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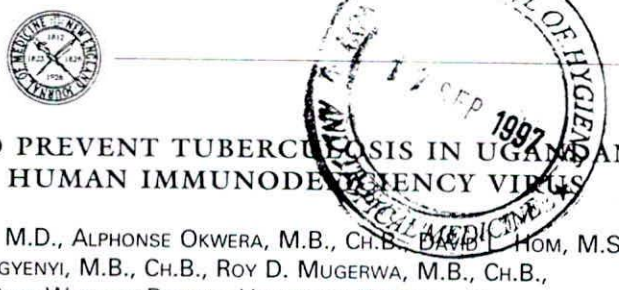

A TRIAL OF THREE REGIMENS TO PREVENT TUBERCULOSIS IN UGANDAN ADULTS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

CHRISTOPHER C. WHALEN, M.D., JOHN L. JOHNSON, M.D., ALPHONSE OKWERA, M.B., CH.B., DAVID L. HOM, M.S., ROBIN HUEBNER, PH.D., M.P.H., PETER MUGYENYI, M.B., CH.B., ROY D. MUGERWA, M.B., CH.B., AND JERROLD J. ELLNER, M.D., FOR THE UGANDA–CASE WESTERN RESERVE UNIVERSITY RESEARCH COLLABORATION

ABSTRACT

Background Infection with the human immunodeficiency virus (HIV) greatly increases the risk of reactivation tuberculosis. We evaluated the safety and efficacy of three preventive-therapy regimens in a setting where exposure to tuberculosis is common.

Methods We performed a randomized, placebo-controlled trial in 2736 HIV-infected adults recruited in Kampala, Uganda. Subjects with positive tuberculin skin tests (induration, ≥5 mm) with purified protein derivative (PPD) were randomly assigned to one of four regimens: placebo (464 subjects), isoniazid daily for six months (536), isoniazid and rifampin daily for three months (556), or isoniazid, rifampin, and pyrazinamide daily for three months (462). Subjects with anergy (0 mm induration in reaction to PPD and candida antigens) were randomly assigned to receive either placebo (323 subjects) or six months of isoniazid (395). The medications were dispensed monthly and were self-administered.

Results Among the PPD-positive subjects, the incidence of tuberculosis in the three groups that received preventive therapy was lower than the rate in the placebo group ($P=0.002$ by the log-rank test). The relative risk of tuberculosis with isoniazid alone, as compared with placebo, was 0.33 (95 percent confidence interval, 0.14 to 0.77); with isoniazid and rifampin, 0.40 (0.18 to 0.86); and with isoniazid, rifampin, and pyrazinamide, 0.51 (0.24 to 1.08). Among the subjects with anergy, the relative risk of tuberculosis was 0.83 (95 percent confidence interval, 0.34 to 2.04) with isoniazid as compared with placebo. Side effects were more common with the multidrug regimens, and particularly with the regimen containing pyrazinamide. Survival did not differ among the groups, but the subjects with anergy had a higher mortality rate than the PPD-positive subjects.

Conclusions A six-month course of isoniazid confers short-term protection against tuberculosis among PPD-positive, HIV-infected adults. Multidrug regimens with isoniazid and rifampin taken for three months also reduce the risk of tuberculosis. (N Engl J Med 1997;337:801-8.)

INFECTION with *Mycobacterium tuberculosis* is the most common human infection worldwide. As the epidemic of human immunodeficiency virus (HIV) infection continues to evolve, the risk of dual infection with HIV and *M. tuberculosis* may be substantial in young adults, especially in developing countries.[1] HIV infection confers the greatest known risk for the development of tuberculosis, both for the reactivation of latent infection and for progressive primary disease.[2-5] Moreover, once active tuberculosis develops in HIV-infected persons, mortality is high, despite good clinical and microbiologic responses to antituberculous therapy.[6-11]

Preventive therapy has been proposed as a strategy to control tuberculosis in HIV-infected populations.[12-14] The potential benefit of preventive therapy was first suggested by observational studies of injection-drug users,[2,3,15,16] but these were uncontrolled studies of selected populations at high risk.[17] Data on the efficacy of preventive therapy in HIV-seronegative persons[18-22] cannot be readily extrapolated to HIV-seropositive persons, because of the confounding effects of progressive immunosuppression related to HIV infection and concern about an in-

From the Division of Infectious Diseases, Department of Medicine, University Hospitals of Cleveland and Case Western Reserve University (C.C.W., J.L.J., D.L.H., J.J.E.), and the Department of Epidemiology and Biostatistics, Case Western Reserve University (C.C.W.) — all in Cleveland; the Ugandan Ministry of Health, National Tuberculosis and Leprosy Programme (A.O.), the Joint Clinical Research Center (P.M.), and Makerere University (R.D.M.) — all in Kampala, Uganda; and the Centers for Disease Control and Prevention, Atlanta (R.H.). Address reprint requests to Dr. Whalen at the Dept. of Epidemiology and Biostatistics, WG-49, Case Western Reserve University, 10900 Euclid Blvd., Cleveland, OH 44106-4945.

Other authors were Peter Nsubuga, M.B., Ch.B., Ministry of Health, Kampala; Michael Vjecha, M.D., University Hospitals of Cleveland and Case Western Reserve University, Cleveland; Harriet Myanja, M.B., Ch.B., M.Med, Makerere University, Kampala; Cissy Kityo, M.B., Ch.B., Joint Clinical Research Center, Kampala; and Anita Loughlin, M.S., John Milberg, M.P.H., and Vukosava Pekovic, M.D., Ph.D., all of University Hospitals of Cleveland and Case Western Reserve University, Cleveland.

creased risk of drug toxicity in HIV-infected persons.[23,24] Because of the relevance of preventive therapy to the strategy for eliminating tuberculosis in the United States and the potential benefit of preventive therapy in targeted populations in resource-poor countries, in March 1993 the Uganda–Case Western Reserve University Research Collaboration began a randomized, placebo-controlled trial of three regimens of therapy to prevent tuberculosis in HIV-infected Ugandan adults who had positive skin tests with purified protein derivative (PPD). In October 1993 enrollment was expanded to include HIV-infected persons with anergy with respect to PPD and candida antigens, on the basis of new information suggesting an increased risk of tuberculosis in HIV-infected persons with anergy.[3,4]

METHODS

Study Design

The objective of this randomized, placebo-controlled clinical trial was to determine the efficacy of three daily, self-administered regimens of preventive therapy for tuberculosis in HIV-infected adults. The trial was designed to obtain at least three years of follow-up data on all enrolled subjects, with annual interim analyses to ensure timely detection of risks and benefits to the participants. All subjects gave oral informed consent before screening and enrollment in the study. The study protocol was approved by the institutional review board at the University Hospitals of Cleveland and Case Western Reserve University and by the Ugandan National AIDS Research Subcommittee.

Study Population

Between March 1, 1993, and April 20, 1995, Ugandan adults 18 years or more of age were screened for enrollment at five medical clinics and counseling centers for persons with HIV type 1 (HIV-1) infection in Kampala, Uganda. Enrollment of subjects with anergy was begun in October 1993. In the PPD-positive cohort, enrollment in the isoniazid and isoniazid-plus-rifampin groups was continued beyond the predetermined sample size to allow us to screen and enroll subjects in the anergy groups. The study's inclusion criteria were HIV infection documented by enzyme-linked immunosorbent assay, a PPD skin test showing at least 5 mm of induration after 48 to 72 hours or anergy, and a Karnofsky performance score of more than 50.[25] Anergy was defined as 0 mm of induration in reaction to both PPD and candida antigens. Candida antigens were used for skin testing because tetanus-toxoid and mumps vaccinations are not routinely used in Uganda. Only one control antigen was used, to enhance acceptance by the subject. The exclusion criteria were the presence of active tuberculosis, previous treatment for tuberculosis, use of antiretroviral drugs, a white-cell count under 3000 per cubic millimeter, a hemoglobin level under 80 g per liter, serum aspartate aminotransferase level over 90 U per liter, serum creatinine level over 1.8 mg per deciliter (160 μmol per liter), a positive urinary β-human chorionic gonadotropin test, residence more than 20 km from a project clinic, advanced HIV disease, or the presence of major underlying medical illness unrelated to HIV infection. Before entry into the trial, all the subjects were screened for active tuberculosis by a history taking and physical examination, chest radiography, sputum microscopy with the Ziehl–Neelsen stain for acid-fast bacilli, and sputum mycobacterial culture.

