

**Comments on the Draft Data Summary and Draft Priority Assignment  
For Nucleoside Analogues (nucleoside analogue reverse transcriptase inhibitors)  
OEHHA Public Workshop – November 19, 2003**

Good morning. My name is Robert Reinhard. These comments are supported by AIDS Project Los Angeles, Project Inform and the San Francisco AIDS Foundation. I request reassigning the draft high priority for the nucleoside analogues: AZT (zidovudine), ddC (zalcitabine), d4T (stavudine).<sup>1</sup> I commented 3 years ago as did several AIDS service organizations and Senator Ortiz<sup>2</sup> on the adverse public health consequences if the Agency were to list AZT under Prop 65 without noting its benefits or physician counseling and on the lack of sufficient evidence of carcinogenicity.

Today the Agency asks if the weight of evidence justifies a high priority for further evaluation to list these drugs: NO. There is no evidence of carcinogenicity in the human studies; the rodent data are insufficient to predict human cancer risk or irrelevant to humans. Followup human monitoring health experts conduct is appropriate, but further OEHHA efforts to list will cause great public harm.<sup>3</sup>

These prescription drugs are approved for only one indication - treatment of HIV infection, the virus that causes AIDS. They are not approved to treat cancer or other diseases generally as stated in OEHHA's data summary except that the drugs restore immunocompetence of HIV patients and help them naturally fight off opportunistic cancers or illnesses that occur when the body's defenses are damaged. The only approved antiretroviral indication is against HIV,<sup>4</sup> a fundamental word the Agency omits from the draft summary descriptions. **[if computer audio link works]**: I begin with a November 6, 2003 news report produced by PBS and the Kaiser Foundation. [start audioclip]

[[http://www.pbs.org/newshour/bb/health/july-dec03/hiv\\_11-06-03.html](http://www.pbs.org/newshour/bb/health/july-dec03/hiv_11-06-03.html)]

Cutting the Number of HIV-Infected Infants

Pregnant women with HIV in the United States face a dramatically lower risk of passing the virus on to

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<sup>1</sup> OEHHA's announcement is at [http://www.oehha.org/prop65/docs\\_state/pdf/bat4notice.pdf](http://www.oehha.org/prop65/docs_state/pdf/bat4notice.pdf) and its draft data summaries at [http://www.oehha.org/prop65/docs\\_state/pdf/batch4sums.pdf](http://www.oehha.org/prop65/docs_state/pdf/batch4sums.pdf).

<sup>2</sup> Previous comments were sent by Sen. Deborah Ortiz (Chair, Health and Human Services Committee), San Francisco AIDS Foundation, AIDS Project Los Angeles, Project Inform, the California HIV Advocacy Coalition, OASIS Clinic and AIDS Program, BIENESTAR (Administrative Record for consideration of AZT by means of the authoritative bodies method). OEHHA received no comments supporting its authoritative body listing effort.

<sup>3</sup> My comments to OEHHA on September 13, 2000 on AZT and a recent published paper confirm this assessment. P Wutzler, R Thust (2001) Genetic Risks of antiviral nucleoside analogues – a survey; *Antiviral Research* **49**; 55-74 (“*The possible mechanisms by which these agents may cause damage in the genetic information are still largely hypothetical, and experimental findings do not permit relevant extrapolations to the situation in man. There is no conclusive evidence that any of the drugs caused tumors in humans.*”). Attached. The observed tumors in rodents in studies by Ayers et al. and NTP are not applicable to humans and not predictive of human cancer risk. Neoplasms in these studies are thought to be a topical effect, unique to rodents, of chronic exposure to unmetabolized AZT at a site with high cell turnover.

