2002-02-15: Symposium to discuss health concerns for offspring of HIV drug-therapy patients

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SYMPOSIUM TO DISCUSS HEALTH CONCERNS FOR OFFSPRING OF HIV DRUG-THERAPY PATIENTS

Session at American Association for Advancement of Science Annual Meeting will review genetic risks to unborn

Scientists will be raising concerns about genetic health risks to the offspring of parents who undergo HIV drug therapies during a symposium to be held February 16, 2002, 9 a.m.–12 p.m., at the American Association for Advancement of Science Annual Meeting in Boston. Entitled “Scientific and Ethical Perspectives on the Risks of HIV/AIDS Therapeutics,” the session will feature presentations by experts in medical ethics, pharmaceutical toxicology, and molecular epidemiology.

To date, media reports on Oprah, Dateline, National Public Radio, and in The Washington Post have focused on success stories of HIV-positive parents using drug therapies, sperm-washing and in vitro fertilization to conceive HIV-free children. Recent research, however, suggests that HIV transmission isn’t the only concern when an HIV-positive patient considers parenthood.

Studies show that some anti-retroviral drugs, such as zidovudine (ZDV or AZT), can enter a patient’s DNA. If the altered DNA is passed on to offspring it may cause mutations, possibly leading to certain kinds of cancer and birth defects, and it may also continue to be passed on to future generations. Sperm-washing, while removing HIV

from the outside of the sperm, doesn't reduce the risk posed by the drug-altered DNA inside the sperm, nor does in vitro fertilization.

The symposium, which aims to provide a factual framework for discussing the ethical and educational issues involved with using anti-retroviral drugs in reproductive protocols, was organized by Stephanie Bird, Special Assistant to the Vice President for Research at Massachusetts Institute of Technology and co-editor of the journal Science and Engineering Ethics, and Rochelle Diamond, chair of the National Organization of Gay and Lesbian Scientists and Technical Professionals (NOGLSTP) and Member of the Professional Staff at California Institute of Technology.

"We want people who take certain HIV antiviral medicines to understand that they need to think carefully before having children, and not just for the obvious reason of protecting their spouses and kids from the virus," says Diamond. "We hope this symposium will begin a national discussion on this important issue."

Speakers will include Vernon Walker, Lovelace Respiratory Research Institute; Sheila Galloway, Merck Research Laboratories; Stephanie J. Bird, Massachusetts Institute of Technology; George Annas, Boston University School of Public Health; and Stephen Smith, American Radio Works/NPR. Rochelle Diamond of NOGLSTP will moderate the symposium.

Symposium Background

"Scientific and Ethical Perspectives on the Risks of HIV/AIDS Therapeutics"
Twenty years ago, the first cases of human immunodeficiency virus (HIV) were reported. Dramatic advances in laboratory and clinical research have been made since then. New classes of anti-retroviral drugs have made their way to care providers and combination cocktail therapies have come into vogue. These treatment modalities have produced better case management, improved quality of life and increased life expectancy for many patients who can afford treatment. Along with this progress, new issues are emerging which affect the HIV+ community.

Since 1994, the public health service has recommended the use of anti-retroviral therapeutics, namely zidovudine (ZDV or AZT) to reduce mother-to-child HIV transmission during pregnancy, labor, and after delivery. This type of drug is a nucleoside analog reverse transcriptase inhibitor (NRTI). This drug acts when the virus tries to reproduce itself by substituting randomly into the DNA of the virus in place of the normal substrate, thymidine. When inserted into the DNA of the virus, the enzyme which generates new DNA cannot function and stops the production of DNA, thereby

not allowing viral replication. This same mechanism is not limited to just the virus. The patient's cellular DNA can also take up this drug when cells divide to make new cells. The drug substituted DNA can then stay with the patient for a lifetime and can be passed on to their offspring. How much effect this will have on children who have gestated and developed with this drug in their system is yet to be fully understood, but animal studies seem to suggest some risk of genotoxicity. These children are being followed for the purpose of assessing the potential teratogenicity of these drugs through the Antiretroviral Pregnancy Registry, a collaborative project of the pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners.

