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Recommendations and Reports

Public Health Service Statement on Management of Occupational Exposure to Human Immunodeficiency Virus, Including Considerations Regarding Zidovudine Postexposure Use

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Public Health Service
Centers for Disease Control
Atlanta, Georgia 30333

Public Health Service Statement on Management of Occupational Exposure to Human Immunodeficiency Virus, Including Considerations Regarding Zidovudine Postexposure Use

FYI

INTRODUCTION

CDC has issued guidelines to reduce the risk of human immunodeficiency virus (HIV) infection among health-care workers, emergency-response and public-safety workers, and others who might be exposed to HIV while performing job duties (*1-4*). The safety practices outlined in these guidelines remain the primary means of preventing occupational acquisition of HIV infection (*5*). Additionally, some physicians and some institutions have offered the option of using zidovudine (azidothymidine, AZT, ZDV, Retrovir) after occupational exposure to HIV (*6*). Data collected in an ongoing CDC surveillance project of health-care workers who have been occupationally exposed to blood from HIV-infected patients (*7*) indicate that during the period April-December 1989, 13 (8.6%) of 151 newly enrolled participants began a postexposure regimen of zidovudine.

This report reviews Public Health Service (PHS) recommendations for postexposure management of workers who have occupational exposures that may place them at risk of acquiring HIV infection, provides background information on zidovudine and experience with zidovudine postexposure prophylaxis, and presents considerations relevant to a decision to offer postexposure prophylaxis.

Definition of Occupational Exposure

For purposes of this document, an occupational exposure (i.e., exposure that occurs during the performance of job duties) that may place a worker at risk of HIV infection is defined as a percutaneous injury (e.g., a needlestick or cut with a sharp object), contact of mucous membranes, or contact of skin (especially when the exposed skin is chapped, abraded, or afflicted with dermatitis or the contact is prolonged or involving an extensive area) with blood, tissues, or other body fluids to which universal precautions apply, including: a) semen, vaginal secretions, or other body fluids contaminated with visible blood, because these substances have been implicated in the transmission of HIV infection (*2*); b) cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid, because the risk of transmission of HIV from these fluids has not yet been determined (*2*); and c) laboratory specimens that contain HIV (e.g., suspensions of concentrated virus).

PHS RECOMMENDATIONS FOR MANAGEMENT OF PERSONS AFTER OCCUPATIONAL EXPOSURES THAT MAY PLACE THEM AT RISK OF ACQUIRING HIV INFECTION

Employers should make available to workers a system for promptly initiating evaluation, counseling, and follow-up after a reported occupational exposure that may place the worker at risk of acquiring HIV infection. Workers should be educated to report exposures immediately after they occur, because certain interventions that may be appropriate, e.g., prophylaxis against hepatitis B, must be initiated promptly to be effective (*3,8,9*). Workers who might reasonably be considered at risk of occupational exposure to HIV should be familiarized with the principles of postexposure management as part of job orientation and ongoing job training.

If an exposure occurs, the circumstances should be recorded in the worker's confidential medical record. Relevant information includes the following:

- date and time of exposure
- job duty being performed by worker at time of exposure
- details of exposure, including amount of fluid or material, type of fluid or material, and severity of exposure (e.g., for a percutaneous exposure, depth of injury and whether fluid was injected; for a skin or mucous-membrane exposure, the extent and duration of contact and the condition of the skin, e.g., chapped, abraded, intact)
- description of source of exposure—including, if known, whether the source material contained HIV or HBV
- details about counseling, postexposure management, and follow-up

After an occupational exposure, both the exposed worker and the source individual should be evaluated to determine the possible need for the exposed worker to receive prophylaxis against hepatitis B according to previously published CDC recommendations (*3,8,9*). Because of the potentially severe consequences of hepatitis B virus infection, hepatitis B vaccine, which is both safe and highly effective (*10*), should be offered to any susceptible health-care worker who has an occupational exposure and has not previously been vaccinated with hepatitis B vaccine. Hepatitis B immune globulin may also be indicated, particularly if the source patient or material is found to be positive for hepatitis B surface antigen (HBsAg) (*3,8,9*).