<sup>4</sup> A sad irony - HIV itself (a virus that OEHHA presumably will not list because it is not a “chemical”) is classified by the International Agency for Research on Cancer as a Group 1 carcinogen because of opportunistic illnesses whereas the animal data for the drugs to combat the virus are either relatively weak as evidence or not relevant to humans. (see IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, [Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses](#) vol. 67 (1996) Lyon, France). If OEHHA were to alert the public that HIV is “known to the state to cause cancer,” individuals might take steps to prevent infection.

their children than they did about a decade ago. Susan Dentzer talks to [doctors and patients about the medical discoveries that have reduced the likelihood of transmitting the virus from mother to child.](#)]

[**if computer link fails**]: I'm sorry that – despite Cynthia Oshita's great efforts- technical problems mean we won't be able to hear the newsclip from PBS/ and the Kaiser Foundation that aired November 6, 2003. I urge everyone to go to the PBS website and view the report of the tremendous success in the U.S. in preventing mother to child transmission of HIV with the use of these drugs, especially AZT. I'm going to give a quick summary of the lessons from this news report. Chief staff from the CDC report that 25-40% of the children born to HIV infected pregnant women in other countries – ¾ of a million babies annually - are born- and most of them die soon after - also with HIV. With the use of these drugs and proper prenatal counseling that number is only 1-2% in the United States and they can be offered treatment. Before treatment was available, in the early 1990's up to 2,000 HIV infected babies were delivered each year. Dr. James Oleske, the physician who discovered the first case of pediatric AIDS in the U.S. and who now co-chairs the U.S. DHHS group that produces guidelines for pediatric use of these drugs is also interviewed. "AIDS was almost always a death sentence for mother and infant" before these drugs. He notes "kids died really horrible painful deaths" until these drugs= AZT especially= lowered the level of HIV virus in blood slowing or halting disease progression. Dr. Oleske was one of the chief investigators in the landmark trial to test the use of AZT to prevent transmission, and it was the first major success in slowing this epidemic.

Also very important for the Prop 65 discussion today, the report describes why a few hundred babies in the U.S. are still infected through their mothers each year.

“BARDAGUEZ: The ones that we still have seen here are patients with no prenatal care that did not receive any medication either before or during labor. So, you know, the painful thing is, like, we know that we can either use drugs or modify obstetrical care, and we still are seeing some cases because of lack of advance knowledge about it.

DR. JAMES OLESKE: This is a tragic public health failure. And it's, by the way, very cost inefficient. Every child who is infected with HIV, lifetime cost is hundreds of thousands of dollars, and prevention is pennies”

One of the main reasons, I'm sorry we cannot hear the report is to see and hear the interviews with HIV infected mothers who gave birth to uninfected children because they were properly treated and continue to thrive themselves. These children grow up to be adults and their mothers watch them graduate from college. Every disease needs a human face- this disease more so than many others. There are a lot of facts and data to look at today and those are convincing but dry numbers. It's important to remember why these workshops are held at all- to make the best public health decisions for real people.

The lead physician in that report - Dr. Oleske - sent his comments to OEHHA on November 15, 2003 about this Prop 65 listing proposal. And it's his view – based as he says on the bitter experience of caring for these children and how hopeless things appeared in the early 1980s –“listing of NRTIs as high risk for cancer, taken out of context, could lead to HIV infected women choosing not to take ARV drugs to prevent transmission and not taking ARV drugs to treat their own or their child's infections.” He warned against releasing a list without explaining

the important benefits of the drugs and the fact that they have not been linked to any human cancers.

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The report helps us see why misstatement of the degree of risk or underestimate of benefits (like branding AZT a human carcinogen as bad as benzene) will contribute to a “tragic public health failure.”<sup>5</sup> HIV populations need no reasons to be scared away from proper health care and need the right inducement and messages to go there and take these drugs when a doctor prescribes them and an informed patient consents.<sup>6</sup>

Since OEHHA first reviewed AZT 3 years ago, over 15 million new worldwide HIV infections have occurred and over 9 million AIDS deaths because these drugs are not available in many countries. Over 40 million people are believed to be infected today.<sup>7</sup>

In wealthy nations those numbers slide for every category. California officials estimate that approximately 126,000 people are HIV infected here,<sup>8</sup> a level of potential exposure to the drugs less than .3% of the total population<sup>9</sup> -- not a high level of exposure concern as the summary says. In comparison, the summaries proposed a medium level of exposure concern to HDB, a chemical “likely to be found in edible mushrooms,”<sup>10</sup> even though more Californians eat mushrooms than exhibit signs of HIV infection. But, in the HIV population wide access to the drugs is crucial,<sup>11</sup> a burden that falls most heavily on women and minorities.

