZT activation. Nat Med. 1997 Aug;3(8):922-4.

"A total of 21 of the *[125]* HIV-1-infected participants died of HIV-related causes during the 3.5-year longitudinal study. Subclinical malnutrition, vitamin B12 deficiency, zinc deficiency, and selenium deficiency over time, but not zidovudine *[AZT]* treatment, were shown to each be associated with HIV-1-related mortality independent of CD4 cell counts

<200/mm3 at baseline, and CD4 counts over time. *[i.e. AZT did not reduce the risk of death]* "

Baum MK et al. High risk of HIV-related mortality is associated with selenium deficiency. J Acquir Immune Defic Syndr Hum Retrovirol. 1997 Aug 15;15(5):370-4.

"The long-term consequences of in-utero and infant exposure to zidovudine *[AZT]* are unknown. The long-term effects of early or short-term use of zidovudine in pregnant women are also unknown...The incidence of adverse reactions *[to AZT]* appears to increase with disease progression, and patients should be monitored carefully, especially as disease progression occurs. *[i.e. AZT does not prevent progression to AIDS]* "

Retrovir (in Compendium of Pharmaceuticals & Specialities). Canadian Pharmaceutical Association. 1997;1357-61.

"*[AZT may]* unmask silent opportunistic infections...Lack of strong evidence exists for sustained immune reconstitution by current therapies...If *[immune reconstitution]* does not occur with time, despite prolonged viral suppression, then the case for immunorestorative strategies...could be justifiably explored *[duh]*. "

Kelleher AD et al. Immunological effects of antiretroviral and immune therapies for HIV. AIDS. 1997;11(Suppl A):S149-155.

"The transient effect of zidovudine *[AZT]* on CD4 cell counts and disease progression may have already ended in patients who used antiretroviral agents before (median time, 22.7 months) the start of TMP-SMZ *[strong antibiotics]* prophylaxis *[or maybe the side effects left the patients weakened, and likely to experience the side effects of TMP-SMZ]* "

Veenstra J et al. Rapid disease progression in human immunodeficiency virus type 1-infected individuals with adverse reactions to trimethoprim-sulfamethoxazole prophylaxis. Clin Infect Dis. 1997 May;24(5):936-41.

"The comparison of the two studies *[one European, one French]*…is interesting. Despite the wider and earlier use of zidovudine *[AZT]* monotherapy in the French study, morbidity or mortality was similar to that in the ECS *[European Collaborative Study]*. This is further indirect evidence of lack of benefit from long-term zidovudine monotherapy "

Blanche S et al. Morbidity and mortality in European children vertically infected by HIV-1. The French Pediatric HIV Infection Study Group and European Collaborative Study. J Acquir Immune Defic Syndr. 1997 Apr 15;14(5):442-50.

"Overall, zidovudine treatment was associated with only a small reduction in circulating levels of plasma RNA...Explanations need to be considered for the apparent lack of association between the observed RNA levels and the effect of zidovudine treatment *[i.e. lower rates of transmission from mothers on zidovudine to their children cannot be due to lower levels of virus!]*"

Sperling RS et al. Maternal viral load, zidovudine treatment and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. N Engl J Med. 1996 Nov 28;335(22):1621-9.

"The Concorde trial showed no difference in the survival rates for symptom-free HIV-positive individuals between those given immediate and those given deferred zidovudine, and Chaisson et al found previous use of zidovudine to be a negative indicator, with an increase in the risk ratio for death or disease progression of 1.7 "

Scott WF. The Delta Trial. Lancet. 1996;348(9036):1238.

"*[in these clinical trials]* it was often difficult to distinguish adverse events possibly associated with administration of Retrovir from underlying signs of HIV disease or intercurrent illnesses *[i.e. AZT can cause AIDS-defining illnesses]* "

Retrovir. PDR. 1996
http://www.virusmyth.com/aids/data/pdrazt.htm.

"AZT can be severely toxic, and there is compelling evidence that the drug probably doesn't help infected people live longer unless they already have full-blown AIDS...AZT clearly isn't a very effective anti-AIDS drug. "

Cohen J. Fulfilling Koch's Postulates [and several others]. Science. 1994 Dec 9;266:1647.

"AZT can be severely toxic, and there is compelling evidence that the drug probably doesn't help infected people live longer unless they already have full-blown AIDS...AZT clearly isn't a very effective anti-AIDS drug. "

Cohen J. Could Drugs, Rather Than a Virus, Be the Cause of AIDS?. Science. 1994 Dec 9;266:1649.

"the efficacy of zidovudine in preventing HIV infection after initial exposure remains unproven "

Gostin LO et al. HIV testing, counseling, and prophylaxis after sexual assault. JAMA. 1994;271(18):1436-44.

"The median CD4 lymphocyte count did not differ in the 3 groups: 54 for the group receiving neither antiretroviral nor P. carinii pneumonia prophylaxis, 53 for the group receiving only antiretroviral therapy, and 52 for the combined treatment group. There were also no major differences in the median CD8 lymphocyte count of the 3 groups...Other illnesses now have elevated incidence rates among persons receiving P. carinii pneumonia prophylaxis *[and AZT or didanosine]*: M. avium complex, nonretinitis cytomegalovirus disease, cytomegalovirus retinitis, candida esophagitis, and wasting syndrome "

Bacellar H et al. Incidence of clinical AIDS conditions in a cohort of homosexual men with CD4+ cell counts < 100/cubic mm. J Infect Dis. 1994;170:1284-7.

"the first results of the Concorde study are a reminder that AZT has limited value when given to patients who do not have advanced disease, and that it is not a very effective drug. "

Fields BN. AIDS: time to turn to basic science. Nature. 1994 May 12;369 (6476):95-6.

"Patients who received zidovudine *[AZT]* before diagnosis *[of AIDS]* had a significantly lower CD4 cell count at diagnosis than patients who did not…improved survival *[over time, including 1987 when AZT was approved for use]* was significant only for patients diagnosed with P carinii pneumonia *[if AZT really had anti-HIV activity it should be effective against all AIDS-defining diseases]*…Overall survival was significantly shorter for patients who received zidovudine before diagnosis, although the survival for these patients within the first year after the diagnosis tended to be better compared with patients who did not receive AZT "

Lundgren JD et al. Survival differences in European patients with AIDS, 1979-89. The AIDS in Europe Study Group. BMJ. 1994 Apr 23;308(6936):1068-73.