Intervention and Randomization

The four study groups received placebo (250 mg of ascorbic acid per day for six months); isoniazid (300 mg per day for six months); isoniazid (300 mg per day) and rifampin (600 mg per day) for three months; or isoniazid (300 mg per day), rifampin (600 mg per day), and pyrazinamide (2000 mg per day) for three months. Blocked randomization was used (in blocks of six) to assign eligible subjects to one of the study regimens. Sequentially numbered, sealed envelopes containing the treatment assignments were drawn in numerical order by a data clerk. Subjects with anergy were assigned only to the placebo and isoniazid groups by a separate, but identical, randomization process. Instruction about HIV and tuberculosis and counseling on compliance were given to all study subjects at enrollment and during follow-up clinic visits. Study nurses dispensed the medication in prepackaged envelopes containing one month of doses with oral and written instructions. A team of five experienced home health visitors traced the subjects who did not keep scheduled appointments and encouraged them to return to the clinic.

Assessment of Outcome

The primary outcome of the study was the development of tuberculosis; secondary outcomes included adverse drug reactions and mortality. The subjects were evaluated monthly during the first six months of the study and every three months thereafter. Active screening for tuberculosis was performed at all scheduled and unscheduled visits by means of a standardized evaluation of the symptoms and signs of tuberculosis; chest radiographs were obtained every six months. If tuberculosis was suspected on the basis of symptoms, signs, or the chest radiograph, three sputum specimens were obtained for mycobacterial smear and culture. Decisions to initiate antituberculous therapy for active tuberculosis were made by on-site investigators after reviewing the clinical, radiographic, and microbiologic data.

Cases of suspected tuberculosis were referred for independent review and classification by two chest physicians who were blinded to the subjects' treatment group. Subjects were selected for review if they had at least one of the following: symptoms or signs consistent with active tuberculosis, a sputum smear positive for acid-fast bacilli, a positive culture for *M. tuberculosis*, abnormal findings consistent with tuberculosis on chest radiography, or empirical therapy for tuberculosis. The reviewers independently classified suspected cases of tuberculosis according to operational definitions of the disease.[26] Definite tuberculosis was defined as culture-confirmed disease (more than five colonies of *M. tuberculosis*). Probable tuberculosis was defined as a clinical illness consistent with tuberculosis on the basis of at least two of the following findings: results of chest radiography consistent with pulmonary tuberculosis, smear of tissue or secretions positive for acid-fast bacilli, or a response to antituberculous therapy. Suspected cases that did not fulfill the criteria for definite or probable tuberculosis were not considered to be active tuberculosis.

During the treatment phase, the subjects were screened for adverse events at all scheduled monthly visits or unscheduled visits. Medical officers recorded the type and grade of reaction with a standard grading system for drug toxicity in HIV-infected persons.[27] The medical officers and study subjects could not be formally blinded to the treatment because of the discoloration of body fluids produced by rifampin; however, the medical officers were instructed to perform the clinical examination and record the findings without reference to the treatment code, and they did not have access to the results of urinary testing. Mortality was assessed through interviews with family members or review of hospital records when available. Autopsies were not performed. The date of death and reports of prominent symptoms at the time of death were also obtained from family members.

Measurements

Demographic and clinical information was obtained through standardized interviews and physical examination. At the time of screening, venous blood was collected for enzyme-linked immunosorbent assay testing for HIV-1, complete blood and differential counts (Coulter T540 system, Coulter Electronics, Hialeah,

Fla.), and serum creatinine and aspartate aminotransferase measurements. HIV infection was documented by enzyme-linked immunosorbent assay (Recombigen HIV-1 env and gag ELISA, Cambridge BioScience, Worcester, Mass.); 1 in 10 HIV-1–positive and 1 in 25 HIV-1–negative serum samples, according to enzyme-linked immunosorbent assay, underwent confirmatory testing by HIV-1 Western immunoblotting (BioRad Novapath, Hercules, Calif.). At the time of screening, all the subjects underwent Mantoux skin testing with 5 tuberculin units of PPD (Tubersol, Connaught Laboratories, Swiftwater, Pa.) and 0.1 ml of candida antigen (*Candida albicans* allergic extract, Berkeley Biologics, Berkeley, Calif.; 1:50 final concentration). After 48 to 72 hours, experienced observers recorded the results of each skin test in millimeters. Posteroanterior chest radiographs were obtained at base line and at six-month intervals during follow-up.

Before randomization, at least one sputum specimen was collected if the subject was able to produce sputum. All sputum specimens were digested, concentrated, and stained for acid-fast bacilli by the Ziehl–Neelsen method at the Uganda Tuberculosis Investigations Bacteriological Unit in Wandegeya. Sputum smears were graded according to the number of acid-fast organisms seen on light microscopy.[28] Specimens were cultured for *M. tuberculosis* on Lowenstein–Jensen slants, incubated at 37°C in air, and examined weekly for eight weeks or until positive results were seen.

Compliance with the prescribed regimen was assessed by the subject's attendance at scheduled visits, urinary testing for isoniazid metabolites (Mycodyn Uritec, DynaGen, Cambridge, Mass.), and self-reports. Ninety-seven subjects in the three treatment groups were randomly selected for unscheduled tests for urinary isoniazid metabolites performed at home between clinic appointments at the beginning of the third month of preventive therapy.

Statistical Analysis

The intention-to-treat approach was used to analyze the data for the primary and secondary end points of tuberculosis, adverse drug reactions, and mortality. The incidence of tuberculosis was estimated by the person-year method; the cumulative proportion was estimated for adverse drug reactions and death. Efficacy was estimated as the relative risk (with 95 percent confidence intervals) of tuberculosis in the treatment groups as compared with the placebo group. The sample size was calculated separately for the PPD-positive and anergy cohorts to achieve a power of 80 percent to detect a reduction of 67 percent in the incidence of tuberculosis with an overall type I error of 5 percent. The sample size was adjusted for expected mortality and losses to follow-up. The target sample size for each treatment or placebo group was 410 for the PPD-positive cohort and 500 for the anergy cohort.

A global test of significance was performed with the log-rank statistic to compare the cumulative incidence of tuberculosis in the treatment groups with that in the placebo group. The nominal significance level, according to the Lan–DeMets error-spending function,[29] was 0.032 when adjusted for a second interim analysis in which 47 of 56 expected events (84 percent) had occurred in the PPD-positive subjects. Three pairwise comparisons were then made between each active-treatment group and the placebo group. The type I error for these pairwise comparisons was adjusted for multiple comparisons by using the nominal significance level from the global test to obtain an adjusted type I error of 0.011 for each comparison, preserving the overall, study-wide type I error of 0.05. A similar procedure was used to adjust the significance level for the subjects with anergy.

