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December 3, 2003

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Re: Nucleoside Analogues- Draft Prioritization and Draft Data Summaries

Dear Ms. Oshita:

Please find attached to this letter a thorough weight of evidence carcinogenicity assessment for the nucleoside analogues OEHHA has considered for prioritization under Proposition 65. The assessment discusses several studies that OEHHA has not yet evaluated to determine the potential for these drugs to cause cancer along with those the Agency has used in its draft prioritization. The assessment shows that the weight of evidence is not enough to assign a "high" priority to nucleoside analogues.

These written comments supplement the presentation made at OEHHA's November 19, 2003 public workshop discussing the adverse public health consequences that would ensue if the drugs were listed under Prop 65 - harming women and minorities most - and the lack of public benefit. I concluded by asking OEHHA to transfer the applicable budgeted funds from its review program to the Dept. of Health Services for the benefit of HIV patients. Since then the need for that response has become even more acute. On November 25, 2003, California newspapers reported the Governor's proposal to reduce funding for AIDS drug assistance and place HIV patients on a waiting list for drugs that are desperately needed. (San Francisco Chronicle, p. A-1). OEHHA's further review of nucleoside analogues would use scarce funds to evaluate a low, hypothetical risk that other experts monitor carefully with the best response tools. The Agency funds for that duplicative effort could be redirected instead to the AIDS Drug Assistance Program to achieve advances in public health and avoid the harmful outcome of a Prop 65 action.

Thank you for your assistance. Please circulate these and my workshop presentation materials to others who may be interested.

Very truly yours,

A handwritten signature in black ink that reads "Robert Reinhard". The signature is written in a cursive style with a prominent initial "R".

Robert J. Reinhard

cc: Senator Deborah Ortiz

Nucleoside Analogues (AZT, d4T and ddC)

Weight of Evidence Assessment for Carcinogenicity

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I. INTRODUCTION AND BACKGROUND.

These comments are submitted in response to the October 17, 2003 “Request for Relevant Information” (Request) by the Office of Environmental Health Hazard Assessment (OEHHA) regarding “Draft Data Summaries” (Summary) and “Draft Priorities for Chemicals With Respect to Their Potential to Cause Cancer” under the Safe Drinking Water and Toxic Enforcement Act (Prop 65).¹ In previous submittals and in participation at OEHHA’s public workshop on November 19, 2003, I provided information to address the significant adverse public health consequences that would result if OEHHA takes steps to list nucleoside analogues as carcinogens under Prop 65. At the workshop, I also presented toxicological assessment information and copies of relevant studies OEHHA has not reviewed in its Summary.

Because there was not sufficient time to present a complete overview of the toxicology studies at the public workshop, these comments principally record a weight of evidence assessment of relevant studies for purposes of assigning a priority. The studies include newly published and available data that OEHHA has not yet considered. Using OEHHA’s Prioritization Procedure,² the weight of evidence is not enough to assign a high priority to evaluate these drugs further as carcinogens. Because – in addition - significant legal and ethical problems would result from listing these drugs when they are in use to mitigate a fatal epidemic, I request that OEHHA end its listing efforts for these drugs as outlined in my November 19th presentation.

II. OVERVIEW OF PROCEDURE AND BASIS FOR ASSIGNING PRIORITY

A. Statutory Basis

OEHHA developed its Procedure as a management tool for presentation of chemicals to the states’ qualified experts for evaluation and listing consideration consistent with statutory criteria. Prop 65 states:

A chemical is known to the state to cause cancerwithin the meaning of this chapter if in the opinion of the state's qualified experts it has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer...³

¹ The data summary for nucleoside analogues appears at http://www.oehha.org/prop65/docs_state/pdf/batch4sums.pdf pp.15-16. Prop 65 is at Calif. Health and Safety Code § 25249.5, et seq.

² Procedure for Prioritizing Candidate Chemicals for Consideration Under Proposition 65 by the "State's Qualified Experts" (Procedure), May, 1997 <http://www.oehha.org/prop65/pdf/priodoc.pdf>

³ Cal. Health and Safety Code § 25249.8(b).