"When considering patients treated with zidovudine*[AZT]*, the death rate was substantially lower within the first year after initiating zidovudine than the death rate in patients who had never taken the drug. Patients in their second year after starting zidovudine treatement experienced a death rate similar to that observed for patients who had never taken zidovudine. In the third and fourth years after starting zidovudine, the death rate was substantially greater *[2-3 times higher in the fourth and fifth years]* for zidovudine-treated patients than for patients who had never taken zidovudine "

Lundgren JD et al. Comparison of long-term prognosis of patients with AIDS treated and not treated with zidovudine. AIDS in Europe Study Group. JAMA. 1994 Apr 13;271(14):1088-92.

"The average time with neither a progression of disease nor an adverse event (symptom or laboratory finding) was 15.7, 15.6, and 14.8 months for patients receiving placebo, 500 mg of zidovudine, and 1500 mg of zidovudine, respectively. The incidence of severe symptoms was 13.8% in the placebo group, 15.2% in the 500-mg group, and 19.9% in the 1500-mg group. After 18 months, the 500-mg group gained an average of 0.5 month without disease progression, as compared with the placebo group, but had severe adverse events an average of 0.6 month sooner. "

Lenderking WR et al. Evaluation of the quality of life associated with zidovudine treatment in asymptomatic human immunodeficiency virus infection. The AIDS Clinical Trials Group. N Engl J Med. 1994 Mar 17;330(11):738-43.

"Despite continuous antiviral therapy, the favorable effect of AZT *[on viral load, not health]* was typically lost within 4-6 months after treatment initiation *[Table 1 shows that 5 of 7 people with disease progression took AZT, but none of 11 without disease progression]*

”

Saksela K et al. Human immunodeficiency virus type 1 mRNA expression in peripheral blood cells predicts disease progression independently of the numbers of CD4+ lymphocytes. Proc Natl Acad Sci U S A. 1994 Feb 1;91(3):1104-8.

“Given that it is widely believed that the effect of zidovudine is of limited duration, a suggestion that the benefit lasts more than two years should be supported by the demonstration of a statistically significant difference in risk between zidovudine and placebo when one considers only the number of person-years at risk after two years of treatment. The small number of patients with end points after more than two years of therapy *[in the study being commented on]* makes it doubtful that such a significant difference was present. Therefore, the assertion that zidovudine has a beneficial effect that lasts for more than 2 1/2 years in these patients is not justified on the basis of the results presented. ”

Phillips, AN, Sabin CA. Zidovudine in Asymptomatic HIV Infection. N Engl J Med. 1993 Dec 16;329:25.

“Some HIV-infected individuals have remained healthy for more than 15 years following seroconversion. Lower numbers of CD4+ peripheral blood lymphocytes have generally been found to indicate the advancement of HIV disease... *[but]* The CD4+ cell counts vary from day to day and laboratory to laboratory, and similar levels do not necessarily reflect the same disease status in all patients. For example, very low CD4+ cell counts (less than 0.05x10**9/L (50/microL)) usually indicate advanced disease; however, some patients with these levels remain asymptomatic for extended periods of time while others succumb rapidly...While knowledge of the clinical use of zidovudine has increased during the last several years, the panel was concerned overall by the drug’s limited effectiveness and durability of response. ”

National Institute of Allergy and Infectious Diseases State-of-the-Art Panel on Anti-Retroviral Therapy for Adult HIV-Infected Patients et al. Anti-retroviral therapy for adult HIV-infected patients. Recommendations from a state-of-the-art conference. JAMA. 1993 Dec 1;270(21):2583-9.

“Early treatment *[before any AIDS-like symptoms]* with zidovudine *[AZT]* is expensive and is very sensitive to the cost of zidovudine and to potential reductions in quality of life of patients who experience side effects. ”

Oddone EZ et al. Cost effectiveness analysis of early zidovudine treatment of HIV infected patients. BMJ. 1993 Nov 20;307(6915):1322-5.

“the high level of plasma virus observed by Piatak et al, was about 99.9 per cent non-culturable, suggesting that it was either neutralized or defective. Therefore, rather than supporting a cytopathic model, this observation actually may help explain the relatively slow dissemination of the infected cell burden and thus the relative ineffectiveness of

therapy with nucleoside analogues which target this process. ”

Sheppard HW, Ascher MS, Krowka JF. Viral burden and HIV disease. Nature. 1993 Jul 22;364(6435):291-2.

“in individuals with fewer than 400 CD4 cells per cubic mm, those treated with AZT for longer than 16 months had the same levels of plasma *[HIV]* RNA as a similar group of patients who never received antiretroviral therapy. ”

Winters MA et al. Biological variation and quality control of plasma Human Immunodeficiency Virus type 1 RNA quantitation by reverse transcriptase Polymerase Chain Reaction. J Clin Microbiol. 1993;31(11):2960-6.

“The large Anglo-French Concorde randomized trial of zidovudine in asymptomatic HIV-infected individuals shows that there is no significant clinical benefit in terms of survival or disease progression to AIDS or AIDS-related complex (ARC) in those who started zidovudine immediately rather than those who waited for the onset of symptomatic disease. The 1749 participants were followed up for an average of 3 years. ”

Press Release: Results from Concorde Trial of AZT vs. Placebo. Medical Research Council. 1993 Apr 2.

“while zidovudine *[AZT]* and P. carinii pneumonia prophylaxis may have been widely available to insured AIDS patients as early as 1987, cases in men who reported sex with men plateaued in late 1986, before the availability of zidovudine. This pre-zidovudine leveling has been previously reported for AIDS-related mortality in New York City. ”

Thomas PA et al. Trends in the first ten years of AIDS in New York City. The New York City Department of Health AIDS Surveillance Team. Am J Epidemiol. 1993 Jan 15;137(2):121-33.

“signs of a progressively increasing level of HIV-1 activity were evident, regardless of antiviral therapy *[AZT in 7 patients]*. ”

Bagnarelli P et al. Molecular profile of Human Immunodeficiency Virus Type 1 infection in symptomless patients and in patients with AIDS. J Virol. 1992;66:7328-35.

“Replication curves and cytopathic effect of a standard inoculum (1 ng of p24) of 66 primary HIV-1 isolates were similar regardless of the clinical stage of the patient...There was no difference between viruses derived from patients sensitive to zidovudine and those derived from patients resistant to zidovudine ”

Lu W, Andrieu J-M. Similar replication capacities of primary human immunodeficiency virus type 1 isolates derived from a wide range of clinical sources. J Virol. 1992 Jan;66(1):334-340.

“Doubts may be raised about the long-term beneficial effects of zidovudine treatment on

AIDS-related cognitive impairments ”

Reinvang I et al. Only temporary improvement in impaired neuropsychological function in AIDS patients treated with zidovudine. AIDS. 1991;5(2):228-9.