In addition, the source individual should be informed of the incident and, if consent is obtained, tested for serologic evidence of HIV infection. If consent cannot be obtained (e.g., patient is unconscious), policies should be developed for testing source individuals in compliance with applicable state and local laws. **Confidentiality of the source individual should be maintained at all times.**

If the source individual has AIDS, is known to be HIV-seropositive, or refuses testing, the worker should be evaluated clinically and serologically for evidence of HIV infection as soon as possible after the exposure (baseline) and if seronegative, should be retested periodically for a minimum of 6 months after exposure (e.g., 6 weeks, 12 weeks, and 6 months after exposure) to determine whether HIV infection has occurred. The worker should be advised to report and seek medical evaluation for any acute illness that occurs during the follow-up period. Such illness, particularly if characterized by fever, rash, myalgia, fatigue, malaise, or lymphadenopathy, may be indicative of acute HIV infection, drug reaction, or another medical condition. During

the follow-up period, especially the first 6-12 weeks after the exposure when most infected persons are expected to seroconvert, exposed workers should follow PHS recommendations for preventing transmission of HIV. These recommendations include refraining from blood, semen, or organ donation and abstaining from or using measures to prevent HIV transmission during sexual intercourse (*11-14*). In addition, in countries such as the United States where safe and effective alternatives to breast-feeding are available, exposed women should not breast-feed infants during the follow-up period in order to prevent the infant's possible exposure to HIV in breast milk. **During all phases of follow-up, confidentiality of the worker should be protected.**

If the source individual is HIV-seronegative and has no clinical manifestations of AIDS or HIV infection, no further HIV follow-up of the exposed worker is necessary unless epidemiologic evidence suggests that the source individual may have recently been exposed to HIV or if testing is desired by the worker or recommended by the health-care provider. In these instances, the guidelines may be followed as described above.

If the source individual cannot be identified, decisions regarding appropriate follow-up should be individualized, based on factors such as whether potential sources are likely to include a person at increased risk of HIV infection.

The employer should make serologic testing available to all workers who are concerned about possible infection with HIV through an occupational exposure. Appropriate psychological counseling may be indicated as well.

ZIDOVUDINE

Background

Zidovudine is a thymidine analogue that has been shown in vitro to inhibit replication of some retroviruses, including HIV, by interfering with the action of viral ribonucleic acid (RNA)-dependent deoxyribonucleic acid (DNA) polymerase (reverse transcriptase) and possibly also by other mechanisms (*15*).

In a double-blind, placebo-controlled trial, zidovudine was shown to increase the length and quality of life of patients with advanced HIV infection and AIDS (*16*). Largely on the basis of the results of this trial, zidovudine was approved for marketing by the Food and Drug Administration (FDA) and is indicated for treatment of adults with symptomatic HIV infection, including AIDS, who have a history of cytologically confirmed *Pneumocystis carinii* pneumonia or an absolute CD_4 lymphocyte count of $<200/mm^3$. The dose of zidovudine originally approved for oral use by patients who have AIDS and advanced symptomatic HIV infection was 200 mg every 4 hours. On January 16, 1990, FDA approved a change in the labeling that now recommends administering the drug at 600 mg/day (100 mg every 4 hours) after a patient has received 1 month of zidovudine therapy at a dose of 1,200 mg/day (200 mg every 4 hours).

Later studies (National Institute of Allergy and Infectious Diseases [NIAID] AIDS Clinical Trial Group Protocols #016 and #019) have indicated that zidovudine can delay disease progression in patients with less advanced HIV infection (patients with an absolute CD_4 count of $<500/mm^3$, whether symptomatic or asymptomatic) (NIAID Administrative Report: "AIDS Clinical Trials Alert," August 29, 1989).

Toxicity

Among patients who have AIDS or symptomatic HIV infection and who are treated with zidovudine, the most frequently reported adverse events are granulocytopenia and anemia. Other adverse events that affect ≥5% of zidovudine recipients include one or more of the following: headache, nausea, insomnia, myalgia, diaphoresis, fever, malaise, anorexia, diarrhea, dyspepsia, vomiting, dyspnea, rash, and taste abnormalities (*17*). Occurrences less commonly reported in the published literature include polymyositis, peripheral neuropathy, and seizures.