Where combination drug therapy is available death rates plummet and the risk of HIV transmission to newborns is reduced[DHS AIDS surveillance slide].The AIDS fatality rate in California has been reduced from 94% to 4%. This success is repeated elsewhere and in special populations such as perinatally HIV infected children.<sup>12</sup> In the time of followup, there is no

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<sup>5</sup> Separate extended interview at: <http://www.pbs.org/newshour/bb/health/july-dec03/hiv-extended1.html>; DR. JAMES OLESKE: Patients suffered so much in the early days with this disease. Kids died really horrible, painful deaths. [http://www.pbs.org/newshour/bb/health/july-dec03/hiv\\_11-06-03.html](http://www.pbs.org/newshour/bb/health/july-dec03/hiv_11-06-03.html)

<sup>6</sup> Comments to OEHHA from Dr. J Oleske, dated November 15, 2003. Dr. Julie Gerberding, director of the federal Centers for Disease Control and Prevention said, as for pregnant women, each case of mother-to-infant infection “represents a failure in the public health system... we want to make sure ... children are tested after birth so they can benefit from lifesaving treatment.” <http://www.cbsnews.com/stories/2003/04/17/health/main549892.shtml>

<sup>7</sup> Based on epidemiological estimates from the Joint United Nations Programme on HIV/AIDS, Report on the Global HIV/AIDS Epidemic, 2002 (available at: <http://www.unaids.org/en/in+focus/topic+areas/estimates+and+projections+-+epidemiology.asp>)

<sup>8</sup> 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).

<sup>9</sup> The California Department of Finance estimates the total state population in 2003 is 35,591,000.

<sup>10</sup> [http://www.oehha.org/prop65/docs\\_state/pdf/batch4sums.pdf](http://www.oehha.org/prop65/docs_state/pdf/batch4sums.pdf) Data Summaries, p. 27. If the HIV infected population were 2 or 5% of the state population, California would be in the middle of a public health catastrophe.

<sup>11</sup> The drugs vary. ddC is less efficacious and less prescribed than other drugs.(IARC Monographs on the Evaluation of Carcinogenic Risk to Humans; Some Antiviral and Antineoplastic Drugs, and other Pharmaceutical Agents (2000) vol. 76, p.130; ddC is “obsolete.”). To induce thymic lymphomas in mice, rodents had to be exposed to ddC at 1,000 times the maximum tolerated dose in humans. The tests on d4T are not long term carcinogenicity assays and used similarly high experimental doses.

<sup>12</sup>D M Gibb, T Duong, P A Tookey, M Sharland, G Tudor-Williams, V Novelli, K Butler, A Riordan,

epidemiological or postmarketing evidence that the drugs responsible for this result cause human tumors.<sup>13</sup>

[SF slide] This next slide shows decline in AIDS deaths in San Francisco with similar results. Note the clear distinction between the rise in persons living with AIDS compared to deaths and incidence. The HAART regimen<sup>14</sup> keeps those lines going in opposite directions.

Drug therapy also reduces the likelihood of HIV transmission between adults because the drugs reduce the level of circulating infectious virus.<sup>15</sup> You would encourage their use to lower the population level in need of taking them in the future. This circumstance does not apply to other drugs on the Prop 65 list for non-transmissible diseases.

However, the benefits are not distributed evenly across all categories of the infected population.[next SF slides] The next two slides show AIDS incidence rates declining sharply but disproportionately between men and women in San Francisco. The main cause is not gender based efficacy; it's the barriers of access to appropriate health care experienced by California women, especially in minority populations.<sup>16</sup>