The Procedure is useful to the extent it puts forward chemicals with reference to generally accepted principles of cancer causation and brings forward first only those that are likely to meet criteria for listing as carcinogenic if the state's experts – in this case the Carcinogen Identification Committee (CIC) - reviewed them. The tests of nucleoside analogue exposure do not clearly show that they cause human cancer or that the weight of evidence would support continued assessment as carcinogens under Prop 65 with high priority.

B. Steps in Prioritization.

Using the Procedure, OEHHA evaluates randomly selected chemicals for consideration of the level of carcinogenic concern. Each chemical receives a screening toxicity evaluation based on a brief review of the available scientific literature. A draft priority ranking of "High" or "Not High" is assigned to each of the chemicals, unless other factors warrant postponement, based on the evidence of carcinogenicity. OEHHA then holds a public workshop, providing a summary of the data used to propose a draft priority assignment and a 60-day public comment period to solicit oral as well as written comment on the draft priority rankings, the period we are now in. Chemicals receiving a final priority ranking of "High" carcinogenicity concern are considered first by the CIC.

C. Weight of Evidence to Assign a Priority.

OEHHA describes the evidence and factors it considers in the Procedure as follows:

Epidemiological studies: The evidence considered will include the study population, exposure situation and quality of studies. ... Both positive and negative studies will be considered in assessing the overall level of hazard concern.

Animal studies: The evidence considered will include the number of experiments and species tested, route of administration, frequency and duration of exposure, numbers of test animals, and consideration of dose-response. Both positive and negative studies will be considered in assessing the overall level of hazard concern.

Other relevant data: Evaluation of other relevant data for use in prioritizing candidates will also be made. Such data include information on mechanism of action, ...metabolism, and genotoxic activity.

Chemicals will be assigned a high level of hazard concern if this preliminary evaluation indicates the existence of evidence that is likely to demonstrate a strong and biologically plausible potential to cause cancer Chemicals which appear to have less evidence will be assigned lower

levels of hazard concern, which reflect OEHHA's preliminary evaluation of the weight of the available information.⁴

The quality of the evidence as well as the balance of both positive and negative results must be considered. If the sum of the evidence does not offer sufficient weight to establish a strong and biologically plausible potential that a chemical causes cancer then it would not be assigned a high priority.

D. Assigning a Level of Exposure Concern

OEHHA also considers "level of exposure" in this process to identify from among those chemicals with a high level of carcinogenicity concern which chemicals would be presented to the CIC first.

These comments provide data relevant to the weight of evidence to assign a priority and the level of exposure.

III. WEIGHT OF EVIDENCE FOR CARCINOGENICITY OF NUCLEOSIDE ANALOGUES.

As discussed below, the sum of the animal, human monitoring and genotoxicity studies of nucleoside analogues does not show a "strong and biologically plausible potential" for these drugs to cause human cancer.

The animal data consist of essentially two types of studies: 1) those that found highly localized, noninvasive vaginal site tumors in mice and rats exposed to high doses of AZT and which are considered irrelevant to humans, and 2) one study in which the conclusion was that AZT is *not* a transplacental carcinogen as tested and a single study (the subject of two published papers) in which the investigators found a "moderately" effective level of transplacental carcinogenicity in mice exposed to levels of AZT many times the levels administered in prescribed treatments. The authors of the latter study subsequently tested for and could not find a mechanism of action that could explain the results in mice and cautioned against using the results to explain human responses at doses that were not equivalent to doses used in animal experiments. The test results from the study – which also are problematic with regard to statistical significance or the adequacy of this particular animal model to evaluate this form of cancer in humans - would not help to establish the plausibility of a human biological response. Human monitoring of children exposed perinatally to AZT and who were successfully protected against infection from HIV fails to show any evidence of drug related carcinogenicity after eight years of followup, and other human studies do not show evidence these drugs cause cancer. The nucleoside analogues may have some genotoxic effects (incorporation

⁴Emphasis added; Procedure, p, 8.

into DNA is not surprising given their function) but in ways that differ from those of other substances confirmed to be human carcinogens.

Overall, the weight of evidence does not meet OEHHA's criteria to assign a high priority to evaluate these drugs. That assessment, combined with significant legal and ethical problems resulting from any potential listing of the drugs under Prop 65, are persuasive to deter further consideration of the drugs for carcinogenicity and listing.