Among 3,200 patients with asymptomatic HIV infection treated in NIAID protocol #019 with placebo or with zidovudine doses of either 1,500 mg or 500 mg daily (either 300 mg or 100 mg given every 4 hours, five times daily), investigators have reported the following toxicity after a median of 44 weeks of therapy: in the 1,500-mg/day group, approximately 12% of the subjects developed moderate to severe hematologic toxicity, defined as hemoglobin of <8 g/dl, granulocytes of <750/mm^3, or platelets of <50,000/mm^3. In the 500-mg/day group, this toxicity occurred at a rate of about 3%, compared with approximately 2% in the placebo group. Nausea was rarely reported in the placebo group; however, 3%-5% of zidovudine recipients, irrespective of dose group, experienced moderate to severe nausea. No statistically significant difference was observed between zidovudine dose and placebo for any other moderate to severe clinical adverse experiences (NIAID Administrative Report: "AIDS Clinical Trials Alert," August 29, 1989).

Preliminary data from a study sponsored by the Burroughs-Wellcome Company of health-care workers who received 200 mg of zidovudine or placebo every 4 hours for 6 weeks after occupational exposure to HIV indicate that adverse effects most frequently consisted of nausea and vomiting. In no instance did the prescribing physician discontinue a participant's study drug or placebo because of hematologic or other serious toxicity; however, during the therapy period, 14 (28.6%) of 49 participants who received zidovudine had a hemoglobin concentration between 9.5 and 12 g/dl, compared with one (2.9%) of 35 participants in the placebo group. Seven (14.3%) of the 49 participants who received zidovudine, compared with one (2.9%) of the 35 placebo recipients, elected to discontinue therapy because of subjective, reversible symptoms, including nausea, vomiting, fatigue, headache, myalgia, or cough.

Several anecdotal reports of short-term toxicity among health-care workers receiving zidovudine have been received by PHS. Symptoms include fever, myalgia, fatigue, nausea, and vomiting. Single reports have been received of severe anemia, reversible peripheral neuropathy, and transient clinical hepatitis.

Although the risk of acute zidovudine toxicity for exposed health-care workers cannot be determined from this limited information, data from the NIAID protocol #019 trial and from the Burroughs-Wellcome study of exposed health-care workers suggest that the risk of acute toxicity associated with short-term use of the drug is lower than the risk observed during long-term therapy of symptomatic HIV-infected individuals.

For healthy persons not infected with HIV, the risk of long-term toxicity, including teratogenic and carcinogenic effects, related to a course of zidovudine is not known. It is not known whether zidovudine can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity (*17*). To assess the

safety of zidovudine use during pregnancy, the Burroughs-Wellcome Company has developed a registry to evaluate pregnancy outcomes of women who took zidovudine during pregnancy. Physicians are encouraged to register such persons by telephoning the pregnancy registry, (919) 248-8465 (collect) or 1-800-722-9292. It is also not known whether zidovudine is excreted in human milk. However, because of the potential for adverse side effects among breast-fed infants, as well as the potential for transmission of HIV if the mother is infected, mothers should be instructed to discontinue breast-feeding whether or not they are receiving zidovudine (*17*).

In other studies conducted by the Burroughs-Wellcome Company (Appendix I), vaginal tumors, including carcinomas, were observed in mice and rats receiving zidovudine at doses that the FDA has determined resulted in plasma levels in mice approximately equal to human plasma levels at the dose originally approved for treatment of persons with symptomatic HIV infection (200 mg every 4 hours). In rats, the plasma levels were determined by the FDA to be about 10 times higher than human plasma levels achieved with the originally approved dose. The results of these rodent carcinogenicity studies are of uncertain predictive value for humans.