RESULTS

Between March 1, 1993, and April 20, 1995, 9095 subjects were screened and 2736 were enrolled in the study. Of the 9095 persons screened for the study, 4306 did not complete the base-line evaluation and 2053 were ineligible for the study. Persons screened for the study were not eligible for one or more of the following reasons: active tuberculosis (smear- or culture-positive; 185 subjects), HIV-seronegative or indeterminate (703), failure to return for skin testing (28), PPD-negative (374), abnormal chest radiograph (884), previous history of tuberculosis or use of preventive therapy (96), poor performance status (233), pregnancy (160), age greater than 50 years (223), or residence more than 20 km from project clinic (226). Information on the progress of subjects through follow-up is available elsewhere.*

In both the PPD-positive and the anergy cohorts, the treatment groups were balanced at base line in terms of demographic factors, performance status, and the results of laboratory tests (Table 1). During follow-up, the numbers of subjects who withdrew from the study, moved out of the study area, or could not be located for unknown reasons did not differ significantly among the study groups. The mean number of scheduled visits, unscheduled visits due to illness, and chest radiographs per person did not differ significantly among the groups. Urine tests for isoniazid metabolites were performed in 1754 subjects in the treatment groups (90 percent), and 75 percent of the results were positive; the results did not differ significantly among the treatment groups. Of the 97 subjects randomly selected for a single spot check at home between clinic appointments, 78 (80 percent) tested positive for isoniazid metabolites. The subjects with positive results on the spot test had a higher proportion of positive tests at the regular monthly visits than the subjects with negative tests (82 percent vs. 46 percent, $P<0.001$).

At the second interim analysis, in December 1995, isoniazid alone was found to reduce the risk of tuberculosis by 67 percent in HIV-infected adults with positive tuberculin skin tests, although there was no significant difference in mortality among treatment groups. Because the benefit of preventive therapy with isoniazid satisfied conservative criteria for statistical significance, the study investigators and officials at the Centers for Disease Control and Prevention, the funding agency for the study, concurred that preventive therapy with isoniazid should be offered to the subjects randomly assigned to the placebo group.

Tuberculosis

In the PPD-positive cohort, 138 subjects met the criteria for new cases of tuberculosis after a mean

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TABLE 1. CHARACTERISTICS OF THE STUDY SUBJECTS.*

CHARACTERISTIC	PPD-POSITIVE COHORT				ANERGY COHORT	
	PLACEBO (N=464)	ISONIAZID (N=536)	ISONIAZID, RIFAMPIN (N=556)	ISONIAZID, RIFAMPIN, PYRAZINAMIDE (N=462)	PLACEBO (N=323)	ISONIAZID (N=395)
Male sex (%)	31	31	29	34	31	32
Mean age (yr)	30	29	29	29	30	30
Karnofsky performance score	91	91	91	91	90	90
Body-mass index†	22.2	22.1	22.6	22.3	22.9	21.9
PPD skin test (mm of induration)	14	14	13	14	0	0
Previous herpes zoster or thrush (%)	25	25	25	27	33	35
Absolute lymphocyte count (per mm³)	2200	2300	2300	2200	2000	2100
Hemoglobin (g/liter)	126	125	127	126	125	123
Person-years of observation	616	645	680	577	327	355
Completion of trial (%)	89	88	86	80	85	86

*Categorical values were compared by the chi-square test for homogeneity; continuous values were compared by analysis of variance. PPD denotes a tuberculin skin test with purified protein derivative.

†The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

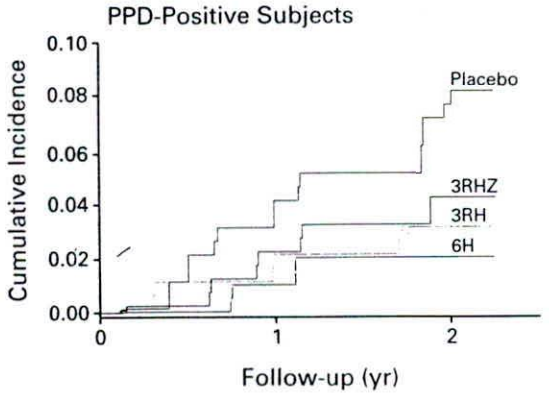
follow-up of 15 months. Forty-seven cases of tuberculosis (24 definite and 23 probable) were observed. In this cohort, the cumulative incidence of tuberculosis was greater in the placebo group than in the treatment groups ($P=0.002$ by the log-rank test) (Fig. 1A). In separate pairwise comparisons of individual treatment regimens with placebo (Table 2), the relative risk of tuberculosis with isoniazid alone was 0.33, a statistically significant value. A similar effect was found with the isoniazid and rifampin group as compared with the placebo groups; the relative risk was 0.40, but in this comparison, the effect narrowly failed to meet the prespecified adjusted level of significance. The relative risk of tuberculosis with the three-drug regimen was 0.51, and the estimate of the effect was of borderline statistical significance. The relative risks of tuberculosis in the treatment groups as compared with the placebo groups remained unchanged for isoniazid and isoniazid with rifampin in a proportional-hazards regression model after adjustment for age, sex, body-mass index, hemoglobin level, white-cell count, Karnofsky performance score, history of HIV-related infection, and presence of chronic diarrhea or weight loss. After this adjustment, the relative risk with the three-drug regimen decreased to 0.43 and was of borderline statistical significance ($P=0.03$).

When the analysis was restricted to definite, culture-confirmed cases of tuberculosis among the PPD-positive cohort, the relative risk of tuberculosis with isoniazid was 0.22 (95 percent confidence interval, 0.06 to 0.77) and with isoniazid and rifampin, 0.14 (95 percent confidence interval, 0.03 to 0.62), whereas the efficacy with isoniazid, rifampin, and pyrazinamide was unchanged.

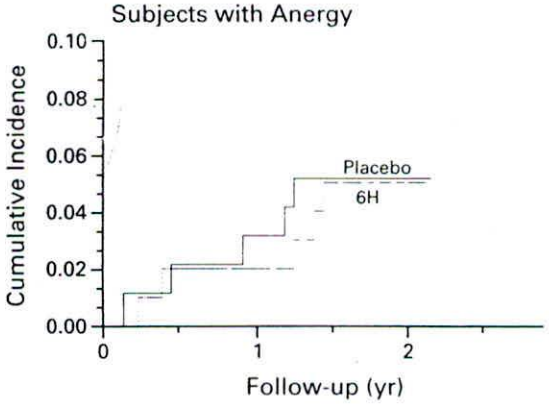
In the anergy cohort, 66 subjects met the criteria for the blinded, independent review after a mean of 12 months of observation. Nineteen cases of definite (9 cases) or probable (10 cases) tuberculosis were detected. The cumulative incidence of tuberculosis was similar in the placebo and isoniazid groups ($P=0.68$ by the log-rank test) (Fig. 1B). The relative risk of tuberculosis in the isoniazid group was 0.83 (Table 2), but the wide confidence intervals did not exclude the hypothesis of no difference in incidence rates. In a proportional-hazards regression analysis adjusted for age, sex, body-mass index, hemoglobin level, white-cell count, Karnofsky performance score, history of HIV-related infection, and presence of diarrhea, the relative risk of tuberculosis in the isoniazid group as compared with the placebo group declined to 0.75, but the confidence intervals remained wide. The relative risk of definite tuberculosis was 0.75 (95 percent confidence interval, 0.20 to 2.79).

Adverse Drug Reactions

A total of 304 adverse events were reported in 279 subjects during the course of therapy in all study groups, including the placebo groups. The frequency of any reported adverse event in the PPD-positive cohort was greater in the treatment groups than in the placebo group, and it was greatest in the group receiving the regimen containing pyrazinamide (Table 3). Treatment was discontinued in 43 subjects.



Study Group			
Placebo	464	288	104
6H	536	280	88
3RH	556	306	109
3RHZ	462	282	87



Study Group			
Placebo	323	167	8
6H	395	155	13

Figure 1. Cumulative Incidence of Tuberculosis among PPD-Positive Subjects (Upper Panel) and Subjects with Anergy (Lower Panel), According to Study Group.