A. Animal Studies.

1. Studies Describing Topical Effects in Rodents of Unmetabolized AZT Are Irrelevant to Humans.

Long term studies in mice and rats have been performed by NTP (1999) and Ayres, et al. (1996) to evaluate AZT. The NTP study concluded that when male and female B6C3F₁ mice are administered AZT alone or with alpha-interferon over a two year period, the data show clear evidence of carcinogenic activity only in female mice and equivocal evidence in male mice. This conclusion was based on observations of statistically significant increases in vaginal squamous cell carcinomas and/or papillomas and increased hyperplasia of the vaginal epithelium and the absence of significant tumor incidence in male mice.⁵

However, NTP found that the female mouse data are *not* physiologically or metabolically applicable to humans and uncertain as to their ability to predict human cancer. Female mouse neoplasms in these studies are thought to be a topical effect of chronic exposure to unmetabolized AZT at a site with high cell turnover.⁶ NTP stated:

Ayers, *et al.* (1996) administered AZT intravaginally to CD-1 mice for 22 months and observed a higher incidence of vaginal neoplasms than occurred in the above referenced gavage study. They also demonstrated that in female mice there is retrograde flow of urine from the discharge point at the base of the vulva into the region of the vagina where the neoplasms occur. Moreover, in mice, at least 90%

⁵ NTP Study, pp. 16 and 77-82. The comparable studies in rats showed similar but much less pronounced sex-based tumorigenic results. Two vaginal epithelial neoplasms were seen only in those rats given the highest dose of AZT (300 mg/kg/day). Treatment with AZT did not affect the incidence of any other benign or malignant tumor in any tissue or organ. Ayers, et al. (1996). PHS (2003) Guidelines at p. 35 describes the rodent tumors as noninvasive.

⁶ The findings of other recognized agencies and studies are consistent with this view. NIAID (1997) stated:
"Scientists have known for a number of years that some nucleoside analogs, including AZT, are sometimes carcinogenic in animals. They have known since 1989 that AZT causes vaginal epithelial neoplasms when given to adult mice. This is believed to be a topical effect in mice, resulting from reflux of urine containing high concentrations of excreted AZT from the bladder into the vagina. No increase in the incidence of tumors in other organ sites has been seen in other studies conducted in adult mice and rats"(NIAID (1997) pp. 1-3) The Public Health Service Task Force adopted this view (PHS (2003)), Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy, November 26, 2003. <http://aidsinfo.nih.gov/guidelines-Perinatal>.

of AZT is eliminated in urine as the parent compound following oral administration. Because there is a high rate of cell turnover in the vaginal epithelium as consequence of the short estrous cycle of mice...Ayers.. concluded that prolonged exposure of the vaginal epithelium to the relatively high concentrations of AZT in urine could explain the observed neoplasm response....

Humans metabolize AZT to a much greater extent than do rats or mice and *no comparable situation regarding urine flow into the vagina exists in humans.* Therefore if the mechanism proposed by Ayers *et al.* (1996) to explain the development of vaginal neoplasms is correct, it is uncertain to what extent the results of these studies will be predictive of human cancer risk. ⁷

NTP explained that its categorizations of levels of evidence for carcinogenic activity are limited to the study conditions. Other factors would need to be considered before judging whether or to what degree data predict human cancer. NTP stated:

Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has potential for hazard to humans...the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies...

When a conclusion statement for a particular chemical is selected, consideration must be given to key factors that would extend the boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels.⁸

2. Studies to Evaluate Transplacental Carcinogenicity of AZT Either Do Not Show Evidence of Carcinogenicity Or Are Not Predictive of Human Cancer Risk, Relatively “Weak,” and Do Not Offer Plausible Explanation of Human Biological Responses.

Four significant papers relevant to assessment of transplacental carcinogenicity and AZT have been published - Ayers (1997), Olivero (1997) Diwan (1999) and Diwan (2000). The Olivero (1997) and Diwan (1999) papers report the initial and then longer term findings of a single study. OEHHA's Summary has not evaluated the Diwan (2000) study. It cites the Ayres (1997) study but incorrectly.