Studies of Zidovudine Postexposure Prophylaxis Involving Animals

Data involving studies of laboratory animals (Appendix II) are limited and must be interpreted with caution, as they have most often been derived by using nonhuman retroviruses having pathogenic mechanisms different from the pathogenesis of HIV infection in humans. In one study using HIV in a mouse model, zidovudine prophylaxis was begun 24 hours before intrathymic injection of a large inoculum of HIV and continued for 2 weeks thereafter. HIV infection was not prevented in any of the animals studied, although the course of infection was modified. It is not known whether prophylaxis would be effective in conditions that more closely resemble occupational exposures, i.e., zidovudine begun after exposure, with the exposure consisting of a percutaneous injection of a lower inoculum of HIV. **Data from animal studies are inadequate to support or reject the hypothesis that zidovudine may be effective prophylaxis for persons who have been occupationally exposed to HIV.**

Studies of Zidovudine Postexposure Prophylaxis Involving Humans

The efficacy of zidovudine prophylaxis for humans after exposure to HIV cannot be assessed because of insufficient data. The Burroughs-Wellcome Company recently sponsored a double-blind, placebo-controlled study to evaluate 6 weeks of zidovudine prophylaxis (200 mg orally every 4 hours) involving health-care workers who had experienced occupational percutaneous, mucous-membrane, or nonintact-skin exposures to HIV-infected blood. Of 84 workers who initially enrolled in the study (49 of whom were given zidovudine), none developed HIV infection after at least 6 months of follow-up. The risk of transmission of HIV per episode of percutaneous exposure to HIV-infected blood is, on the average, approximately 0.4% (*7*). Thus, the absence of seroconversions in this small group of participants is not unexpected, regardless of whether they took zidovudine. Enrollment in this study was terminated in June 1989.

NIAID has enrolled three persons in an ongoing open trial of zidovudine prophylaxis after a "massive exposure" to HIV. The first person received a blood transfusion from an HIV-infected donor, was started on zidovudine 7 days after exposure, and

was culture-positive for HIV 4 months after completing 6 weeks of chemotherapy. The second person was exposed to a high concentration of HIV on abraded skin in a research laboratory, was started on zidovudine within 24 hours postexposure, and remains HIV-seronegative after 11 months. The risk of seroconversion after this type of laboratory exposure is unknown. The third person was exposed to a high concentration of HIV on broken skin in a research laboratory, was started on zidovudine within 24 hours after the exposure, and is HIV-seronegative 3 months after the exposure. The risk of seroconversion after this type of laboratory exposure also is unknown. All individuals were able to complete a 6-week course of therapy (200 mg orally every 4 hours) without clinically significant adverse effects. Information regarding enrollment in this study can be obtained by calling the NIAID study coordinator at (800) 537-9978.

Prophylaxis Schedules Currently Used After Occupational Exposure

Various regimens have been prescribed for zidovudine prophylaxis after occupational exposure. No data are available to enable investigators to determine the efficacy or compare the toxicity of these or other regimens. At the National Institutes of Health Clinical Center, workers who elect to receive zidovudine are treated with 200 mg every 4 hours (six times daily) for 6 weeks (*6*). At San Francisco General Hospital, workers who elect to receive zidovudine are treated with 200 mg every 4 hours (five times daily; no dose is given at 4:00 a.m.) for 4 weeks (*6*). Some clinicians have used an initial dose of 400 mg, and others have prescribed treatment courses ranging from 4 days to 4 months. At several institutions, attempts are made to begin prophylaxis within 1 hour after exposure for workers who elect to receive the drug.

DISCUSSION

Data from animal and human studies are inadequate to establish the efficacy or safety of zidovudine for prophylaxis after occupational exposure to HIV. However, some physicians believe that zidovudine should be offered as prophylaxis to persons after certain occupational exposures for the following reasons: the severity of the illness that may result from HIV infection, the documented antiviral effect of zidovudine in the treatment of persons with established HIV infection, the apparent reversibility of acute toxicity in persons taking zidovudine for a brief period, and the suggestion that in some animal studies, zidovudine postexposure may modify the course of some retroviral infections. Other physicians believe that zidovudine should not be recommended for uninfected persons after occupational exposures because of the lack of data demonstrating efficacy in postexposure prophylaxis, the limited data on toxicity in uninfected individuals, and the fact that zidovudine has been shown to be carcinogenic in rats and mice.

At this time, prophylaxis with zidovudine cannot be considered a necessary component of postexposure management. However, workers who might be at risk of occupational exposure to HIV should be informed, as part of job orientation and ongoing job training, of the considerations pertaining to the use of zidovudine for postexposure prophylaxis. The PHS recommends that if a physician decides to offer zidovudine to a worker after an exposure incident, that decision by the physician and the decision by the worker to take zidovudine should take into account the following considerations.

