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A CASE–CONTROL STUDY OF HIV SEROCONVERSION IN HEALTH CARE WORKERS AFTER PERCUTANEOUS EXPOSURE

DENISE M. CARDO, M.D., DAVID H. CULVER, PH.D., CAROL A. CIESIELSKI, M.D., PAMELA U. SRIVASTAVA, M.S., RUTHANNE MARCUS, M.P.H., DOMINIQUE ABITEBOUL, M.D., JULIA HEPTONSTALL, M.R.C.PATH., GIUSEPPE IPPOLITO, M.D., FLORENCE LOT, M.D., PENNY S. MCKIBBEN, DAVID M. BELL, M.D., AND THE CENTERS FOR DISEASE CONTROL AND PREVENTION NEEDLESTICK SURVEILLANCE GROUP

ABSTRACT

Background The average risk of human immunodeficiency virus (HIV) infection after percutaneous exposure to HIV-infected blood is 0.3 percent, but the factors that influence this risk are not well understood.

Methods We conducted a case–control study of health care workers with occupational, percutaneous exposure to HIV-infected blood. The case patients were those who became seropositive after exposure to HIV, as reported by national surveillance systems in France, Italy, the United Kingdom, and the United States. The controls were health care workers in a prospective surveillance project who were exposed to HIV but did not seroconvert.

Results Logistic-regression analysis based on 33 case patients and 665 controls showed that significant risk factors for seroconversion were deep injury (odds ratio = 15; 95 percent confidence interval, 6.0 to 41), injury with a device that was visibly contaminated with the source patient's blood (odds ratio = 6.2; 95 percent confidence interval, 2.2 to 21), a procedure involving a needle placed in the source patient's artery or vein (odds ratio = 4.3; 95 percent confidence interval, 1.7 to 12), and exposure to a source patient who died of the acquired immunodeficiency syndrome within two months afterward (odds ratio = 5.6; 95 percent confidence interval, 2.0 to 16). The case patients were significantly less likely than the controls to have taken zidovudine after the exposure (odds ratio = 0.19; 95 percent confidence interval, 0.06 to 0.52).

Conclusions The risk of HIV infection after percutaneous exposure increases with a larger volume of blood and, probably, a higher titer of HIV in the source patient's blood. Postexposure prophylaxis with zidovudine appears to be protective. (N Engl J Med 1997;337:1485-90.)

THE average risk of transmission of human immunodeficiency virus (HIV) to a health care worker after percutaneous exposure to HIV-infected blood has been estimated as 0.3 percent.[1-4] However, the factors that influence this risk have not been determined, and the efficacy of postexposure prophylaxis with antiretroviral drugs has not been clinically evaluated. If postexposure prophylaxis is effective, it would offer an entirely new strategy for preventing HIV transmission in nonoccupational settings as a supplement to the preferred strategy of preventing exposure. Study of occupational exposure to HIV presents an important opportunity to evaluate postexposure prophylaxis, because the source, time, and many details of the exposure are known. A nationwide, prospective, placebo-controlled trial of prophylaxis with zidovudine after percutaneous exposure to HIV among health care workers was discontinued when only 84 health care workers enrolled after one year, since many thousands would be needed to assess reduction of a 0.3 percent risk of transmission.[1,5] Nevertheless, occupational exposure to HIV and infection continue to occur, and there is a compelling public health need for data on the efficacy of postexposure prophylaxis.

We conducted a case–control study to identify

From the Hospital Infections Program, National Center for Infectious Diseases (D.M.C., D.H.C., P.U.S., R.M., P.S.M., D.M.B.), and the Division of HIV/AIDS, National Center for HIV, STD, and TB Prevention (C.A.C.), Centers for Disease Control and Prevention, Atlanta; the Institut National de Recherche et de Sécurité and Groupe d'Étude sur le Risque d'Exposition au Sang, Paris (D.A.); the Public Health Laboratory Service Communicable Disease Surveillance Centre, London (J.H.); the Centro di Riferimento AIDS–Coordinamento Studio Italiano sul Rischio di Infezione Occupazionale da HIV, Rome (G.I.); and the Réseau National de Santé Publique, Saint Maurice, France (F.L.). Address reprint requests to Dr. Cardo at the Centers for Disease Control and Prevention, 1600 Clifton Rd., Mail Stop E-68, Atlanta, GA 30333.

risk factors for the transmission of HIV to a health care worker after percutaneous exposure to HIV-infected blood.