“treatment with ZDV*[AZT]* does not decrease the levels of HIV DNA in PBMCs *[peripheral blood mononuclear cells]* ”

Donovan RM et al. HIV-1 proviral copy number in blood mononuclear cells from AIDS patients on zidovudine therapy. J Acquir Immune Defic Syndr. 1991;4 (8):766-9.

“thirteen subjects of 146 tested (9%) who were negative for HIV antigen *[although positive for HIV antibodies]* before treatment later had detectable levels of antigen during the 128 weeks of treatment *[huh? AZT makes you HIV-positive?]* ”

Fischl MA et al. A randomized controlled trial of a reduced daily dose of Zidovudine in patients with the Acquired Immunodeficiency Syndrome. N Engl J Med. 1990;323(15):1009-14.

“a tragic accident in our hospital reveals that even when it is begun very soon after exposure, treatment with zidovudine will not necessarily prevent HIV-1 infection…Within 45 minutes after the recipient's exposure to HIV-1 *[a syringe with 100 to 200 microliters of blood from someone dying of AIDS]*, zidovudine *[AZT]* treatment was begun *[for about 3 months]*…On day 30 HIV-1 p24 antigen was detected, and on day 41 there was serconversion for HIV-1 antibodies ”

Lange JM et al. Failure of zidovudine prophylaxis after accidental exposure to HIV-1. N Engl J Med. 1990 May 10;322(19):1375-7.

“zidovudine monophosphate concentrations peaked at 1.3µM *[1,300 nM]* at 2h…diphosphate concentration was on average 18-fold lower…triphosphate peaked 4h after initiation of therapy at 14.5nM *[without triphosphorylation, AZT cannot be effective against retroviruses, and this shows that only about 1% of AZT ever is]* ”

Avramis VI et al. Biochemical pharmacology of zidovudine in human T-lymphoblastoid cells (CEM). AIDS. 1989;3:417-422.

“In the placebo-controlled trial *[of AZT]*, CD4 cell counts increased for four to eight weeks following the initiation of zidovudine *[AZT]* therapy. Following this initial increase, CD4 counts gradually diminished through week 24,, at which time on average they stabilized at entry values. ”

Richman DD, Andrews J. Results of continued monitoring of participants in the placebo-controlled trial of zidovudine for serious human immunodeficiency virus infection. Am J Med. 1988 Aug 29;85(2A):208-13.

AZT and Mitochondria

Mitochondria are the energy regulating organelles in every living cell. Because they are self-replicating and therefore have their own DNA they are susceptible to damage from drugs (such as AZT) that interfere with DNA replication (mitosis). In fact, they are more susceptible, because they don't have the same repair mechanisms as the DNA in the cell's nucleus. Symptoms of mitochondrial damage are varied, but often include muscle damage, as the ability of the cells to obtain energy is diminished.

"In umbilical cords from 6 of 9 infants born to HIV-1-infected mothers taking Combivir *[combination of the nucleoside analogs AZT and 3TC]* moderate to severe mitochondrial morphological damage was observed, while none of 7 unexposed infants showed similar damage. Compared to unexposed infants, statistically significant mtDNA *[mitochondrial DNA]* depletion was observed in umbilical cord and cord blood from drug-exposed infants…Several additional factors related to mother and child health were compared to extent of mitochondrial damage to explore differences in the Combivir-exposed and unexposed groups of infants. Self-reports of maternal smoking, alcohol use, and illicit drug use during pregnancy were limited and were not correlated with mitochondrial damage in infants. Medical chart reviews did not reveal use of legal drugs/medications, other than NRTI, that are suspected or known to affect mitochondrial structure or function. There was no significant correlation between maternal age and the degree of mitochondrial damage in Combivir-exposed infants, nor was there any correlation between prematurity and mitochondrial damage in Combivir-exposed infants."

Divi RL et al. Mitochondrial damage and DNA depletion in cord blood and umbilical cord from infants exposed in utero to Combivir. AIDS. 2004 Apr 30;18 (7):1013-1021.

"We report fatal portal hypertension, liver failure, and persistent mitochondrial dysfunction in a man aged 65 years with HIV-1 infection who had recovered from nucleoside-analogue-induced acute hepatitis and lactic acidaemia more than 18 months previously. "

Carr A et al. Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidaemia. Lancet. 2001 May 5;357:1412.

"To explore fetal mitochondrial consequences of this exposure *[to AZT]*, pregnant Erythrocebus patas monkeys were given daily doses of 1.5 mg (21% of the human daily dose) and 6.0 mg (86% of the human daily dose) of AZT/kg body weight (bw), for the second half of gestation. At term, electron microscopy of fetal cardiac and skeletal muscle showed abnormal and disrupted sarcomeres with myofibrillar loss. Some abnormally shaped mitochondria with disrupted cristae were observed in skeletal muscle myocytes. Oxidative phosphorylation (OXPHOS) enzyme assays showed dose-dependent alterations. At the

human-equivalent dose of AZT (6 mg of AZT/kg bw), there was an approximately 85% decrease in the specific activity of NADH dehydrogenase (complex I) and three- to six-fold increases in specific activities of succinate dehydrogenase (complex II) and cytochrome-c oxidase (complex IV). Furthermore, a dose-dependent depletion of mitochondrial DNA levels was observed in both tissues. ”

Gerschenson M et al. Fetal mitochondrial heart and skeletal muscle damage in Erythrocebus patas monkeys exposed in utero to 3'-azido-3'-deoxythymidine.. AIDS Res Hum Retro. 2000 May 1;16(7):645-44.

“Eight children with mitochondrial dysfunction were found...the first patient presented with visual impairment...*[and]* died aged 13 months because of respiratory and cardiac-rhythm disorders...The second patient, from age 4 months until until death at 11 months, had refractory epilepsy and deterioration of cognitive and psychomotor abilities...At age 8 months...patient three had a seizure...At age 4 years, the child’s cardiac function was normal, but moderate muscular deficit persisted...In the fourth patient...between ages 14 and 27 months, the child had four episodes of febrile seizures...From age 7 months until 15 months, patient five had repeated seizures...at age 16 months...large necrotic lesions of the *[brain]*...At age 3-1/2 years the child had severe sequelae and microcephaly *[abnormally small head]*. Patient 6 was symptom-free until age 14 months, but persistent biochemical abnormalities were seen on standard follow-up...Patient 7 was symptom-free until age 4 months, at which time he became hypotonic *[low muscle tone] [and stopped breathing]*... The eighth child was symptom-free. Persistent hepatic and pancreatic abnormalities were seen from birth...At age 20 months, biological abnormalities persisted...electroretinography... was abnormal, and cerebral NMR imaging...showed abnormalities of the periventricular white matter...No child was infected with HIV-1 *[but because their mothers were HIV-positive]* all children were treated after birth with zidovudine *[AZT]* alone or with zidovudine and lamivudine *[also a nucleoside analog]*. Treatment continued for 6 weeks in four children and was stopped prematurely because of haematological or biochemical intolerance in four children...The observation of several cases *[of mitochondrial abnormalities]* in a population of about 1700 exposed children *[as compared with 1/5,000 to 1/20,000 in normal populations]* strongly suggests an acquired mitochondrial dysfunction...Pregnant women should be informed of the potential effects associated with these treatments during pregnancy. ”

Blanche S et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet. 1999 Sep 25;354:1084-9.