Considerations Regarding Use of Zidovudine After an Occupational Exposure

Risk of HIV infection after exposure

Evaluation of the risk of HIV infection after exposure should take into account existing knowledge from prospective studies of exposed workers, which demonstrate that on the average the risk of transmission of HIV per episode of percutaneous exposure (e.g., a needlestick or cut with a sharp object) to HIV-infected blood is approximately 0.4%. These studies also suggest that the risk of HIV transmission per episode of mucous-membrane or skin exposure to HIV-infected blood is less than that after a percutaneous exposure (*7,18-21*). The risk of HIV transmission after occupational exposure to body fluids other than blood, for which universal precautions are recommended, is unknown. The risk of HIV infection for persons who take zidovudine postexposure prophylaxis cannot be determined at present because of the small number of persons studied.

Risk evaluation should also include an assessment of factors that may increase or decrease the probability of HIV transmission after an individual occupational exposure. These factors are not well understood, but include the likelihood that the source fluid contained HIV and probably also the concentration of HIV in the source fluid, the route of exposure, and the volume of fluid involved. For example, a percutaneous exposure to concentrated HIV in a research laboratory is probably more likely to result in transmission of infection than a similar exposure to HIV-infected blood in a clinical setting. A percutaneous exposure to HIV-infected blood is probably more likely to result in transmission than a mucous-membrane exposure to the same blood. Finally, an exposure to a larger quantity of HIV-infected blood, such as injection of several milliliters, is probably more likely to result in HIV transmission than an exposure to a smaller quantity of the same blood, such as in a needlestick exposure.

Interval between exposure and initiation of prophylaxis, if given

Data from animal studies suggest that prophylaxis against certain retroviral infections other than HIV may be more effective when started within hours after exposure (*22,23*). Because in vitro studies indicate that human HIV infection may be established in human lymphocytes within hours after exposure (*24*), and epidemiologic studies of exposed health-care workers indicate that acute retroviral illness may occur as early as 2 weeks after exposure (*7*), it appears that if the decision is made to use postexposure prophylaxis, prophylaxis should be initiated promptly.

Counseling and informed consent

If zidovudine prophylaxis is being considered, the worker should be counseled regarding a) the theoretical rationale for postexposure prophylaxis, b) the risk of occupationally acquired HIV infection due to the exposure, c) the limitations of current knowledge of the efficacy of zidovudine when used as postexposure prophylaxis, d) current knowledge of the toxicity of zidovudine (including the data from animal and human studies) and the limitations of this knowledge in predicting toxicity in uninfected individuals who take the drug after occupational exposures, and e) the need for postexposure follow-up (including HIV serologic testing), regardless of whether zidovudine is taken. **The worker should also be informed that there are diverse opinions among physicians regarding the use of zidovudine for postexposure**

prophylaxis, and the PHS cannot make a recommendation for or against the use of zidovudine for this purpose because of the limitations of current knowledge.

The duration of follow-up needed to detect evidence of HIV transmission or delayed toxicity among workers who take zidovudine is presently unknown. Workers taking zidovudine postexposure may require follow-up to detect HIV seroconversion for a longer period than that recommended for workers who do not take zidovudine. Regardless of the length of follow-up, mechanisms should be developed to permit workers taking zidovudine to be contacted if future information indicates the need for additional evaluation.

If a physician offers zidovudine as prophylaxis after an occupational exposure and the exposed worker elects to take the drug, the physician or other appropriate health-care provider should obtain written informed consent from the worker for this use of this drug. The consent document should reflect the information presented in the counseling session, as outlined above, emphasizing the need for follow-up medical evaluations and for precautions to prevent the transmission of HIV infection during the follow-up period, including refraining from blood, semen, or organ donation, refraining from breast-feeding, and either abstaining from sexual intercourse or using latex condoms during sexual intercourse, as discussed below.

Considerations regarding sexual intercourse for exposed workers taking zidovudine include 1) the possible risk of teratogenesis associated with zidovudine use, and 2) the risk of transmission of HIV to a sexual partner. The risk of teratogenesis among offspring of either men or women taking zidovudine is unknown. Therefore, men and women of reproductive age who are receiving zidovudine should abstain from, or use effective contraception during, sexual intercourse throughout the time zidovudine is being taken. In addition, to prevent HIV transmission to sexual partners, all exposed workers, including pregnant women, should abstain from, or use latex condoms during, sexual intercourse throughout the follow-up period.