For PPD-positive subjects, the incidence rates of tuberculosis in the groups receiving preventive therapy were lower than the rate in the placebo group ($P=0.002$ by the log-rank test). For subjects with anergy, the incidence rates of tuberculosis did not differ between the placebo and isoniazid groups ($P=0.68$ by the log-rank test). 6H denotes patients receiving isoniazid for six months, 3RH patients receiving isoniazid and rifampin for three months, and 3RHZ patients receiving isoniazid, rifampin, and pyrazinamide for three months. The numbers below the graphs are the numbers of subjects at risk.

The most common reason for stopping therapy was the development of rash or pruritus (25 subjects), followed by nausea and vomiting (8 subjects). The frequency of rash increased from less than 1 percent in the placebo group to 5.8 percent in the group receiving three drugs ($P<0.001$ by chi-square test for trend). No cases of Stevens–Johnson syndrome were reported. Arthralgias were more common in the treated groups than with placebo (1.5, 2.8, 3.1, and 10.8 percent of subjects in the groups receiving placebo, isoniazid, isoniazid with rifampin, and isoniazid with rifampin and pyrazinamide, respectively). Paresthesias were more common in the group receiving isoniazid, rifampin, and pyrazinamide than in the placebo group (6.5 percent vs. 2.4 percent, $P<0.001$) but were reported with similar frequency in the groups receiving isoniazid and isoniazid with rifampin (2.4 and 3.1 percent, respectively).

Seven cases of clinical hepatitis were detected by medical officers during the routine evaluations. Of the 1631 subjects whose serum aspartate aminotransferase levels were measured during therapy, 65 had elevated levels. Fifty-two of these subjects had peak elevations of 135 U per liter or lower. Of the 13 subjects with values greater than 135 U per liter, 6 were subjects with anergy who were receiving isoniazid; 5 were PPD-positive subjects receiving isoniazid, rifampin, and pyrazinamide; 1 was a PPD-positive subject receiving isoniazid; and 1 was a PPD-positive subject receiving placebo.

Mortality

During follow-up, there were 399 deaths: 237 among PPD-positive subjects and 162 among subjects with anergy. The overall mortality rate was greater in the anergy cohort than in the PPD-positive cohort ($P=0.001$). The proportion surviving at one year was 0.78 in the anergy cohort and 0.90 in the PPD-positive cohort ($P=0.001$ by the log-rank test). When the analysis was stratified according to the presence of anergy, there was no significant difference between placebo and each treatment with regard to either the mortality rate or the cumulative proportion of deaths ($P>0.2$ by the log-rank test) in either the PPD-positive cohort or the anergy cohort (Table 4). Of the 66 subjects in whom tuberculosis developed, 13 died, for a cumulative mortality rate of 20 percent.

DISCUSSION

In this randomized, placebo-controlled clinical trial of therapy to prevent tuberculosis in HIV-infected Ugandan adults, self-administered isoniazid taken daily for six months reduced the risk of tuberculosis by 67 percent in subjects with positive PPD skin tests (induration, ≥5 mm). This level of short-term protection was achieved with a minimum of adverse effects. The efficacy of isoniazid in this study

TABLE 2. INCIDENCE OF DEFINITE OR PROBABLE TUBERCULOSIS ACCORDING TO STUDY GROUP AND RELATIVE RISK OF TUBERCULOSIS.*

GROUP	DEFINITE OR PROBABLE TUBERCULOSIS		CRUDE RELATIVE RISK (95% CI)	P VALUE†	ADJUSTED RELATIVE RISK (95% CI)‡
	NO. OF CASES	RATE§			
PPD-positive cohort¶					
Placebo	21	3.41	1.0		1.0
Isoniazid	7	1.08	0.33 (0.14–0.77)	0.01	0.32 (0.14–0.76)
Isoniazid, rifampin	9	1.32	0.40 (0.18–0.86)	0.02	0.41 (0.19–0.89)
Isoniazid, rifampin, pyrazinamide	10	1.73	0.51 (0.24–1.08)	0.08	0.43 (0.20–0.92)
Anergy cohort					
Placebo	10	3.06	1.0		1.0
Isoniazid	9	2.53	0.83 (0.34–2.04)	0.68	0.75 (0.30–1.89)

*CI denotes confidence interval. The relative risk is as compared with the placebo group.

†The P values were determined with the Wald chi-square statistic. The nominal critical value was 0.011, adjusted for the second interim analysis and multiple comparisons with placebo.

‡The relative risks have been adjusted for age, sex, white cell count, hemoglobin level, Karnofsky performance score, body-mass index, history of HIV-related infection, and presence of chronic diarrhea by Cox proportional-hazards regression analysis.

§The rate is the number of cases per 100 person-years.

¶PPD-positive denotes a positive tuberculin skin test with purified protein derivative.

TABLE 3. CUMULATIVE INCIDENCE OF ADVERSE EVENTS, GRADE OF REACTION IN STUDY SUBJECTS, AND FREQUENCY OF DISCONTINUATION OF THERAPY ACCORDING TO STUDY GROUP AND THE PRESENCE OR ABSENCE OF CUTANEOUS ANERGY.

GROUP	CUMULATIVE INCIDENCE OF REPORTED ADVERSE EVENTS	GRADE OF REACTION			DISCONTINUATION OF THERAPY
		MILD	MODERATE	SEVERE	
	number (percent)				
PPD-positive cohort*					
Placebo	23 (5.0)	23 (5.0)	0	0	1 (0.2)
Isoniazid	60 (11.2)	56 (10.4)	4 (0.7)	0	3 (0.6)
Isoniazid, rifampin	54 (9.7)	48 (8.6)	6 (1.1)	0	13 (2.3)
Isoniazid, rifampin, pyrazinamide	114 (24.7)	101 (21.9)	12 (2.6)	1 (0.2)	26 (5.6)
Anergy cohort					
Placebo	22 (6.8)	22 (6.8)	0	0	0
Isoniazid	31 (7.8)	29 (7.3)	2 (0.5)	0	0

*PPD-positive denotes a positive tuberculin skin test with purified protein derivative.

was similar to the efficacy of 71 percent found in a randomized clinical trial of isoniazid in Haiti,[30] but the current study addressed some of the methodologic issues raised about the Haitian study.[31] In particular, the current analysis was based on a larger number of cases of tuberculosis, with half the cases confirmed by sputum culture. The incidence rates of tuberculosis were lower in the current study than in the Haitian study, perhaps as a result of the stricter entry criteria used to exclude subjects with active tuberculosis. Nevertheless, the consistent findings of these two studies, in addition to the preliminary reports of other clinical trials,[32,33] support the validity of the observed protective effect. The duration of this effect, however, remains to be established, since variability in the annual risk of infection among populations may affect the risk of tuberculosis after preventive therapy has been completed, especially in persons with advanced immunosuppression.

The current study extends previous observations by evaluating the safety and efficacy of two multidrug, three-month regimens, isoniazid and rifampin

TABLE 4. MORTALITY RATE AND CUMULATIVE PROPORTION OF DEATHS ACCORDING TO STUDY GROUP.

GROUP	DEATHS	MORTALITY RATE*	RELATIVE RISK (95% CI)†	P VALUE
	no. (%)			
PPD-positive cohort‡				
Placebo	64 (13.8)	10.2	1.0	
Isoniazid	58 (10.8)	8.9	0.9 (0.6–1.2)	0.44
Isoniazid, rifampin	57 (10.3)	8.3	0.8 (0.5–1.2)	0.25
Isoniazid, rifampin, pyrazinamide	58 (12.6)	9.8	0.96 (0.7–1.4)	0.83
Anergy cohort				
Placebo	76 (23.5)	22.3	1.0	
Isoniazid	86 (21.6)	23.5	1.05 (0.77–1.42)	0.77

*The mortality rate is the number of deaths per 100 person-years. Total person-years for the PPD-positive cohort were as follows: placebo, 625; isoniazid, 652; isoniazid and rifampin, 689; and isoniazid, rifampin, and pyrazinamide, 589. Total person-years for the anergy cohort were as follows: placebo, 340; and isoniazid, 367.