⁷ NTP Study, pp.79 and 82; emphasis added.The physiological, metabolic and pharmacokinetic explanations applicable to mice are controlling in rats also (Ayers (1996)).

⁸ NTP Study, p. 14. This explanation appears in all NTP bioassay reports.

The Ayers (1997) study did not show evidence of transplacental carcinogenicity when pregnant mice were administered AZT in doses intended to achieve blood levels approximately three fold higher than those achieved with humans in clinical practice and offspring groups were exposed to AZT not only perinatally but also in drinking water and by gavage after birth for up to two years. The earliest tumor observed in this lifetime treatment study was after 23 months of dosing. There were no treatment related tumors in offspring groups that were exposed to AZT both perinatally and either up to postnatal day 90 or day 21. The authors concluded that, “under the conditions tested, [AZT] was not a transplacental carcinogen.” Any observations of tumors were no different from and explained by the earlier studies of adult rodents experiencing topical effects of unmetabolized AZT, results which are irrelevant to humans.

The study that reported a transplacental carcinogenic effect in mice was the Olivero (1997) study, and the data were later reanalyzed in Diwan (1999) when the team reported longer term observations of the test animals. In Olivero (1997), pregnant female CD-1 mice were given AZT by gavage in various doses ranging up to 25 to 50 times the prescribed human dose and near the maximum dose beyond which lethal fetal toxicity would be observed. The results in offspring up to 52 weeks after delivery were analyzed.

The scientific team pointed to their measurements of increased tumor incidence and selected examples of tumor multiplicity in the lungs, liver and female reproductive organs of offspring as evidence of transplacental carcinogenicity. However, interpretation of the data using equally valid methods would not reach the same conclusion and would be equally powerful. Further, the scientific team later found mechanistic support was unavailable to explain reproductive tract tumors.

Several factors indicate that the data from the Olivero (1997) and Diwan (1999) studies of transplacental carcinogenicity do not provide enough weight to give a high priority to evaluate AZT as causing cancer:

- 1. The scientific team itself revised its conclusions in 1999 to indicate the strength of the evidence was weaker than at first supposed.** In 1997, the scientific team concluded that “AZT is a moderately strong transplacental carcinogen in mice...the relevance of mouse studies to human exposure must be considered in the context of dose-equivalency.” However, in Diwan (1999) when offspring were examined after two years, the same team found less strength for their evidence and concluded, “AZT is a moderately effective perinatal carcinogen in mice... *It is difficult to extrapolate the relevance of our findings in mice to children exposed prenatally or as newborns to AZT...our studies suggest the possibility* of some carcinogenic risk in humans related to perinatal exposures to AZT.” Considering also that the investigators themselves found the relevance of their findings to humans to depend on dose-equivalency, the high levels of the experimental doses in animals would not provide strong predictive power.

2. **Data analyzed in 1999 is less significant than earlier results.** In 1997, the scientific team found statistically significant increases in tumor incidence and tumor multiplicity in the offspring of AZT treated mice. In 1999, descriptions of significance are markedly changed from 1997 and in several ways. Significant increased tumor incidence levels at each site were achieved by adding adenomas and carcinomas, melding numbers of tumors between the sexes when each sex did not demonstrate significance, use of trend tests in the absence of other statistical significance and attributing weight to increases that approached significance but did not achieve that level. The scientific team did not consider metabolic and physiological mechanisms unique to the mouse.⁹ Had the authors differentiated between the types of tumors more clearly, reanalyzed the data to account for sex differences, evaluated whether tumor progression to carcinomas in humans operates the same as in rodents, given less weight to increases that were not truly significant and/or used other equally valid quantitative techniques, other summary conclusions would have resulted. If the data had been more persuasive, the scientific team would not have had to resort to measures such as use of trend tests.
3. **The 1999 results do not adequately interpret the incidence of tumor decreases in AZT exposed mice.** Although hematopoietic neoplasms in offspring exposed transplacentally to AZT decreased compared to controls, the scientific team did not completely account for this observation when analyzing the data for total tumor incidence of all offspring.
4. **The scientific team did not find supportive mechanistic evidence as originally intended to explain reproductive tract tumors.** In 1997 and 1999, the scientific team posed the question whether AZT might operate as a carcinogen by a mechanism or effect similar to that shown in studies of DES which induces hormonal changes and causes reproductive tract damage. The team noted, “genital tract tumors have *only* been associated with early exposure to sex hormones.” Diwan (2000) published the results of a new experiment that failed to show any structural or functional alterations in the male or female reproductive organs of F1 and F2 generations derived from female mice exposed to AZT. Accordingly, the team reported that “The underlying mechanism of AZT-induced reproductive tract tumors in male and female offspring is unknown.” Thus the strength of evidence that may be