“Myopathy *[muscle damage]* in long-term therapy with ZDV *[AZT]* due to mitochondrial damage has been described by several investigators ”

Brinkman K et al. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as a common pathway. AIDS. 1998 Oct 1;12(14):1735-44.

“Zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) are the reference antiretroviral

therapy in patients with AIDS. A toxic mitochondrial myopathy can be observed in patients treated with AZT, but not with ddI and ddC. ”

Benbrik E et al. Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells. J Neurol Sci. 1997 Jul;149(1):19-25.

“AZT … induces significant toxic effects in humans exposed to therapeutic doses... Cytogenetic observations on H9-AZT cells showed an increase in chromosomal aberrations and nuclear fragmentation when compared with unexposed H9 cells...The toxicities explored here suggest that the mechanisms of AZT induced cytotoxicity in bone marrow of the patients chronically exposed to the drug in vivo may involve both chromosomal and mitochondrial DNA damage. ”

Agarwal RP, Olivero OA. Genotoxicity and mitochondrial damage in human lymphocytic cells chronically exposed to 3'-azido-2',3'-dideoxythymidine. Mutat Res. 1997 May 23;390(3):223-231.

“AZT causes mitochondrial DNA chain replication termination in vitro *[in lab systems]*, possibly by the inhibition of DNA polymerase-gamma, it has been theorized that AZT inhibits cardiac *[heart]* mitochondrial DNA replication in vivo *[in the body]*”

Domanski MJ et al. Effect of zidovudine and didanosine treatment on heart function in children infected with human immunodeficiency virus. J Pediatr. 1995 Jul;127(1):137-46

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“Clinical manifestations of ANA *[Antiviral Nucleoside Analogs, such as AZT]* toxicity: It is self-evident that ANAs, like all drugs, have side-effects. However, the prevalent and at times serious ANA mitochondrial toxic side-effects are particularly broad ranging with respect to their tissue target and mechanisms of toxicity: … Haematalogical toxicity *[anemia, and other blood disorders]* … Myopathy *[muscle disorders]* … Cardiotoxicity *[heart disorders]* … Hepatic toxicity *[liver disorders]* … Peripheral neuropathy *[nerve damage]* ”

Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. Nat Med. 1995 May;1(5):417-22.

“typical mitochondrial myopathy *[muscle damage]* has been reported to be expressed among many patients with AIDS treated with long-term azidothymidine (AZT) therapy…for AIDS patients, it is urgently necessary to develop a remedy substituting this toxic substance, AZT ”

Hayakawa M et al. Massive conversion of guanosine to 8-hydroxy-guanosine in mouse liver mitochondrial DNA by administration of azidothymidine. Biochem Biophys Res Commun. 1991;176:87-93.

AZT and Pregnant Women, Fetuses and Children

AZT is the main drug prescribed to reduce HIV transmission from mother to child. One study showed that this reduction was from 25% (placebo) to 8% (AZT). Other studies have showed widely varying results, and some have showed transmission as high as 25% with AZT. The long term health consequences of HIV transmission versus exposure to AZT are not known. However, these references show that there is room for concern.

"you are justified in sounding a warning against the long-term therapeutic use of AZT, or its use in pregnant women, because of its demonstrated toxicity and side effects. Unfortunately, the devastating effects of AZT emerged only after the final level of experiments were well underway, that is the experiments which consisted of giving AZT to large numbers of human patients over a long period of time. Your effort is a worthy one…I hope you succeed in convincing your government not to make AZT available *[Anthony Brink quoting Richard Belz, the first person to synthesize the drug AZT]*"

Brink A. AZT and HAART are beneficial for infants and adults. tig.org.za. 2005 Sep [accessed].

"Zidovudine *[AZT]* administered during the perinatal period may result in a small but significant and durable effect on hematopoiesis *[blood production]* up to the age of 18 months. "

Le Chenadec J et al. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. AIDS. 2003 Sep 26;17(14):2053-61.

"An exhaustive study in a large prospective cohort with predetermined algorithm of the unexplained symptoms compatible with mitochondrial dysfunction. A total of 2644 of 4392 children were exposed to antiretrovirals…All the children with 'established' or 'possible' mitochondriopathy *[mitochondrial damage]* diagnosed in this study had been exposed to antiretroviral drugs. One of these children was treated with zidovudine *[AZT]* only during the prenatal period and received no treatment after birth…For the other children, the treatment was administered in the pre, per- and post-partum periods. It was zidovudine alone in five cases, a combination of zidovudine-lamivudine in 14 cases and another combination in one. 20 of the mothers received zidovudine by intravenous perfusion during labor. "

Barret B et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. AIDS. 2003 Aug 15;17(12):1769-1785.

"children of HIV+ mothers are at risk for mitochondrial damage *[mitochondria are the energy regulating organelles essential to every living cell, and that have their own DNA]* that is further increased in infants of mothers receiving AZT during pregnancy "

Poirier MC et al. Long-Term Mitochondrial Toxicity in HIV-Uninfected Infants Born to HIV-Infected Mothers. J Acquir Immune Defic Syndr. 2003 Jun 1;33 (2):175-183.

"A total of 38 subjects were enrolled from June 1997 through June 1999 *[1 was later excluded]*…Zidovudine *[AZT]* was generally well tolerated in this high-risk population. The percent of patients who had selected adverse events is shown in Table II *[32%-Anemia grade >=2; 11%-Neutropenia; 13%-Thrombocytopenia; 45%-Received transfusion; 26%-Received erythropoetin; 11%-HIV infection; 8%-Died]* Slightly more than half of the subjects had anemia severe enough to require a transfusion *[giving new meaning to the term 'well tolerated']*…Three infants (8%) died at 3, 23, and 31 weeks of age. All 3 were born at <=26 weeks' GA and each death was thought to be related to a complication of prematurity… "

Capparelli E et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. J Pediatr. 2003 Jan;142(1):47-52
http://www2.us.elsevierhealth.com/scripts/om.dll/serve?action=searchDB&searchDBfor=pub&id=pd.