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L Farrelly, J Masters, C S Peckham, D T Dunn, on behalf of the National Study of HIV in Pregnancy and Childhood (NSHPC) and the Collaborative HIV Paediatric Study (CHIPS) (2003) Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland; *BMJ* **327**:1019 (1 November) (online: <http://bmj.bmjournals.com/cgi/content/full/327/7422/1019?ck=nck>); A Mocroft, S Vella, T L Benfield, A Chiesi, V Miller, P Gargalianos, A d'Arminio Monforte, I Yust, J N Bruun, A N Phillips, J D Lundgren, for the EuroSIDA Study Group (1998) Changing patterns of mortality across Europe in patients infected with HIV-1 *Lancet* **352**; 172530.(online: [http://www.thelancet.com/journal/vol362/iss9392/full/llan.352.9142.original\\_research.5426.1](http://www.thelancet.com/journal/vol362/iss9392/full/llan.352.9142.original_research.5426.1) )

<sup>13</sup> No reported human cancer during eight years of followup -- <http://www.pbs.org/newshour/bb/health/july-dec03/hiv-extended3.html> see also Footnote 3 and Culnane, M., Fowler, M., Lee, S.S., McSherry, G., Brady, M., O'Donnell, K., Mofenson, L., Gortmaker, S.L., Shapiro, D.E., Scott, G., Jimenez, E., Moore, E.C., Diaz, C., Flynn, P.M., Cunningham, B., Oleske, J. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams *JAMA*. 1999 Jan 13; **281**(2):151-7. See also Hanson, I.C., Antonelli, T.A., Sperling, R.S., Oleske, J.M., Cooper, E., Culnane, M., Fowler, M.G., Kalish, L.A., Lee, S.S., McSherry, G., Mofenson, L., Shapiro, D.E. 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. See also - BH Pollock, HB Jenson, CT Leach, KL McClain, RE Hutchison, L Garzarella, VV Joshi, RT Parmley, SB Murphy SB. (2003) Risk factors for pediatric human immunodeficiency virus-related malignancy *JAMA* May 14; **289**(18):2393-9. ("zidovudine use .. not associated with the development of malignancy in HIV-infected children"). On April 11, 2002, I submitted data for the administrative record (attached.) for prioritization of AZT, including a study of mechanistic issues that is not reviewed in the Draft data summary. OEHHA replied on April 16, 2002 that the study would be evaluated in the prioritization. The mechanistic study is a followup to two of the studies OEHHA cites and by the same investigators. Diwan, B.A., Olivero, O.A., Poirier, M.C., (2000) Absence of structural or functional alterations in male and female reproductive organs of F1 and F2 generations derived from female mice exposed to 3'-azido-3'-deoxythymidine during pregnancy; *Toxicology Letters* **115**, 9-15. Considering the weight of this negative evidence is directed by the Agency's Prioritization Procedure.

<sup>14</sup> Highly Active AntiRetroviral Therapy.

<sup>15</sup> See Quinn, T. C., Wawer, M. J., Sewankambo, N. et al. (2000). Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *New England Journal of Medicine* **342**, 921-9.

<sup>16</sup> [http://www.kff.org/content/2003/3380/3380\\_Final.pdf](http://www.kff.org/content/2003/3380/3380_Final.pdf) [http://www.kff.org/content/2003/6092/6092\\_Final.pdf](http://www.kff.org/content/2003/6092/6092_Final.pdf) and JD Ruiz, F Molitor, T Bruckner, D Zukowski (2002) Ethnic disparity in HIV prevalence and zidovudine treatment among childbearing women and pediatric AIDS cases in California. *AIDS*; Dec 6; **16**(18):2469-72.

Social, psychological and emotional barriers result in reduced health care access and drug treatment for all HIV patients. My notes direct you to documentation prepared by the ACLU and the Kaiser Foundation to describe those problems. HIV infected individuals experience significant discrimination that can lead to loss of housing or employment, denial of care, personal attack. The ACLU reported 1/3 of HIV-infected individuals avoid treatment because they are “terrified” of others, uninformed, distrust the health system.<sup>17</sup>

For those reasons accepted treatment guidelines say that counseling must use appropriate messages and that communications must be clear and compare known risk and benefit relative to each other not separately.<sup>18</sup>