†CI denotes confidence interval.

‡PPD-positive denotes a positive tuberculin skin test with purified protein derivative.

and isoniazid, rifampin, and pyrazinamide. These regimens substantially reduced the risk of tuberculosis, but the reduction did not reach the conservative level of statistical significance. These regimens were included in the trial because of the greater sterilizing activity of rifampin,[34] with or without pyrazinamide, and because of the potential for improved compliance with shorter regimens.[19] In addition, fixed-dose combinations of these drugs are available. The slight difference in efficacy between the two- and three-drug regimens may be due to the greater frequency of adverse events associated with the use of pyrazinamide and its possible effect on compliance.

In this study, there was evidence of a small benefit of preventive therapy with isoniazid in subjects with anergy, but the confidence intervals were wide and did not rule out the null hypothesis. The reason isoniazid did not confer the same degree of protection in the subjects with anergy is unclear. We speculate that subjects with anergy may be at greater risk than PPD-positive subjects for primary failure of preventive therapy because of drug malabsorption[35-37] or other host factors associated with advanced disease. Alternatively, exogenous reinfection with progressive primary disease may occur because of the more advanced degree of immunosuppression.

The safety of isoniazid as preventive therapy in HIV-seronegative persons may not be readily extrapolated to HIV-seropositive persons, because of the enhanced drug hypersensitivity associated with HIV infection.[4,23,24] In the current trial, no serious toxic effects were reported with six months of isoniazid, and the rate of clinical hepatitis was similar to that observed in HIV-seronegative persons of similar age.[38] Other side effects, such as rash, arthralgias, and paresthesias, were detected more frequently in the treatment groups than in the placebo groups and were more common in subjects receiving the regimen containing pyrazinamide. Because medical officers were not blinded to the subjects' treatment assignments, it is possible that this observed difference resulted from detection or reporting bias. Nonetheless, since these regimens are intended to prevent tuberculosis in asymptomatic or minimally symptomatic persons at risk, the treatment should not produce unacceptable side effects. Although the reported side effects were not severe, they may have led to higher rates of noncompliance or to the withdrawal of therapy by physicians.

In this study, short-term survival did not differ significantly between the placebo and treatment groups in either the PPD-positive or the anergy cohort. If the survival benefit of preventive therapy is conferred through a reduction in the tuberculosis-related case fatality rate, then the use of isoniazid in the PPD-positive cohort prevented 14 cases of tuberculosis and approximately 3 deaths, assuming a case fatality rate of 20 percent. Thus, a large, randomized clinical trial of preventive therapy would be needed to detect a clinically important reduction in the relative risk of cause-specific mortality from tuberculosis. However, the absolute difference in the mortality rates observed in this study between PPD-positive subjects receiving isoniazid and those receiving placebo may indicate important public health benefits in terms of survival if preventive therapy is used widely in HIV-infected persons. The conclusions regarding survival are limited, however, because the average duration of follow-up was short.

The implications of the findings of this study depend on the setting and the target population for preventive therapy. In the United States, where the annual risk of infection and the incidence of tuberculosis are in general low, preventive therapy in dually infected patients is both a standard medical practice and central to tuberculosis control. In developing countries, where dual infection is common and continued exposure to infectious cases of tuberculosis is likely, preventive therapy provides benefit to the individual patient, at least for a short time, but the effect on tuberculosis control remains to be established.

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Editorials

The Ethics of Clinical Research in the Third World

An essential ethical condition for a randomized clinical trial comparing two treatments for a disease is that there be no good reason for thinking one is better than the other.[1,2] Usually, investigators hope and even expect that the new treatment will be better, but there should not be solid evidence one way or the other. If there is, not only would the trial be scientifically redundant, but the investigators would be guilty of knowingly giving inferior treatment to some participants in the trial. The necessity for investigators to be in this state of equipoise[2] applies to placebo-controlled trials, as well. Only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo. When effective treatment exists, a placebo may not be used. Instead, subjects in the control group of the study must receive the best known treatment. Investigators are responsible for all subjects enrolled in a trial, not just some of them, and the goals of the research are always secondary to the well-being of the participants. Those requirements are made clear in the Declaration of Helsinki of the World Health Organization (WHO), which is widely regarded as providing the fundamental guiding principles of research involving human subjects.[3] It states, "In research on man [*sic*], the interest of science and society should never take precedence over considerations related to the wellbeing of the subject," and "In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method."

One reason ethical codes are unequivocal about investigators' primary obligation to care for the human subjects of their research is the strong temptation to subordinate the subjects' welfare to the objectives of the study. That is particularly likely when the research question is extremely important and the answer would probably improve the care of future patients substantially. In those circumstances, it is sometimes argued explicitly that obtaining a rapid, unambiguous answer to the research question is the primary ethical obligation. With the most altruistic of motives, then, researchers may find themselves slipping across a line that prohibits treating human subjects as means to an end. When that line is crossed, there is very little left to protect patients from a callous disregard of their welfare for the sake of research goals. Even informed consent, important though it is, is not protection enough, because of the asymmetry in knowledge and authority between researchers and their subjects. And approval by an institutional review board, though also important, is highly variable in its responsiveness to patients' interests when they conflict with the interests of researchers.

A textbook example of unethical research is the Tuskegee Study of Untreated Syphilis.[4] In that study, which was sponsored by the U.S. Public Health Service and lasted from 1932 to 1972, 412 poor African-American men with untreated syphilis were followed and compared with 204 men free of the disease to determine the natural history of syphilis. Although there was no very good treatment available at the time the study began (heavy metals were the standard treatment), the research continued even after penicillin became widely available and was known to be highly effective against syphilis. The study was not terminated until it came to the attention of a reporter and the outrage provoked by front-page stories in the *Washington Star* and *New York Times* embarrassed the Nixon administration into calling a halt to it.[5] The ethical violations were multiple: Subjects did not provide informed consent (indeed, they were deliberately deceived); they were denied the best known treatment; and the study was continued even after highly effective treatment became available. And what were the arguments in favor of the Tuskegee study? That these poor African-American men probably would not have been treated anyway, so the investigators were merely observing what would have happened if there were no study; and that the study was important (a "never-to-be-repeated opportunity," said one physician after penicillin became available).[6] Ethical concern was even stood on its head when it was suggested that not only was the information valuable, but it was especially so for people like the subjects — an impoverished rural population with a very high rate of untreated syphilis. The only lament seemed to be that many of the subjects inadvertently received treatment by other doctors.

Some of these issues are raised by Lurie and Wolfe elsewhere in this issue of the *Journal*. They discuss the ethics of ongoing trials in the Third World of regimens to prevent the vertical transmission of human immunodeficiency virus (HIV) infection.[7] All except one of the trials employ placebo-treated control groups, despite the fact that zidovudine has already been clearly shown to cut the rate of vertical transmission greatly and is now recommended in the United States for all HIV-infected pregnant women. The justifications are reminiscent of those for the Tuskegee study: Women in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what would happen to the subjects' infants if there were no study. And a placebo-controlled study is the fastest, most efficient way to obtain unambiguous information that will be of greatest value in the Third World. Thus, in response to protests from Wolfe and others to the secretary of Health and Human Services, the directors of the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention

controlled, if at all possible. That rigidity may explain the NIH's pressure on Marc Lallemant to include a placebo group in his study, as described by Lurie and Wolfe.[7] Sometimes journals are blamed for the problem, because they are thought to demand strict conformity to the standard methods. That is not true, at least not at this journal. We do not want a scientifically neat study if it is ethically flawed, but like Lurie and Wolfe we believe that in many cases it is possible, with a little ingenuity, to have both scientific and ethical rigor.