"The subjects were 37 infants *[group C (C)]* who were born to antiretroviral drug naïve HIV-1 infected mothers (MC) and 80 infants *[group Z (Z)]* who were born to HIV-1 infected mothers (MZ) that received a short-course ZDV *[AZT]* regimen…Of the whole cohort, there were 12 HIV-1 infected infants, seven in group Z *[mothers were given AZT during pregnancy]* (Z11, Z13, Z24, Z27, Z44, Z48, and Z51) and five in group C *[mothers did not take AZT]* (C3, C10, C13, C21, and C46)…The clinical category of all 12 infants was classified as EN *[without any symptoms]* at the age of 1–2 months. There were 6/12 (50%) infants who developed symptoms at the age 6 months. Of these rapid disease progression, five (83.3%) were infants in group Z *[whose mothers used AZT]* (Z11, Z24, Z44, Z48, and Z51) and one was in group C (C10). This revealed that more infants in group Z (5/7; 74%) than in group C (1/5; 20%) developed symptoms by 4–6 months (P=0.02). The clinical symptoms of these infected infants included oral thrush (4/6), dermatitis (1/6), splenomegaly *[enlarged spleen]* (5/6), hepatomegaly *[enlarged liver]* (5/6), and lymphadenopathy (3/6)."

Sutthent R et al. Effect of perinatal short-course zidovudine on the clinical and virological manifestations of HIV-1 subtype E infection in infants. J Clin Virol. 2002 Jul;25(1):47-56.

"In univariate analysis, maternal peripartum zidovudine *[AZT]* had no effect on mortality up to day 230, but a negative effect beyond 8 months of age. Neonatal anaemia *[quite possibly due to the maternal AZT]*, a diagnosis of HIV-1 infection on or before day 12 and between days 13 and 45, paediatric AIDS, a maternal CD4 lymphocyte count of less than 200/cubic mm, and a high maternal plasma viral load were risk factors for child death…The 18 month mortality rate in these HIV-1-infected children was 590 per 1000 in the zidovudine group

and 510 per 1000 in the placebo group…The 18 month mortality rate in these HIV-uninfected children was 53 per 1000 in the zidovudine group and 78 per 1000 in the placebo group *[meaning that AZT makes HIV-infected children sicker, but HIV-uninfected children healthier!]*…11 of the 51 deaths of the HIV-1-infected children were attributed to a cause belonging to the AIDS clinical syndrome"

Dabis F et al. 18-month mortality and perinatal exposure to zidovudine in West Africa. AIDS. 2001 Apr 13;15(6):761-70.

"In our study, we found a slightly higher risk for disease progression among ZDV*[AZT]*-exposed, HIV-infected children during the 18-month follow-up period *[as compared to HIV-infected children whose mothers were given a placebo]*, although this difference was not statistically significant. "

Chotpitayasunondh T et al. Safety of Late In Utero Exposure to Zidovudine in Infants Born to Human Immunodeficiency Virus-Infected Mothers: Bangkok. Pediatrics. 2001 Jan;107(1):e5
http://www.pediatrics.org/cgi/content/full/107/1/e5.

"*[Table 3 shows that congenital abnormalities occurred in 7% of infants when both mother and child had the long course of AZT (long-long), and only 1% when both had the short course (short-short). Neutropenia and leukopenia occurred in 7% of infants on the long-long course and 2% on short-short. Infections or other HIV-related events occurred in 43% on long-long and 33% on short-short. Neonatal or other obstetrical events occurred in 22% on long-long and only 14% on short-short. Number of deaths, severe anemia were similar (although severe anemia occurred significantly less (0%/1%) in the long-short and short-long treatment arms). Mothers who received the long AZT treatment had a higher rate of stillbirth (8% vs. 4%), severe anemia (7% vs 4%), infection or other HIV events (20% vs 17%), events related to pregnancy or delivery (24% vs 17%) than mothers who received the short course, although fewer died (3% vs 8%)]* "

Lallemant M et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. N Engl J Med. 2000 Oct 5;343(14):982-91.

"Other factors associated with lower cumulative survival included suppressed CD4 cell counts, a history of zidovudine therapy *[Table 1 shows that children who had taken AZT had a 37.5% risk of death over the study period versus 22.8% for those who had not. There was a 97% probability that this increase was not due to chance]*, and Pneumocystis carinii pneumonia diagnosed before the initial echocardiogram. "

Lipshultz SE et al. Cardiac Dysfunction and Mortality in HIV-Infected Children. Circulation. 2000 Sep 26;102(13):1542-8
http://circ.ahajournals.org/cgi/content/full/102/13/1542.

"Infants with early positive HIV-1 cultures demonstrated a notable decrement in

neurodevelopmental functioning within the first 30 months of life. They achieved motor developmental scores that were increasingly and significantly discrepant *[worse]* both from the average and from scores achieved by late HIV-1-positive children over the course of the study period. Those children with early HIV-1-positive cultures also demonstrated a trend toward a similar decline in mental functioning over time...The mothers of infants with early *[HIV]* positive cultures were more likely to receive ZDV *[AZT]* treatment during pregnancy, and their infants were more likely to receive ZDV treatment prophylactically during the first 6 weeks of life...Because antiretroviral therapy has been shown to improve neurodevelopmental function in children whose CNS has been affected by the HIV-1 virus... Infants with early HIV-1 culture positivity should be treated with multiple drugs with well-established CNS penetration to reduce the likelihood that resistance will develop in the CNS compartment *[translation: this study showed that one drug may negatively affect neurological development, so multiple drugs must do the opposite!]*"

Smith R et al. Timing of perinatal human immunodeficiency virus type 1 infection and rate of neurodevelopment. Pediatr Infect Dis J. 2000 Sep;19(9):862-71.

"In a multicenter observational cohort study of 325 HIV-infected children born during 1986-1997, clinical progression was compared among infected children exposed or unexposed to Zdv *[AZT]* during prenatal and perinatal periods. Zdv exposure was associated with 1.8-fold (95% confidence interval, 1.02-3.11) increased risk of progressing to AIDS or death after adjusting for year of birth, maternal CD4 cell count, maternal AIDS diagnosis, and subsequent antiretroviral therapy of the child. Mean log10 viral copies at 712 weeks were higher among Zdv-exposed children (P = .004). "

Kuhn L et al. Disease Progression and Early Viral Dynamics in Human Immunodeficiency Virus Infected Children Exposed to Zidovudine during Prenatal and Perinatal Periods. J Infect Dis. 2000 Jul;182(1):104-11.