The scientific and ethical issues of HIV, fertility, and the right to bear children are only now beginning to be discussed in scientific forums and in the media. Last August an Australian HIV+ woman won her case for the right to fertility treatment. HIV discordant couples are participating in studies to be treated using NRTI cocktails and assisted reproduction technology – spermwashing and in vitro fertilization- to conceive HIV-free children. The information about these treatment protocols is becoming commonplace appearing in forums like, Oprah, Dateline, National Public Radio, The Washington Post, and magazines targeting HIV+ people. Institutions such as the Center for Disease Control are funding research to look at HIV transmission statistics with an eye toward deliberating a change in their guidelines and policies. Everyone is trying to be as safe as possible for parents and children alike and still provide the right to have children knowing the risks. The focus of these public discussions has been on the washing of the sperm free of HIV and keeping the viral load down in the participating mothers and fathers. This entails treatment with the successful cocktails that include NRTIs. It's time to take a closer look at these protocols. We can wash away the HIV on the outside of our gametes, but what have the drug cocktails done to the DNA of the sperm cells and the cells of our developing children? Have these risks been evaluated?

This symposium will provide a framework for opening a discussion of the ethical and educational issues involved with the risk of using these drugs in reproductive protocols, and making informed reproductive decisions. Lessons learned from the thalidomide and diethylstilbestrol (DES) experiences of generations past and present may shed light on possible approaches to the uncertain outcomes of the use of NRTI protocols.

Symposium Abstracts for "Scientific and Ethical Perspectives on the Risks of HIV/AIDS Therapeutics"

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LESSONS FROM THALIDOMIDE: STRATEGIES FOR MINIMIZING RISKS TO FETUSES

G. J. Annas; Boston U. Sch. Public Health, Boston, MA. USA

Since thalidomide was removed from the market, both new laws and new technologies, specifically recognition of a woman's right to terminate a pregnancy, and the development of accurate ultrasonography have made it possible to prevent the birth of severely affected fetuses. Together with specific informed consent, detailed counseling, birth control and reasonable monitoring, these developments radically alter the risk/benefit ratio and mean that is not justifiable to deny fertile women beneficial drugs because of their teratogenic potential. The risk-reduction strategies developed for the introduction of Thalidomide to the market have lessons for other drugs as well.

LESSONS FROM DES: IMPLICATIONS FOR THE BABIES OF HIV+ PARENTS

S.J. Bird; Massachusetts Institute of Technology, Cambridge, MA. USA

Diethystilbesterol (DES) was originally prescribed to pregnant women at risk for miscarriage. Unfortunately, as the children born of those pregnancies reached childbearing age themselves, it became apparent that many of those offspring, especially young women, developed mild to life-threatening abnormalities, primarily of the anatomy and physiology of the reproductive system. The unexpected negative long-term side effects of DES provide a cautionary tale to inform our thinking with regard to prophylactic strategies in general and the use of nucleoside-analog reverse transcriptase inhibitors (NTRI) in particular. NRTIs are employed both to treat those who are HIV+ and to prevent transmission of HIV from mother to fetus. However, because they can be genotoxic, they have the potential for unintended serious long-term consequences. Like any effective pharmaceutical agent, the potential benefits of therapy must be weighed against the potential harm. The uncertainties and the extent of both possible benefits and possible harm must be carefully and explicitly evaluated.

GENETIC TOXICOLOGY IN THE EVALUATION OF DRUG SAFETY

S.M. Galloway; Merck Research Laboratories, West Point, PA. USA

We test drugs for potential to alter DNA because DNA-damaging chemicals can induce mutations or cancer in animals, and in some cases cancer in people. A variety of tests for DNA damage and mutations have been used since the 1970's; in 1996 international agreement by regulatory agencies was reached on a standard battery of tests required for drugs. Before a new drug may be given to people even once, it must be tested for induction of mutations in bacteria, and for mutations or chromosome aberrations in