⁹Of the various tumor sites examined in 1999 the only AZT-related statistically significant increases occurred in the lungs of female mice and, to only a certain extent, in the female mouse reproductive tract. The reproductive tract and also liver exhibited AZT-related tumor incidence increase when analyzed by trend tests and not by means of a pairwise test (Fisher’s exact test). AZT-related tumor incidence increases in male mice were not significant at any tumor site.

accorded to the 1997 and 1999 results was not increased by explanation of mechanism.¹⁰

3. Overall Weight of Evidence from Animal Studies.

The U.S. Public Health Service Task Force – PHS (2003) - prepares official guidelines recommending proper use of nucleoside analogues to prevent perinatal transmission of HIV. In doing so, the PHS has prepared an overview of the carcinogenicity studies reviewed here and the weight of evidence appropriate for those studies. The PHS quite properly confirms that the data will not provide assurance that there is “no carcinogenic risk” but weighs the evidence and finds the transplacental risk to be merely “theoretical” and not of sufficient weight to advise pregnant women to avoid AZT use. To the contrary, use of AZT or other antivirals to prevent transmission of HIV is highly encouraged as I discussed on November 19, 2003. A copy of the PHS discussion is attached.

Thus, the evidence from studies of a possible transplacental carcinogenicity effect of AZT is not a strong and biologically plausible demonstration of the potential for this drug to cause cancer. The evidence in other animal studies of AZT is irrelevant to humans because it describes a topical effect of unmetabolized AZT that could not occur in humans.

As to the studies of d4T and ddC, the experimental doses at which tumors were observed in the ddC studies were over 1,000 times the equivalent maximum tolerated dose in humans and, in the d4T studies, at more than 250 times the recommended clinical dose. Their usefulness to predict human cancer risk is slight. The animal studies of nucleoside analogues would not justify assigning a high priority to these drugs.

B. Human Studies - Confirmatory Data in Humans So Far Does Not Support a High Priority.

The Summary does not review any of the studies of humans exposed to nucleoside analogues. Published data have so far reported on the monitoring of children exposed perinatally to AZT to prevent HIV infection only up to 5.2 years of age, no malignancies have been detected.(Culnane (1999) and Hanson (1999)). In a recent November 6, 2003

¹⁰This result was anticipated and expected earlier by NIAID(1997). NIAID stated: “The panel noted that, in general, very little is known regarding the sensitivity or reliability of this mouse model system in predicting transplacental carcinogenicity in humans. Demonstration of the utility of the mouse model in predicting transplacental carcinogenicity of drugs in humans would require comparison of long-term effects for a large number of different drugs given to both mice and women during pregnancy. However, only a few other drugs have been studied in the mouse model. Furthermore, long-term follow-up data in humans are available only for diethylstilbestrol (DES). Approximately 15 percent of the offspring of pregnant mice given DES within the range of doses received by humans develop vaginal tumors similar to those seen in the children of women given DES to prevent miscarriage. Approximately 1/1000 exposed daughters develop vaginal tumors. The mechanisms of carcinogenicity of DES and AZT are likely to differ substantially.”

interview, Dr. Mary Glenn Fowler of the Centers for Disease Control (CDC) reported that those followup studies have now lasted eight years and still without evidence of carcinogenicity.¹¹ Additional monitoring studies are conducted by states and they too report that use of AZT to prevent transmission of HIV does not show evidence of a transplacental carcinogenic effect (CDC (2002)).¹²

Studies in HIV infected adults and children do not show evidence of drug related cancer (Levine (1995), Pollock (2003)). This is to be expected since the nucleoside analogues restore immunocompetence of HIV infected patients whose natural body defenses have been damaged leaving them susceptible otherwise to opportunistic cancers. AZT has been in use since 1987 when it was first approved by FDA, and d4T and ddC were approved soon after. Patient experience in that time does not indicate these drugs are human carcinogens. There is no indication from human studies that the nucleoside analogues cause cancer.