The retreat from ethical principles may also be explained by some of the exigencies of doing clinical research in an increasingly regulated and competitive environment. Research in the Third World looks relatively attractive as it becomes better funded and regulations at home become more restrictive. Despite the existence of codes requiring that human subjects receive at least the same protection abroad as at home, they are still honored partly in the breach. The fact remains that many studies are done in the Third World that simply could not be done in the countries sponsoring the work. Clinical trials have become a big business, with many of the same imperatives. To survive, it is necessary to get the work done as quickly as possible, with a minimum of obstacles. When these considerations prevail, it seems as if we have not come very far from Tuskegee after all. Those of us in the research community need to redouble our commitment to the highest ethical standards, no matter where the research is conducted, and sponsoring agencies need to enforce those standards, not undercut them.

MARCIA ANGELL, M.D.

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THE DOUBLE BURDEN OF HIV INFECTION AND TUBERCULOSIS IN SUB-SAHARAN AFRICA

THE World Health Organization (WHO) estimated that by June 1996 14 million people were living with human immunodeficiency virus (HIV) infection in sub-Saharan Africa. Although it contains only 10 percent of the world's population, sub-Saharan Africa is home to about 65 percent of all the world's HIV-infected people. In several urban centers, more than 10 percent of the asymptomatic adults and about 15 to 30 percent of the women attending prenatal-care clinics are infected. A 1994 paper reported that in rural Uganda more than 80 percent of the deaths among men and women 25 to 44 years of age were attributable to HIV infection.[1] The reported risk of perinatal transmission of HIV is generally higher in African studies (30 to 45 percent) than in European and American studies (7 to 30 percent). Although the median length of time from seroconversion to the appearance of the acquired immunodeficiency syndrome (AIDS) is approximately 10 years in the United States, it is only 4.4 years among female sex workers in Nairobi, Kenya.[2]

The death of one or both parents from HIV infection has left many African children without social, emotional, or economic support. HIV infection has also put additional strains on the already overstretched health care systems. The average annual per capita expenditure on health is $11 for the region, and in several countries it is less than $4. Many areas lack essential drugs and medical supplies, including antibiotics, antiseptics, and gloves. With the increasing privatization of the health care sector, many health services (excluding prenatal care and other prevention programs) are available — but at a price. Although mechanisms have been developed to waive the fees for those who cannot afford them, these may be difficult to implement when the majority of patients are poor. In fact, over 50 percent of the adult patients admitted to the hospital in Africa are infected

with HIV, and many of them are unable to pay for care. Given that HIV infection is most prevalent among the economically productive age groups, patients' families suffer tremendously because of the frequent illnesses and eventual death of those infected.

A secondary epidemic of tuberculosis is accompanying the rise in the number of HIV-infected persons. WHO estimates that worldwide nearly 5 million people are infected with both HIV and tuberculosis, and three quarters of them live in Africa.[3] Prevention of tuberculosis among those with HIV infection is a logical public health goal, given that such patients are at high risk for tuberculosis, which in turn is associated with an increased likelihood of death. Long before the advent of AIDS, preventive therapy with isoniazid was shown to reduce the occurrence of tuberculosis significantly among contacts of patients with active disease and among those with conversion of a tuberculin skin test to positive.[4] Because of concern about the increased adverse effects of antituberculosis therapy in HIV-positive patients, a number of trials have examined the safety and efficacy of chemoprophylaxis in this population. Placebo-controlled studies were carried out in Haiti, Zambia, and Kenya with varying designs and results. In the Haitian study, a 12-month course of isoniazid significantly reduced the incidence of tuberculosis among HIV-positive subjects with positive tuberculin skin tests. However, about 40 percent of the new cases were based on presumptive diagnoses of tuberculosis.[5] In the Zambian study, a six-month course of isoniazid reduced the incidence of tuberculosis among patients with positive tuberculin skin tests.[6] But in the study from Kenya there was no effect of six months of therapy with isoniazid among HIV-positive subjects, although the number who had positive tuberculin skin tests was too small to permit the effect of therapy to be examined in this subgroup.[7]

In this issue of the *Journal*, Whalen et al. report that a six-month course of isoniazid among HIV-infected Ugandans with positive tuberculin skin tests reduced the risk of tuberculosis by about 70 percent after a mean follow-up period of 15 months.[8] Isoniazid therapy may have reduced the risk of tuberculosis among subjects with anergy as well. This study also adds to our knowledge of the role of preventive therapies that include drugs other than isoniazid, such as rifampin and pyrazinamide. For the subjects who received a three-month course of isoniazid and rifampin, there was about a 60 percent reduction in the risk of tuberculosis as compared with those given placebo. The reduction in the risk of tuberculosis for those given isoniazid, rifampin, and pyrazinamide was 49 percent. Alternative regimens are needed for those infected with isoniazid-resistant strains, and the shorter courses are likely to improve compliance. However, they are also associated with a higher risk of adverse events and are most costly. Although none of the treatments in this study reduced mortality significantly, the sample size and duration of follow-up were inadequate for this question to be examined.

The results of the study from Uganda support the administration of isoniazid as preventive therapy for persons in sub-Saharan Africa who are infected with HIV and have positive tuberculin skin tests. Before any such program can be implemented on a communitywide level, research on the operational and programmatic questions is urgently needed. Is preventive therapy feasible in sub-Saharan Africa? Is it cost effective, as compared with other uses of scarce health care dollars? The introduction of a program of preventive therapy requires human resources, laboratory supplies, drugs, and transport facilities in order to carry out voluntary counseling and testing for HIV infection, to identify and exclude all those with active tuberculosis, to perform tuberculin skin testing, and to provide follow-up care. The exclusion of those with active tuberculosis is important, since treatment with isoniazid alone is insufficient and would lead to the development of drug-resistant organisms. It is also important to exclude people with liver problems at base line and to terminate therapy among those in whom hepatotoxicity develops during follow-up. In one report, unsupervised preventive therapy in Uganda was associated with poor compliance.[9] On the other hand, directly observed therapy for tuberculosis given by nonmedical staff was reported to be successful in a South African community,[10] and a similar system could be instituted for preventive therapy.

A number of scientific issues still need to be addressed. These include the question of how long the protection afforded by preventive therapy lasts. The protection afforded by 6 to 12 months of isoniazid therapy is probably lifelong in the parts of the world where the risk of transmission of tuberculosis is low. In sub-Saharan Africa, however, the duration of efficacy may be much shorter because the risk of infection or reinfection is so high. The efficacy and economics of providing long-term preventive therapy or lifelong therapy and the risk of accelerating drug resistance need to be examined.[11] Given our current state of knowledge, however, future studies should not include a placebo group, since preventive therapy should be considered the standard of care.

In sub-Saharan Africa, where there is little access to antiretroviral drugs, preventive therapy for tuberculosis may be the single most affordable intervention for the prolongation of a healthy life in HIV-infected persons. By preventing tuberculosis, these regimens will also help reduce the transmission of tuberculosis in African communities. Although we agree with WHO that interrupting the transmission of tuberculosis by curative treatment of infectious cases should continue to be the priority for tuberculosis programs,[12] efforts need to be made to apply these important findings about preventive therapy to the community and the region where the study was

carried out. It is clear that African programs of tuberculosis and AIDS control will be unable to undertake this additional responsibility alone, since they rely largely on donor support. Extension of these programs will be possible only through the cooperation of many governments, pharmaceutical companies, and international agencies.