Research Needs

Further data are needed to determine risk factors for occupational exposure to HIV, to evaluate measures for preventing these exposures, and to identify risk factors for HIV transmission after occupational exposure. Appropriate animal models of HIV infection are needed, and animal studies should be conducted under experimental conditions that mimic the circumstances of occupational exposure affecting humans. Studies involving humans should be conducted to determine whether postexposure prophylaxis with zidovudine or other agents is effective, and, if effective, should define the optimal time that postexposure prophylaxis should be initiated and the optimal duration of prophylaxis. Studies should also assess the toxicity of candidate prophylactic agents, establish the optimal dosage for healthy individuals and for persons with preexisting hepatic or renal dysfunction, and define the duration of follow-up needed to detect evidence of HIV infection in persons receiving prophylaxis. Strains of HIV isolated from treated workers should be monitored to detect development of drug resistance.

Expanded Surveillance of Workers with Occupational Exposures to HIV

CDC has expanded its ongoing surveillance of workers with occupational exposures to HIV (7) to collect additional information on postexposure chemoprophylaxis. No names or other personal identifiers of workers are collected.

Information is collected on the following:

- circumstances associated with exposures
- extent to which zidovudine and other antiretroviral agents are prescribed for postexposure chemoprophylaxis, including dosage and timing
- incidence of associated toxicity
- rate of HIV seroconversion among workers who do and do not receive postexposure chemoprophylaxis

All physicians who provide care to a worker within 1 month after an occupational exposure to HIV, regardless of whether an antiretroviral agent is prescribed, are encouraged to enroll the worker in the CDC surveillance system. Enrollment and follow-up requirements have been simplified; in particular, it is no longer necessary to send blood specimens to CDC for HIV serologic testing unless the enzyme immunoassay (EIA) performed by a licensed local laboratory is reactive or equivocal. CDC will continue, however, to offer EIA testing at no charge on specimens from surveillance participants on request. Additional information and enrollment materials can be obtained from the Hospital Infections Program, Center for Infectious Diseases, Centers for Disease Control, Mail Stop C-10, Atlanta, GA 30333; telephone (404) 639-1644.

CONTACTS FOR PHYSICIANS AND FOR INFECTION CONTROL AND OCCUPATIONAL HEALTH PROFESSIONALS

- To enroll persons who have had a "massive exposure" to HIV in NIAID study of zidovudine prophylaxis, telephone (800) 537-9978.
- To report adverse effects associated with zidovudine to FDA, use "Adverse Reaction Report" forms (FDA #1639), obtainable from:
  Food and Drug Administration
  Office of Epidemiology and Biostatistics
  HFD-730
  Rockville, MD 20857
  (301) 443-4580.
- To enroll an exposed worker in the CDC prospective surveillance system, telephone (404) 639-1644.
- To enroll pregnant women who receive zidovudine during pregnancy, contact:
  Zidovudine in Pregnancy Registry
  Epidemiology, Information, and Surveillance Division
  Burroughs-Wellcome Company
  3030 Cornwallis Road
  Research Triangle Park, NC 27709
  (919) 248-8465 (collect) or (800) 722-9292.

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APPENDIX I

Results of Studies Conducted by the Burroughs-Wellcome Company of Zidovudine Carcinogenicity Involving Animals

In lifetime carcinogenicity bioassays, mice and rats were given various doses of zidovudine, up to the maximum tolerated doses, for most of their lifespans. Dose reductions were necessary for both species during the study because of the onset and persistence of drug-related anemia. Mice were treated initially with 30, 60, or 120 mg/kg/day; after 90 days, these doses were reduced to 20, 30, or 40 mg/kg/day, respectively. Rats were treated initially with 80, 220, or 600 mg/kg/day; after 90 days, the 600-mg/kg/day group was reduced to 450 mg/kg/day; and after 280 days, this group was further reduced to 300 mg/kg/day. Although anemia persisted at the reduced doses, drug treatment did not adversely affect survival in either species.