C. Genotoxicity.

Wutzler et al. (2001) surveyed the genetic risks of antiviral nucleoside analogues. That study has not been reviewed in OEHHA's Summary. The authors conclude, "Existing data of genotoxic and/or carcinogenic properties of nucleoside analogues do not allow a reliable assessment of the long term genetic risks posed by these drugs in man. it remains an important ...challenge to clarify what the experimental findings mean with regard to the clinical setting. ... human carcinogenicity of antiviral nucleosides is at present a purely speculative assumption. ... The mechanisms of damage induction in the genetic information [of nucleoside analogues] are still largely hypothetical, particularly complex and appear to vary in a drug specific manner because with respect to biological activities, among nucleoside analogues there is no such thing as a close congener." The OEHHA Summary considers whether structural similarities with other nucleoside analogues may be relevant. Since the structural differences are important, that consideration should not affect the assessment. The genetic risks do not add to the weight of evidence for prioritization.

D. Overall Weight of Evidence Assessment – Factors Affecting OEHHA Decisionmaking in Assigning Priority.

The overall weight of evidence from animal, human and genotoxicity studies does not show a strong and biologically plausible potential for these nucleoside analogues to cause cancer in humans. The weight of evidence has been described repeatedly by experts in the field ranging from federal and international government agencies to the researchers

¹¹ <http://www.pbs.org/newshour/bb/health/july-dec03/hiv-extended3.html>

¹² See my letter to OEHHA dated April 11, 2002. The principal investigator in the CDC review of Michigan data is Dr. Eve Mokotoff, Michigan Department of Community Health. She reported on February 12, 2002 that the state looks for incidence of cancer in this population and "has not identified any ... cancers associated with [AZT] exposure." Dr. Mokotoff can be reached at mokotoffe@michigan.gov.

most crucially involved in HIV treatment as no more than “theoretical,” “hypothetical,” “speculative,” “suggestive but inconclusive” and without any clear basis for extrapolation or relevance to humans or support in human experience. It would not be a close question for those authorities if they had the task to assign a Prop 65-like priority. The evidence is not compelling enough to make the priority “High.”

The evidence supports the judicious approach to public health already in place: Followup monitoring, combined with appropriate physician counseling and use of the package inserts for these drugs which discuss the results of animal tests, is a responsible reaction to data that does not reach a “high” level of concern. Monitoring activity is being carried out assiduously by numerous agencies and researchers. At the same time, those experts and others have documented their knowledge of the harm that would be caused by using Prop 65 warning methods or messages that deter anyone who needs these drugs from obtaining them or that would raise the level of concern in a way that interferes with mitigation of the epidemic. For the reasons set out here and in earlier comments, I request that OEHHA end efforts to list these drugs as carcinogens under Prop 65. No public benefit and only harm to the HIV population will result if those efforts are pursued.¹³

IV. LEVEL OF EXPOSURE CONCERN.

The level of exposure concern is used only to determine which chemicals already designated as high priority for carcinogenicity would be brought to the CIC’s attention first. For purposes of the Summary description, the level of exposure concern for these drugs should be revised to “low” level of exposure. The California Department of Health Services estimates 126,000 Californians are infected with HIV in the State, less than .3% of the total population.¹⁴ The number of potential exposures from that estimate that might be increased as a result of using nucleoside analogues to prevent perinatal transmission would be a negligible amount.

¹³ On November 19, 2003, I presented data to document the scope of the epidemic, barriers to medical treatment and the importance of other state AIDS drug assistance programs. Almost daily those statistics become more urgent as they are updated. On November 25, 2003 the United Nations released its annual report showing increases in the scope of the epidemic and the discrimination faced by the HIV population. <http://www.unaids.org/wad/2003/press/index.html#related>
http://www.unaids.org/wad/2003/press/factsheets/FS_stigma2003_en.pdf. The UN writes:

“Prejudiced and stigmatizing thoughts frequently lead people to do, or not do, something that denies services or entitlements to another person. For example, they may prevent health services being used by a person living with HIV/AIDS.... This is discrimination.”