"Children of study women who were prescribed ZDV *[AZT]* had increased adjusted odds of any anomaly (adjusted odds ratio *[OR]*, 1.55; 95% CI, 1.01-2.29) *[i.e. more than one-and-one-half times the risk of a birth anomaly than the HIV+ population being studied in general]*...The prevalence of major anomalies in the full cohort based on definition 1 was significantly higher than that observed in the general New York State population...the SMR *[Standardized Morbidity Ratio]* adjusted for race, gender, and location suggests that the risk of a major anomaly in the study cohort was 2.79 times greater than the general population... the lack of data on potential adverse effects of this therapy is still a concern...we compared anomaly rates of subgroups defined by ZDV exposure history within the cohort of HIV-infected mothers. Babies whose mothers had ZDV exposure during pregnancy had a greater incidence of major malformations than those whose mothers did not. "

Newschaffer CJ et al. Prenatal Zidovudine Use and Congenital Anomalies in a Medicaid Population. J Acquir Immune Defic Syndr. 2000 Jul 1;24(3):249-256.

"Objective: To investigate zidovudine prophylaxis with caesarean section to reduce mother-

to-infant HIV transmission. Interventions: Elective caesarean section before labour, usually at 36–38 weeks of gestation, plus a short oral course of zidovudine, normally starting at week 32, intravenous zidovudine before caesarean section and for 10 days for the neonate (the reduced Berlin regimen).

Results: Of 179 mother–infant pairs 104 received no antiretroviral prophylaxis or therapy (control group), 48 received the reduced Berlin prophylaxis regimen, 18 received combination therapy and nine received only part of the prophylaxis regimen. Of the antiretroviral group, 68 were delivered by elective caesarean section. The HIV transmission rate was zero in the antiretroviral group *[95% confidence interval (CI) 0– 4.7]* and 12.6% (6.4–19.0) in the control group. The reduction in vertical transmission was 90% for the Berlin regimen, with an 80 and 70% reduction in risk associated with antiretroviral treatment and caesarean section, respectively. Maternal CD4 cell count but not viral load had some confounding effect on the reduction in risk attributed to caesarean section and the prophylactic regimen. Neonatal haematological abnormalities associated with antiretroviral intervention lasted for up to 7 weeks. Weight and length, although significantly lower at birth, were normal by 6–8 weeks.

Conclusion: A much reduced three-arm regimen of zidovudine prophylaxis in combination with caesarean section before labour is highly effective in reducing the risk of vertical HIV transmission and is safe for the infant. ”

Grosch-Wörner I et al. An effective and safe protocol involving zidovudine and caesarean section to reduce vertical transmission of HIV-1 infection. AIDS. 2000;14:2903-11.

“*[Human Use of AZT]* In the United States each year approximately 7000 pregnant women infected with the Human Immunodeficiency Virus (HIV-1) are treated with Highly Active Antiretroviral Therapy (HAART), either for their own disease or to inhibit maternal-fetal viral transmission. The HAART combinations of drugs typically include two nucleoside analogs and a protease inhibitor, and the nucleoside analogs zidovudine (AZT) and lamivudine (3TC) are used most frequently in combination in human pregnancy. Originally (1994) the CDC recommended that AZT be given orally for the last 6 months of pregnancy, by infusion to the mother during labor, and orally to the infant for the first 6 weeks, as standard-of-care for inhibition of vertical HIV-1 transmission.

*[Animal Models]*In 1997 AZT was reported to be a moderately-strong transplacental carcinogen in offspring of pregnant mice given the drug during the last week of gestation. Drug-induced tumor incidences in lung, liver, reproductive organs and skin from mice at 1 year of age were 2-8-fold higher than those observed in unexposed controls. Incorporation of AZT into nuclear and mitochondrial DNA (7.7-100.9 molecules AZT/106 nucleotides) of liver, lung and skin, and shortened telomeres in lung, brain and liver, were found at birth in

mice exposed in utero to tumorigenic AZT doses. In addition, HPRT somatic mutation frequencies in spleen and thymus of similarly-exposed mice necropsied at 15 days of age increased in a dose-related fashion.

Subsequent modeling of human exposures in pregnant Erythrocebus patas monkeys, using human equivalent protocols for AZT or the combination AZT/3TC, demonstrated that full-term fetal monkey organs contained AZT-DNA levels higher than those found in the mouse tumor study. In addition, the combination of AZT/3TC, given for the last half of the patas monkey gestation, caused both drugs to become incorporated into fetal organ DNA and to shorten telomeres in almost every fetal organ examined. Based on animal studies and in vitro indicators of genotoxicity, the International Agency for Research on Cancer declared AZT a 'possible human carcinogen'.

In order to explore transplacental nucleoside analog genotoxicity in human pregnancies we have examined cord blood leukocyte DNA from infants of HIV-1-infected women taking AZT or AZT/3TC. We found that 68% of infant cord blood leukocytes (n=22) were positive for AZT-DNA incorporation, with positive values ranging from 22 to 451 molecules of AZT/106 nucleotides In addition, a correlation was found between AZT-DNA incorporation and levels of intracellular AZT-triphosphorylated metabolite in cord blood leukocytes from 9 infants

Mutagenesis, presumed to be a consequence of AZT-DNA incorporation, was examined in infant cord blood leukocytes at the glycophorin A (GPA) and HPRT loci. The mean frequency of GPA N/N somatic mutant variants in umbilical cord blood erythrocytes was 2-3 fold higher in infants exposed in utero to AZT or AZT/3TC (n=27), compared to unexposed infants in the same study (n=30) or literature values for newborns (n=156). Infants exposed to AZT alone had half the induced N/N mutant frequency as infants exposed to the combination AZT/3TC (7).

The HPRT mutant frequency in cord blood lymphocytes of 66 unexposed children was half that of 37 children exposed to the combination of AZT/3TC, and sequence analysis indicated that the formation of single-base transversion substitutions was >2-fold higher in the treated group. HPRT mutant frequency increases with age in unexposed populations, and the mean mutant frequency of newborns in the AZT/3TC group was similar to that seen in adolescents, while ~30% of these infants had values comparable to adults. At 1 year of age, 30% of children exposed in utero to AZT/3TC (n=18) had HPRT mutant frequencies similar to values reported for children 6-17 years, while unexposed children (n=17) had mutant frequencies comparable to children < 6 years of age.

[Conclusions] Overall, the data indicate that children of HIV-1-infected women, exposed in utero to nucleoside analog drugs, may sustain significant genotoxic insult and should

therefore be subjected to long-term surveillance"

Poirier MC et al. Transplacental Genotoxicity of Antiretroviral Nucleoside Analog Drugs. Aspen Cancer Conference. 2000 http://www.aspencancerconference.amc.org/3t2001Poirer.htm.