There would be no public benefit to make a Prop 65 priority of these drugs. By means of drug label warnings and physician guidance, those patients who receive proper care will continue to get that information. The Los Angeles Superior Court found that FDA prescription labels preempt Prop 65.<sup>19</sup> But harm will result in several ways if the drugs are listed:

1. The 1/3 of the HIV population who don't see a doctor will be hurt the most. Patients who are afraid or not inclined to see a doctor will be misinformed about risk from the CCR. OEHHA will tell them only that these drugs cause cancer in humans and not inform them about hypothetical risk or real benefit.
2. If a foreign health ministry were to misinterpret California's hazard identification of these drugs, it may interfere with federal risk communication programs to treat HIV abroad.
3. Because successful treatment depends on vigilant adherence, even those who get the drugs by prescription warning may be discouraged from their resolve to continue medication. A Prop 65 cancer listing would send a relative risk message that competes with a physician's warning.

California law singles out AZT and the nucleoside analogues by name. There is a “**compelling state interest** [ to ensure] that its citizens infected with [HIV] have access to these drugs.” [show slide, HS Code sec. 120950]. The safety of AZT is a statutory determination. The legislature “finds and declares ...AZT improves and prolongs the quality of life for those suffering from AIDS.” [slide Health and Safety Code Sec. 12095]. The State legislature also declared that these drugs should be affordably accessible worldwide to address a health emergency. [show slide]The question of Prop 65 priority has already been decided and the answer is NOT a high priority. When federal support to low income patients to buy the drugs was reduced, California Dept. of Health Services led the effort to restore it.

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<sup>17</sup> T. Lange (2003) HIV and Civil Rights: A Report From the Frontlines of the HIV/AIDS Epidemic; American Civil Liberties Union (ACLU) AIDS Project <http://www.aclu.org/HIVAIDS/HIVAIDS.cfm?ID=14363&c=258> and endnote ii of that report.

<sup>18</sup> U.S. government guidelines and those of the World Health Organization can be found at: [http://www.aidsinfo.nih.gov/guidelines/perinatal/PER\\_092203.pdf](http://www.aidsinfo.nih.gov/guidelines/perinatal/PER_092203.pdf) (“The hypothetical risks of these drugs during pregnancy should be placed in the perspective with [their] proven benefit.” p. 12) [http://aidsinfo.nih.gov/guidelines/adult/AA\\_111003.pdf](http://aidsinfo.nih.gov/guidelines/adult/AA_111003.pdf) [http://aidsinfo.nih.gov/guidelines/pediatric/PED\\_092203.pdf](http://aidsinfo.nih.gov/guidelines/pediatric/PED_092203.pdf) <http://www.who.int/hiv/topics/arv/ISBN9241545674.pdf>; see also footnote 16.

<sup>19</sup> *The Vaccine Cases* California Superior Court, County of Los Angeles, Case No. JCCP 4246, Ruling, May 16, 2003.

The Prioritization Procedure is not a regulation and may not conflict with compelling state interests in statute. A conflict would occur if the Agency's hazard identification were to create a barrier to informed access. To save lives, err on the side of caution and do everything possible to make sure Californians are not confused about benefits.

The public comments OEHHA received three years ago are the only comment record till now. They offer the one reasonable alternative if the Agency is determined, nevertheless, to continue with a listing: Before proceeding further (listing first and explaining after would only allow the harm, even the draft data summary is harmful), before deciding a final priority- change 22 C.C.R. §12000 so it could tell the public *in regulation* that these drugs have benefits as well as hypothetical risks that can only be properly explained by a qualified physician. That alternative is the least preferable course. There is no scientific basis to list these drugs using Prop 65 criteria or make them a priority. If this proceeding is not suspended, I request you reassign nucleoside analogues to the category of "not high." The evidence would merit "supplemental analysis" according to the Prioritization Procedure to address the key toxicological issues of relevance of animal data to humans and lack of an understood mechanism of action that could explain how these chemicals could be carcinogenic in humans but, frankly, the Agency should stop the entire listing effort now. Give the money you would otherwise spend to the Dept. of Health Services program that buys these drugs for the population that cannot afford them.[show ADAP slide] or to educate women and minorities about their benefits.