Among mice dosed for approximately 22 months, seven vaginal neoplasms occurred in 60 female animals at the highest dose. The earliest a tumor was discovered was after 19 months of continuous dosing; most tumors were discovered after 21 months of treatment. The tumors consisted of five nonmetastasizing squamous cell carcinomas and two benign tumors (one squamous cell papilloma and one squamous cell polyp). One benign vaginal tumor (squamous cell papilloma) was discovered in the middle-dose group after 22 months of treatment. In all instances, these lesions were discovered during histologic examination of tissues from animals that either died or were sacrificed, late in life from nontreatment-related causes, or sacrificed upon completion of lifetime dosing.

Among rats dosed for approximately 22 months, two nonmetastasizing vaginal squamous cell carcinomas were diagnosed on the basis of histologic examination of tissues from animals receiving the highest dose. These carcinomas were discovered after 20-22 months of dosing. No vaginal tumors occurred among rats given the middle or low dose.

No other drug-related tumors were observed among animals of either sex or of either species (Burroughs-Wellcome Company [letter to physicians], Dec. 5, 1989).

APPENDIX II

Studies of Zidovudine Prophylaxis Involving Animals

Studies of retrovirus infections other than HIV in mice and cats suggest that zidovudine may alter the course of some retroviral infections when given before or shortly after exposure to the virus. In one study, mice were injected with a large challenge inoculum (1×10^4 plaque-forming units) of Rauscher murine leukemia virus (RMLV) and were given a 20-day course of zidovudine, at various doses, beginning 4 hours after inoculation. By day 69, all untreated mice had died of RMLV infection, whereas those treated with high doses of zidovudine had no clinical signs of infection and were not viremic. Both the protective effect of zidovudine and the incidence of zidovudine-induced bone marrow depression were greater with increasing doses (*1*).

In another study, cats were injected with a large challenge dose (2×10^3 focus-inducing units) of Rickard feline leukemia virus (RFLV) and were given zidovudine at various doses and various intervals after inoculation. Of eight cats injected with RFLV and treated with a 6-week course of zidovudine beginning 1 hour after inoculation, none developed clinical evidence of RFLV disease, none had virus isolated from serum, and one had evidence of infection manifested by the development of neutralizing antibody within 3 months after treatment with zidovudine was stopped. In contrast, 11 of 12 untreated cats either became viremic or died of infection in the same period. When zidovudine prophylaxis was initiated 3 or 7 days after inoculation, a substantial proportion of animals in different dosage groups became viremic, developed neutralizing antibody, or both. All animals treated beginning 28 days after inoculation were viremic when zidovudine treatment was initiated (*2*).

Limited studies involving primates have not shown success in postexposure prophylaxis against simian immunodeficiency virus (SIV). In one study, macaque monkeys were inoculated with a small dose (10 $TCID_{50}$) of a rapidly lethal variant of SIV (SMM/PBj-14) and later treated with zidovudine for 14 days. Of three animals whose treatment was begun 1 hour after inoculation, two developed infection, and one died. Of three animals treated within 24 hours, all developed infection, and two died. Of three animals treated within 72 hours, all developed infection, and two died. Of three control animals that were inoculated with the virus but not given zidovudine treatment, all developed infection, and two died (*3*). In another study of macaque monkeys, a 1-week course of zidovudine begun 8 hours before the animals were inoculated with SIV did not prevent viremia, but delayed its onset until 1-2 days after the zidovudine treatment was completed (*4*).

Finally, studies have been conducted by using the SCID-hu mouse model, an immunodeficient mouse with an immune system that has been reconstituted with transplanted human hematolymphoid organs susceptible to infection with HIV (*5*). Seventeen mice were treated with zidovudine for 24 hours before and for 2 weeks after intrathymic injection of a standard challenge dose of HIV (400-4,000 IU), the smallest dose causing infection in all animals. At 2 weeks after injection, none of the mice tested positive for HIV DNA by the polymerase chain reaction (PCR), although the presence of HIV RNA in some cells was detected by in situ hybridization. Four weeks after zidovudine was stopped, HIV DNA was detected by PCR in all 17 mice. In comparison, all of 40 mice not receiving zidovudine tested positive for HIV DNA by PCR 2 weeks after injection (*6*).

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