¹⁴ See <http://www.dhs.ca.gov/ps/ooa/aboutoa/pdf/FastFacts101502.pdf> (estimates of HIV-infected population not including AIDS patients) and <http://www.dhs.ca.gov/ps/ooa/Statistics/pdf/Stats2003/Oct03Stats.pdf> (AIDS surveillance report, surviving AIDS patients).

V. REFERENCES.

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Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States (2003) <http://aidsinfo.nih.gov/guidelines/> - Perinatal

Public Health Service Task Force, Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy (2003) <http://aidsinfo.nih.gov/guidelines/> - Perinatal

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Zidovudine (Retrovir®) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies

Prolonged, continuous, high-dose zidovudine administration to adult rodents is associated with the development of nonmetastasizing vaginal squamous tumors in 13% of female rodents (at estimated drug concentrations 3 and 24 times that of human therapeutic exposure in mice and rats, respectively) [14]. In rodents, unmetabolized zidovudine is concentrated in urine with reflux into the vaginal vault. Therefore, vaginal tumors could be a topical effect of chronic zidovudine exposure on the vaginal mucosa. The observation that vaginal squamous cell carcinomas were observed in rodents exposed to 20 mg/mL zidovudine intravaginally is consistent with this hypothesis [14]. In humans, only metabolized zidovudine is excreted in the urine. No increase in tumors in other organ sites has been seen in adult rodent studies.

Two transplacental carcinogenicity studies of zidovudine were conducted in mice, with differing results. In one study, two very high daily doses of zidovudine were administered during the last third of gestation in mice [15]. These doses were near the maximum dose beyond which lethal fetal toxicity would be observed and approximately 25 and 50 times greater than the daily dose given to humans (although the cumulative dose was similar to the cumulative dose received by a pregnant woman taking 6 months of zidovudine). In the offspring of zidovudine-exposed pregnant mice at the highest dose level followed for 12 months, a statistically significant increase in lung, liver, and female reproductive organ tumors was observed; the investigators also documented incorporation of zidovudine into the DNA of a variety of newborn mouse tissues, although this did not clearly correlate with the presence of tumors. In the second study, pregnant mice were given one of several regimens of zidovudine, at doses intended to achieve blood levels approximately threefold higher than human therapeutic exposure [16]. The daily doses received by the mice during gestation ranged from one-twelfth to one-fiftieth the daily doses received in the previous study. Some of the offspring also received zidovudine for varying periods of time over their lifespan. No increase in the incidence of tumors was observed in the offspring of these mice, except among those that received additional lifetime zidovudine exposure, in which vaginal tumors were again noted.

Transplacental carcinogenicity studies have not been performed for any of the other available antiretroviral drugs or combinations of drugs. In January 1997, the National Institutes of Health convened an expert panel to review these animal data [17]. The panel concluded that the known benefit of zidovudine in reducing vertical transmission of HIV by nearly 70% (7.2 versus 21.9% with placebo) [18] far outweighs the theoretical risks of transplacental carcinogenicity. The panel also concluded that infants with *in utero* exposure to zidovudine (or any other antiretroviral) should have long-term follow-up for potential adverse effects. No tumors have been observed in 727 children with *in utero* ZDV exposure followed for over 1,100 person-years [19]. While these data are reassuring, follow-up is still limited and needs to be continued into adulthood before it can be concluded that there is no carcinogenic risk.

Stavudine (Zerit®, d4T) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies

Some *in vitro* and *in vivo* mutagenesis and clastogenicity tests are positive. In 2-year carcinogenicity studies in mice and rats, d4T was noncarcinogenic in doses producing exposures 39 (mice) and 168 (rats) times human exposure at the recommended therapeutic dose. At higher levels of exposure (250 [mice] and 732 [rats] times human exposure at therapeutic doses), benign and malignant liver tumors occurred in mice and rats and urinary bladder tumors occurred in male rats.

Zalcitabine (HIVID®, ddC) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies

High doses of zalcitabine (over 1,000 times that of human therapeutic exposure) have been associated with the development of thymic lymphomas in rodents.