"After adjusting for prematurity and maternal clinical characteristics, RPD *[rapid disease progression]* was three times more likely to occur in infants born to *[mothers]* treated *[with AZT]* compared with findings in untreated mothers (RR=2.8; p = .021). "

de Souza RS et al. Effect of prenatal zidovudine on disease progression in perinatally HIV-1-infected infants. J Acquir Immune Defic Syndr. 2000 Jun 1;24 (2):154-161.

"All women *[in this study]* received oral zidovudine *[AZT]* prior to delivery and/or intravenous zidovudine at delivery...Of 42 subjects...24 had a CVL *[cervicovaginal lavage]* taken...Of these 24 women, 7 transmitted HIV-1 to their infants and 17 did not...In the CVL samples, 41% yielded culturable HIV-1, 67% were PCR positive for proviral HIV-1 DNA, 30% were positive for cell-free HIV-1 RNA and 45% were positive for cell-associated HIV-1 RNA. Peripheral CD4 cell counts did not correlate with levels of HIV-1 in the CVL by DNA or RNA PCR or by amount of genital tract inflammation...Although all subjects in our study received zidovudine therapy in the third trimester, the high rate (29%) of HIV-1 perinatal transmission in this data set does not agree with the largest prospective, randomized study addressing this question, ACTG 076 *[in fact, this rate is higher than the transmission rate in the placebo arm of ACTG 076]* "

Panther LA, Tucker L, Xu C et al. Genital tract human immunodeficiency virus type 1 (HIV-1) shedding and inflammation and HIV-1 env diversity in perinatal HIV-1 transmission. J Infect Dis. 2000 Feb;181:555-63.

"Eight children with mitochondrial dysfunction were found...the first patient presented with visual impairment...*[and]* died aged 13 months because of respiratory and cardiac-rhythm disorders...The second patient, from age 4 months until until death at 11 months, had refractory epilepsy and deterioration of cognitive and psychomotor abilities...At age 8 months...patient three had a seizure...At age 4 years, the child's cardiac function was normal, but moderate muscular deficit persisted...In the fourth patient...between ages 14 and 27 months, the child had four episodes of febrile seizures...From age 7 months until 15 months, patient five had repeated seizures...at age 16 months...large necrotic lesions of the *[brain]*...At age 3-1/2 years the child had severe sequelae and microcephaly *[abnormally small head]*. Patient 6 was symptom-free until age 14 months, but persistent biochemical abnormalities were seen on standard follow-up...Patient 7 was symptom-free until age 4 months, at which time he became hypotonic *[low muscle tone] [and stopped breathing]*... The eighth child was symptom-free. Persistent hepatic and pancreatic abnormalities were seen from birth...At age 20 months, biological abnormalities persisted...electroretinography...

was abnormal, and cerebral NMR imaging...showed abnormalities of the periventricular white matter...No child was infected with HIV-1 *[but because their mothers were HIV-positive]* all children were treated after birth with zidovudine *[AZT]* alone or with zidovudine and lamivudine *[also a nucleoside analog]*. Treatment continued for 6 weeks in four children and was stopped prematurely because of haematological or biochemical intolerance in four children...The observation of several cases *[of mitochondrial abnormalities]* in a population of about 1700 exposed children *[as compared with 1/5,000 to 1/20,000 in normal populations]* strongly suggests an acquired mitochondrial dysfunction...Pregnant women should be informed of the potential effects associated with these treatments during pregnancy."

Blanche S et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet. 1999 Sep 25;354:1084-9.

"The UK's Committee on Safety of Medicines has issued a warning to doctors about the risk of mitochondrial dysfunction in infants born to HIV infected mothers treated with zidovudine (AZT) to prevent vertical transmission...The warning comes in advance of the publication of data from a French study in which it was discovered that 8 out of approximately 200 infants developed mitochondrial dysfunction following exposure to zidovudine, with or without 3TC treatment, for the prevention of vertical transmission of HIV infection. "

Perinatal AZT: New warning on potential risk to infants [URL no longer functional]. www.aidsmap.com. 1999 Jul 21.

"The data show that AZT crosses the human placenta and becomes rapidly incorporated into DNA of placental tissue in a dose-dependent fashion, suggesting that even short exposures to this drug might induce fetal genotoxicity and might also inhibit maternal-fetal viral transmission. "

Olivero OA et al. 3'-azido-3'-deoxythymidine (AZT) transplacental perfusion kinetics and DNA incorporation in normal human placentas perfused with AZT. Mutat Res Fundam Mol Mech Mutagen. 1999 Jul 16;428(1-2):41-7.

"Incorporation of ZDV *[AZT]* into DNA was detected in most of the samples from ZDV-exposed adults and infants. Therefore, the biologic significance of ZDV-DNA damage and potential subsequent events, such as mutagenicity, should be further investigated in large cohorts of HIV-positive individuals. "

Olivero OA et al. Incorporation of zidovudine into leukocyte DNA from HIV-1-positive adults and pregnant women, and cord blood from infants exposed in utero. AIDS. 1999 May 28;13:919-25.

"Comparison of HIV-1-infected children whose mothers were treated with ZDV *[AZT]* with children whose mothers were not treated showed that the former group had a *[1.8 times]* higher probability of developing severe disease or severe immune suppression *[2.4 times*

higher risk] and a lower survival (72.2% versus 81.0%)."

The Italian Register for HIV Infection in Children. Rapid disease progression in HIV-1 perinatally infected children born to mothers receiving zidovudine monotherapy during pregnancy. AIDS. 1999 May 28;13:927-33.

"transplacental exposure studies demonstrated that AZT is a moderate to strong transplacental carcinogen in mice...Since AZT-DNA incorporation in human placenta occurs rapidly by 2 hr of AZT perfusion, infants exposed to AZT even for short periods of time during gestation may sustain genotoxic damage. In previous studies AZT has been shown to produce both, large scale DNA damage and point mutations...the consequences of any fetal exposure to a nucleoside analog, in utero, remain unknown "

Olivero OA et al. 3'-azido-3'-deoxythymidine (AZT) transplacental perfusion kinetics and DNA incorporation in normal human placentas perfused with AZT. Third Conference on Environmental Mutagens in Human Populations. 1999 Feb 18.

"…these two *[HIV+ babies taking AZT+3TC]* died of an extremely rare disease caused by genetic damage to the mitochondrial DNA - which is found in the cell body rather than in the nucleus with the genes. One died at 11 months and one died at 13 months, both from severe brain damage. Blanche *[of the French medical research institute INSERM]* told the meeting that there was no proof the drugs caused the damage. But he said there was also no evidence the babies had inherited abnormalities, and HIV drugs are known to cause mitochondrial damage. "

HIV drugs may show adverse effects in babies. Reuters. 1999 Feb 2.