mammalian cells. Before a drug is give to large numbers of people, an in vivo test for chromosome damage in rodents is required. When positive results are obtained in genotoxicity tests these are evaluated in the light of the risk vs benefit. For example, genotoxicity might be considered acceptable in treating cancer or a life threatening infection, but not childhood asthma, especially if other treatment is available. Some drugs do damage DNA, by binding to it, breaking it, or becoming incorporated into it and leading to mutations. Others might induce, for example, chromosomal aberrations in cell culture, yet research into the mechanism may indicate that this is not due to direct DNA damage and does not represent a risk to people. Laboratory tests use very high doses of drugs compared with the amounts to which patients are exposed. The body can repair damaged DNA and has a variety of natural defenses against toxic chemicals including the highly reactive oxygen derivatives that are normal product of our metabolism. When high, toxic concentrations of drugs are tested effects on DNA are sometimes seen that are secondary to disruption of normal cellular processes or occur when normal defenses are overwhelmed, so are not relevant at lower doses. The field of risk evaluation has made progress in recent years. The greatest challenge now is the difficulty of evaluating risk in the light of increasing knowledge of the high background level of DNA damage in the body, revealed especially by sensitive techniques for detecting altered DNA (DNA adducts), and the fact that many body chemicals and natural dietary components are highly mutagenic.

EVADING THE VIRUS – COUPLES WITH HIV/AIDS USE INFERILITY TREATMENTS TO CONCEIVE CHILDREN.

S. Smith; American Radio Works-NPR, St. Paul, MN. USA

New medications that control HIV have helped many people with the disease live dramatically healthier lives. With improved prospects for longevity, more and more couple with HIV want to star families. But most American adoption agencies won’t accept them as clients. These couples face a difficult choice: should they try to conceive a child and risk passing the virus to the baby? Is it fair to the child to be born into a family where one or both parents as a serious illness? A small but growing number of scientists and doctors are helping couples like these get pregnant, using experimental medical techniques that promise to reduce substantially the risk of passing on HIV. Journalist Stephen Smith tracked HIV/AIDS couples over several years as they struggled with these issues and produced families. This presentation will demonstrate the personal and ethical dimensions of reproduction when HIV/AIDS is involved. Stephen Smith is the managing editor of American Radio Works, the documentary project of Minnesota Public Radio and NPR News.

OVERVIEW OF ANTIRETROVIRAL NUCLEOSIDE ANALOGS: CLINICAL USE AND TOXICITIES

V.E. Walker (Lovelace Respiratory Research, Albuquerque NM); M.C. Poirier (National Cancer Institute, Bethesda MD)

Antiretroviral drug combinations that include nucleoside analogs (NRTIs) are superior to single agent regimens for effective treatment of HIV-1 infection and for reduction of maternal-fetal transmission of HIV. However, potential health risks associated with the use of NRTIs exists because the molecular basis for their effectiveness (via incorporation into pro-viral DNA) also actuates their potential toxicities (via incorporation into host cell nuclear and mitochondrial DNA). The benefits of inhibiting disease progression outweigh the potential risks of NRTI use in HIV infected patients, but the long term health risks related to cancer and mitochondrial toxicity need to be characterized. Especially at risk are infants of HIV-infected mothers exposed in utero to NRTIs. Clinical studies have demonstrated a largely reversible short-term mitochondrial dysfunction in NRTI-exposed infants/young children. The potential for cancer risk in children receiving perinatal HIV prophylaxis is based on the broad mutagenic properties and the transplacental carcinogenicity, in CD-1 mice of the most commonly used NRTI, zidovudine (ZDV). Our research groups have shown the incorporation of ZDV into nuclear DNA of lymphocytes from most newborns and their HIV-infected mothers. Drug combinations using ZDV, ZDV-lamivudine (3TC), and stavudine-3TC induced significant mutagenic effects in cord blood cells of newborns exposed in utero compared with unexposed control infants born to women not infected with HIV. The mutagenic responses were greatest following in utero ZDV-3TC exposure and the mutations persisted for at least one year after birth. Thus, significant differences in toxicity/mutagenicity occur depending upon the drug combination used. These findings indicate the critical need for long-term follow-up of infants exposed in utero to NRTIs and for the expansion of pre-clinical toxicology studies to make informed decisions concerning the safest combination therapies for the lasting health of all patients.