GERNARD I. MSAMANGA, M.D., SC.D.
Muhimbili Medical Center
Dar es Salaam, Tanzania

WAFAIE W. FAWZI, M.B., B.S., DR.P.H.
Harvard School of Public Health
Boston, MA 02115

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PHARMACOLOGIC ADVANCES IN THE TREATMENT OF SCHIZOPHRENIA

ALTHOUGH medications have dramatically improved the lives of many people with schizophrenia, treatment resistance remains a serious problem. Three quarters of patients with schizophrenia become ill before the age of 25. The manifestations of the disease include two types of symptoms — "positive" and "negative." Positive symptoms are distortions of normal functioning. Distortion of perceptions may appear as hallucinations; distortion of inferential thinking may lead to delusions. Negative symptoms involve the loss of normal functioning — the loss of will, range of affect, pleasure, and fluency and content of speech. The intensity of these symptoms and the residual disability they cause may prevent people with schizophrenia from beginning a career, completing an education, or enjoying a life that may once have been filled with great promise. Rates of employment among people with schizophrenia rarely exceed 20 percent.

Schizophrenia is a chronic illness; less than 20 percent of patients recover from a single episode of psychosis and return to the lives they knew before. More frequently, patients have repeated episodes, with decrements in base-line functioning accompanying each one; a few never recover from the first episode and continue to have pervasive psychotic symptoms.

For 35 years, the pharmacologic approach to schizophrenia involved antipsychotic medication based on D2 dopamine-receptor antagonism. The dopamine hypothesis of schizophrenia was proposed in 1963,[1] 10 years after the first antipsychotic medication was introduced. This hypothesis was based on the observation that all antipsychotic drugs had a strong affinity for a particular dopamine receptor (D2) and that dopamine agonists, such as methylphenidate and dextroamphetamine, could produce a psychotic condition. Standard antipsychotic drugs differed only in their side effects, not in their mechanisms of action. Consistent side effects were those associated with D2 antagonism, most likely in the nigrostriatal dopamine tracts, which led to extrapyramidal symptoms of stiffness, tremor, pseudoparkinsonism, and akathisia. Subjectively, these side effects were unpleasant, leading to cycles of noncompliance and relapse. Estimates of 40 percent rates of noncompliance among patients treated with antipsychotic agents were not unusual; when noncompliance was combined with the therapeutic limitations of the drugs, rates of relapse were quite high.

Clozapine, the first novel antipsychotic drug to appear, was introduced in the United States in 1989. A conventional antipsychotic drug, such as haloperidol, produced its antipsychotic effects after binding to 80 percent of dopamine D2 receptors; clozapine produced an antipsychotic effect after binding to less than 20 percent of D2 receptors. Hypotheses about clozapine's principal mechanism of action have been hotly debated, but without resolution. Proposed mechanisms of action have focused, separately and in combination, on other dopamine receptors (D1 and D4) and on clozapine's effects on the serotonin receptor 5-hydroxytryptamine. The initial interest in serotonin receptors was stimulated by lysergic acid diethylamide (LSD), which has high serotonergic activity. Until clozapine was developed, however, investigation of serotonin receptors in the context of schizophrenia had fallen off. This was because the main psychotic symptoms associated with

Sounding Board

Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries

IT has been almost three years since the *Journal*[1] published the results of AIDS Clinical Trials Group (ACTG) Study 076, the first randomized, controlled trial in which an intervention was proved to reduce the incidence of human immunodeficiency virus (HIV) infection. The antiretroviral drug zidovudine, administered orally to HIV-positive pregnant women in the United States and France, administered intravenously during labor, and subsequently administered to the newborn infants, reduced the incidence of HIV infection by two thirds.[2] The regimen can save the life of one of every seven infants born to HIV-infected women.

Because of these findings, the study was terminated at the first interim analysis and within two months after the results had been announced, the Public Health Service had convened a meeting and concluded that the ACTG 076 regimen should be recommended for all HIV-positive pregnant women without substantial prior exposure to zidovudine and should be considered for other HIV-positive pregnant women on a case-by-case basis.[3] The standard of care for HIV-positive pregnant women thus became the ACTG 076 regimen.

In the United States, three recent studies of clinical practice report that the use of the ACTG 076 regimen is associated with decreases of 50 percent or more in perinatal HIV transmission.[4-6] But in developing countries, especially in Asia and sub-Saharan Africa, where it is projected that by the year 2000, 6 million pregnant women will be infected with HIV,[7] the potential of the ACTG 076 regimen remains unrealized primarily because of the drug's exorbitant cost in most countries.

Clearly, a regimen that is less expensive than ACTG 076 but as effective is desirable, in both developing and industrialized countries. But there has been uncertainty about what research design to use in the search for a less expensive regimen. In June 1994, the World Health Organization (WHO) convened a group in Geneva to assess the agenda for research on perinatal HIV transmission in the wake of ACTG 076. The group, which included no ethicists, concluded, "Placebo-controlled trials offer the best option for a rapid and scientifically valid assessment of alternative antiretroviral drug regimens to prevent [perinatal] transmission of HIV."[8] This unpublished document has been widely cited as justification for subsequent trials in developing countries. In our view, most of these trials are unethical and will lead to hundreds of preventable HIV infections in infants.

Primarily on the basis of documents obtained from the Centers for Disease Control and Prevention (CDC), we have identified 18 randomized, controlled trials of interventions to prevent perinatal HIV transmission that either began to enroll patients after the ACTG 076 study was completed or have not yet begun to enroll patients. The studies are designed to evaluate a variety of interventions: antiretroviral drugs such as zidovudine (usually in regimens that are less expensive or complex than the ACTG 076 regimen), vitamin A and its derivatives, intrapartum vaginal washing, and HIV immune globulin, a form of immunotherapy. These trials involve a total of more than 17,000 women.

In the two studies being performed in the United States, the patients in all the study groups have unrestricted access to zidovudine or other antiretroviral drugs. In 15 of the 16 trials in developing countries, however, some or all of the patients are not provided with antiretroviral drugs. Nine of the 15 studies being conducted outside the United States are funded by the U.S. government through the CDC or the National Institutes of Health (NIH), 5 are funded by other governments, and 1 is funded by the United Nations AIDS Program. The studies are being conducted in Côte d'Ivoire, Uganda, Tanzania, South Africa, Malawi, Thailand, Ethiopia, Burkina Faso, Zimbabwe, Kenya, and the Dominican Republic. These 15 studies clearly violate recent guidelines designed specifically to address ethical issues pertaining to studies in developing countries. According to these guidelines, "The ethical standards applied should be no less exacting than they would be in the case of research carried out in [the sponsoring] country."[9] In addition, U.S. regulations governing studies performed with federal funds domestically or abroad specify that research procedures must "not unnecessarily expose subjects to risk."[10]

The 16th study is noteworthy both as a model of an ethically conducted study attempting to identify less expensive antiretroviral regimens and as an indication of how strong the placebo-controlled trial orthodoxy is. In 1994, Marc Lallemant, a researcher at the Harvard School of Public Health, applied for NIH funding for an equivalency study in Thailand in which three shorter zidovudine regimens were to be compared with a regimen similar to that used in the ACTG 076 study. An equivalency study is typically conducted when a particular regimen has already been proved effective and one is interested in determining whether a second regimen is about as effective but less toxic or expensive.[11] The NIH study section repeatedly put pressure on Lallemant and the Harvard School of Public Health to conduct a

placebo-controlled trial instead, prompting the director of Harvard's human subjects committee to reply, "The conduct of a placebo-controlled trial for [zidovudine] in pregnant women in Thailand would be unethical and unacceptable, since an active-controlled trial is feasible."[12] The NIH eventually relented, and the study is now under way. Since the nine studies of antiretroviral drugs have attracted the most attention, we focus on them in this article.

ASKING THE WRONG RESEARCH QUESTION

There are numerous areas of agreement between those conducting or defending these placebo-controlled studies in developing countries and those opposing such trials. The two sides agree that perinatal HIV transmission is a grave problem meriting concerted international attention; that the ACTG 076 trial was a major breakthrough in perinatal HIV prevention; that there is a role for research on this topic in developing countries; that identifying less expensive, similarly effective interventions would be of enormous benefit, given the limited resources for medical care in most developing countries; and that randomized studies can help identify such interventions.