"At present, data regarding the effects of ZDV use on vertical transmission rates are inconclusive and incomplete. In addition, the long-term effects of ZDV use during pregnancy and after birth on the woman and any resulting child are yet to be discovered…the possibility has not yet been ruled out that this "risk-reducing" measure may not be effective and may prove detrimental to the health of both mother and child. "

Bennett R, Foster G. Mandatory testing of pregnant women and newborns: a necessary evil? and Realistic alternatives to breastfeeding in the HIV/AIDS era. AIDS Information Exchange. 1998.

"Conclusions: In HIV-infected pregnant women treated with two RTI *[nucleoside analogs, of which AZT was the most common]* with or without protease inhibitors, one or more adverse events occurred in 29 out of 37 women and in 14 out of 30 babies. "

Lorenzi P et al. Antiretroviral therapies in pregnancy: maternal fetal and neonatal effects. AIDS. 1998;12:F241-247.

"Similar levels of AZT-DNA incorporation were detected in peripheral blood from HIV-1-positive mothers and cord blood from their infants and tissues from newborn mice exposed

to tumorigenic *[cancer-causing]* doses of AZT in utero. Therefore, the biologically effective dose (i.e. the amount of AZT that incorporated into DNA) was similar in both species even though the mouse daily dose of AZT was much higher than that received by humans. ”

Olivero AO et al. AZT, a genotoxic transplacental carcinogen in rodents, is incorporated into human fetal and maternal DNA. 2nd National AIDS Malignancy Conference. 1998 Apr 6;8.

“We present two cases of severe PCP *[pneumocystis carinii pneumonia]* in infants who were perinatally exposed to HIV *[and AZT]* but who were uninfected with HIV…Both children had a transient decrease in their CD4 cell counts that was concomitant with the acute PCP episode…A survey of healthy 4-year-old children showed that the seroprevalence of PCP was ~67%. Thus, children with PCP usually have asymptomatic infection. It has been suggested that immunosuppression allows P. carinii to progress to serious disease. The two children described herein were not significantly immunosuppressed, and it is unclear if any of the recognized antecedents (a mother with AIDS and severe immunosuppression, zidovudine *[AZT]* treatment, and concomitant herpesvirus infection) set the stage for PCP ”

Heresi GP et al. Pneumocystis carinii pneumonia in infants who were exposed to human immunodeficiency virus but were not infected: an exception to the AIDS surveillance case definition. Clin Infect Dis. 1997 Sep;25(3):739-40.

“The authors selected six patients who were HIV positive and who had requested termination of pregnancy to study the passage of zidovudine through the placenta...1 gram of zidovudine *[AZT]* was given in five doses of 200 mg each orally...At a mean age of 17.5 weeks *[into the pregnancy]*, samples were taken from the mothers’ blood, from the amniotic fluid and from the fetal blood...The concentrations of *[AZT]* in the *[amniotic fluid]* and in the fetal blood were higher or equaled those found in the maternal blood...The drug remains contraindicated in pregnancy ”

Patterson TA et al. Transplacental pharmacokinetics and fetal distribution of azidothymidine, its glucoronide, and phosphorylated metabolites in late-term rhesus macaques after maternal infusion. Drug Metab Dispos. 1997 Apr;25 (4):453-9.

“Treatment of HIV-infected pregnant women with anti-HIV therapeutics may, therefore, inadvertently expose many uninfected and healthy fetuses to these maternally administered and potentially toxic drugs. ”

Patterson TA et al. Transplacental pharmacokinetics and fetal distribution of azidothymidine, its glucoronide, and phosphorylated metabolites in late-term rhesus macaques after maternal infusion. Drug Metab Dispos. 1997 Apr;25 (4):453-9.

"AZT and/or its metabolites were found in every *[macaque ape]* fetal tissue examined, including plasma and amniotic fluid. The greatest amount of AZT-derived compound was found in the fetal kidney, "

Patterson TA et al. Transplacental pharmacokinetics and fetal distribution of azidothymidine, its glucoronide, and phosphorylated metabolites in late-term rhesus macaques after maternal infusion. Drug Metab Dispos. 1997 Apr;25 (4):453-9.

"Initiation of ZDV *[AZT]* therapy during pregnancy did not result in a significant decrease in viral load at delivery when controlling for the effect of pregnancy…Mother-to-child transmission of HIV-1 occurred in one of 27 (4%) ZDV-treated women and in two of 16 (12.5%) untreated women. "

Melvin AJ et al. Effect of pregnancy and zidovudine therapy on viral load in HIV-1-infected women. J Acquir Immune Defic Syndr. 1997 Mar 1;14(3):232-6.

"In reviewing the frequency of birth defects in this population *[of HIV+ women taking AZT during pregnancy]* we noted eight birth defects (10%) out of 80 live births *[and 8 spontaneous fetal losses, for a total of 17% abnormal pregnancies]*"

Kumar RM et al. Zidovudine Use in Pregnancy: A Report on 104 Cases and the Occurrence of Birth Defects. J Acquir Immune Defic Syndr. 1994 Oct;7(10):1034-9.

"Treatment with trimethoprim-sulfamethoxazole and zidovudine *[AZT]* was started earlier and was more frequent among the 16 children born to mothers with class IV disease *[AIDS]*. At 18 months,…13 had received zidovudine *[81%]*, as compared with…81…of the 130 children *[62%]* born to mothers with class II *[HIV+, without symptoms]* or III disease *[swollen glands]*. "

Blanche S et al. Relation of the course of HIV infection in children to the severity of the disease in their mothers at delivery. N Engl J Med. 1994 Feb 3;330(5):308-12.

"Children treated with zidovudine continued to have bacterial and opportunistic infections. The effect of the drug on the frequency of these events could not be assessed because of the lack of control groups...One or more episodes of hematologic toxicity occurred in 54 children (61 percent)—anemia (hemoglobin level, <75g per liter) in 23 children (26 percent) and neutropenia (neutrophil count, <0.75X10^9 per liter) in 42 (48 percent) "

McKinney RE et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. N Engl J Med. 1991 Apr 11;324 (15):1018-25.

"The concentrations of the drug *[AZT]* in the liquor and in the fetal blood *[of 6 aborted human fetuses]* were higher or equaled those found in the maternal blood...The drug

remains contraindicated in pregnancy. ”

Gillet JY et al. Preliminary study on the transport of AZT (Retrovir-zidovudine) through the placenta. J Gynecol Obstet Biol Reprod. 1990;19(2):177-180.

Feedback

We appreciate your comments, feedback, questions and suggestions for improvements to this site.

Provided courtesy of Alberta Reappraising AIDS Society

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