The sole point of disagreement is the best comparison group to use in assessing the effectiveness of less-expensive interventions once an effective intervention has been identified. The researchers conducting the placebo-controlled trials assert that such trials represent the only appropriate research design, implying that they answer the question, "Is the shorter regimen better than nothing?" We take the more optimistic view that, given the findings of ACTG 076 and other clinical information, researchers are quite capable of designing a shorter antiretroviral regimen that is approximately as effective as the ACTG 076 regimen. The proposal for the Harvard study in Thailand states the research question clearly: "Can we reduce the duration of prophylactic [zidovudine] treatment without increasing the risk of perinatal transmission of HIV, that is, without compromising the demonstrated efficacy of the standard ACTG 076 [zidovudine] regimen?"[13] We believe that such equivalency studies of alternative antiretroviral regimens will provide even more useful results than placebo-controlled trials, without the deaths of hundreds of newborns that are inevitable if placebo groups are used.

At a recent congressional hearing on research ethics, NIH director Harold Varmus was asked how the Department of Health and Human Services could be funding both a placebo-controlled trial (through the CDC) and a non–placebo-controlled equivalency study (through the NIH) in Thailand. Dr. Varmus conceded that placebo-controlled studies are "not the only way to achieve results."[14] If the research can be satisfactorily conducted in more than one way, why not select the approach that minimizes loss of life?

INADEQUATE ANALYSIS OF DATA FROM ACTG 076 AND OTHER SOURCES

The NIH, CDC, WHO, and the researchers conducting the studies we consider unethical argue that differences in the duration and route of administration of antiretroviral agents in the shorter regimens, as compared with the ACTG 076 regimen, justify the use of a placebo group.[15-18] Given that ACTG 076 was a well-conducted, randomized, controlled trial, it is disturbing that the rich data available from the study were not adequately used by the group assembled by WHO in June 1994, which recommended placebo-controlled trials after ACTG 076, or by the investigators of the 15 studies we consider unethical.

In fact, the ACTG 076 investigators conducted a subgroup analysis to identify an appropriate period for prepartum administration of zidovudine. The approximate median duration of prepartum treatment was 12 weeks. In a comparison of treatment for 12 weeks or less (average, 7) with treatment for more than 12 weeks (average, 17), there was no univariate association between the duration of treatment and its effect in reducing perinatal HIV transmission ($P = 0.99$) (Gelber R: personal communication). This analysis is somewhat limited by the number of infected infants and its post hoc nature. However, when combined with information such as the fact that in non–breast-feeding populations an estimated 65 percent of cases of perinatal HIV infection are transmitted during delivery and 95 percent of the remaining cases are transmitted within two months of delivery,[19] the analysis *suggests* that the shorter regimens may be equally effective. This finding should have been explored in later studies by randomly assigning women to longer or shorter treatment regimens.

What about the argument that the use of the oral route for intrapartum administration of zidovudine in the present trials (as opposed to the intravenous route in ACTG 076) justifies the use of a placebo? In its protocols for its two studies in Thailand and Côte d'Ivoire, the CDC acknowledged that previous "pharmacokinetic modelling data suggest that [zidovudine] serum levels obtained with this [oral] dose will be similar to levels obtained with an intravenous infusion."[20]

Thus, on the basis of the ACTG 076 data, knowledge about the timing of perinatal transmission, and pharmacokinetic data, the researchers should have had every reason to believe that well-designed shorter regimens would be more effective than placebo. These findings seriously disturb the equipoise (uncertainty over the likely study result) necessary to justify a placebo-controlled trial on ethical grounds.[21]

DEFINING PLACEBO AS THE STANDARD OF CARE IN DEVELOPING COUNTRIES

Some officials and researchers have defended the use of placebo-controlled studies in developing coun-

tries by arguing that the subjects are treated at least according to the standard of care in these countries, which consists of unproven regimens or no treatment at all. This assertion reveals a fundamental misunderstanding of the concept of the standard of care. In developing countries, the standard of care (in this case, not providing zidovudine to HIV-positive pregnant women) is not based on a consideration of alternative treatments or previous clinical data, but is instead an economically determined policy of governments that cannot afford the prices set by drug companies. We agree with the Council for International Organizations of Medical Sciences that researchers working in developing countries have an ethical responsibility to provide treatment that conforms to the standard of care in the sponsoring country, when possible.[9] An exception would be a standard of care that required an exorbitant expenditure, such as the cost of building a coronary care unit. Since zidovudine is usually made available free of charge by the manufacturer for use in clinical trials, excessive cost is not a factor in this case. Acceptance of a standard of care that does not conform to the standard in the sponsoring country results in a double standard in research. Such a double standard, which permits research designs that are unacceptable in the sponsoring country, creates an incentive to use as research subjects those with the least access to health care.

What are the potential implications of accepting such a double standard? Researchers might inject live malaria parasites into HIV-positive subjects in China in order to study the effect on the progression of HIV infection, even though the study protocol had been rejected in the United States and Mexico. Or researchers might randomly assign malnourished San (bushmen) to receive vitamin-fortified or standard bread. One might also justify trials of HIV vaccines in which the subjects were not provided with condoms or state-of-the-art counseling about safe sex by arguing that they are not customarily provided in the developing countries in question. These are not simply hypothetical worst-case scenarios; the first two studies have already been performed,[22,23] and the third has been proposed and criticized.[24]

Annas and Grodin recently commented on the characterization and justification of placebos as a standard of care: "'Nothing' is a description of what happens; 'standard of care' is a normative standard of effective medical treatment, whether or not it is provided to a particular community."[25]

JUSTIFYING PLACEBO-CONTROLLED TRIALS BY CLAIMING THEY ARE MORE RAPID

Researchers have also sought to justify placebo-controlled trials by arguing that they require fewer subjects than equivalency studies and can therefore be completed more rapidly. Because equivalency studies are simply concerned with excluding alternative interventions that fall below some preestablished level of efficacy (as opposed to establishing which intervention is superior), it is customary to use one-sided statistical testing in such studies.[11] The numbers of women needed for a placebo-controlled trial and an equivalency study are similar.[26] In a placebo-controlled trial of a short course of zidovudine, with rates of perinatal HIV transmission of 25 percent in the placebo group and 15 percent in the zidovudine group, an alpha level of 0.05 (two-sided), and a beta level of 0.2, 500 subjects would be needed. An equivalency study with a transmission rate of 10 percent in the group receiving the ACTG 076 regimen, a difference in efficacy of 6 percent (above the 10 percent), an alpha level of 0.05 (one-sided), and a beta level of 0.2 would require 620 subjects (McCarthy W: personal communication).

TOWARD A SINGLE INTERNATIONAL STANDARD OF ETHICAL RESEARCH

Researchers assume greater ethical responsibilities when they enroll subjects in clinical studies, a precept acknowledged by Varmus recently when he insisted that all subjects in an NIH-sponsored needle-exchange trial be offered hepatitis B vaccine.[27] Residents of impoverished, postcolonial countries, the majority of whom are people of color, must be protected from potential exploitation in research. Otherwise, the abominable state of health care in these countries can be used to justify studies that could never pass ethical muster in the sponsoring country.

With the increasing globalization of trade, government research dollars becoming scarce, and more attention being paid to the hazards posed by "emerging infections" to the residents of industrialized countries, it is likely that studies in developing countries will increase. It is time to develop standards of research that preclude the kinds of double standards evident in these trials. In an editorial published nine years ago in the *Journal*, Marcia Angell stated, "Human subjects in any part of the world should be protected by an irreducible set of ethical standards."[28] Tragically, for the hundreds of infants who have needlessly contracted HIV infection in the perinatal-transmission studies that have already been completed, any such protection will have come too late.

PETER LURIE, M.D., M.P.H.
SIDNEY M. WOLFE, M.D.
Public Citizen's Health Research Group
Washington, DC 20009

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