METHODS

Definitions

Case patients were health care workers who had a documented occupational, percutaneous exposure to HIV-infected blood by a needle stick or a cut with a sharp object, HIV seroconversion that was temporally associated with the exposure, and no other reported concurrent exposure to HIV. Control subjects were health care workers with a documented occupational, percutaneous exposure to HIV-infected blood who were HIV seronegative at the time of exposure and at least six months later.

Identification of Case Patients and Controls

Case patients were identified through reports to national surveillance systems for occupationally acquired HIV infection that were operated by the Centers for Disease Control and Prevention (CDC), in cooperation with state and local health departments in the United States; the Réseau National de Santé Publique in France; the Centro di Riferimento AIDS in Italy; and the Public Health Laboratory Service Communicable Disease Surveillance Centre in the United Kingdom. Controls were identified through reports to a voluntary CDC surveillance project, Prospective Evaluation of Health Care Workers Exposed to Blood of Patients Infected with HIV, also called the CDC Needlestick Study. This project has enrolled health care workers from approximately 300 health care institutions in the United States since 1983.[1]

All case patients reported in the United States by August 1994 who were exposed after 1987 and all controls exposed after 1987 whose six-month follow-up evaluation was completed as of August 1994 were studied. Case patients and controls reported in the United States before 1988 were excluded from the analysis because information on many variables of interest was not routinely collected before 1988 and because postexposure prophylaxis was rare.[1] For the same reason, the analysis was limited to all case patients reported in France and Italy after 1989 and in the United Kingdom after 1987. Information on two case patients from Italy had been collected but was not available for analysis in an earlier brief report.[6]

Case patients were normally reported to public health authorities after seroconversion. Most variables of interest were obtained by reviewing incident reports that had been completed at the time of exposure and other records in which documentation was considered to be objective (e.g., medical records). Controls were reported to the CDC at the time of exposure; information was collected with a standardized protocol.[1] Information regarding the date of death of source patients was retrospectively collected for case patients and controls.

Data Collection

For each case patient and control, personal information was collected as well as information on the source patient and the injury. Information about the health care worker included age, sex, occupation, work location, whether antiretroviral agents were offered after exposure, and if taken, the interval between exposure and the first dose and the regimen followed. Information about the source patient included the stage of HIV disease (the acquired immunodeficiency syndrome [AIDS], symptomatic, or asymptomatic) at the time of the health care worker's exposure, use of antiretroviral drugs at that time, and whether the source patient died of AIDS within two months after the health care worker's exposure (referred to as terminal illness). Information about the injury included the type of device involved, the gauge of hollow-bore needle, the type of procedure performed, the urgency of the procedure, the use of gloves, the interval between the use of the device and injury, the presence or absence of visible blood from the source patient on the device, and the severity of injury. Procedures involving a needle placed in the source patient's artery or vein (e.g., phlebotomy, insertion of an intravenous catheter, and arterial-blood gas collection) were distinguished from other procedures (e.g., intramuscular injection and injection into an intravenous catheter). The severity of injury was defined as superficial (surface scratch and the absence of bleeding), moderate (penetration of the skin and bleeding), or deep (deep puncture or wound with or without bleeding).

Statistical Analysis

Univariate and stratified multivariate analyses were performed with Fisher's exact test and Cochran–Mantel–Haenszel techniques. All variables that were either statistically significant in univariate analyses or potentially important with respect to prevention (e.g., the use of gloves, whether zidovudine was offered after exposure, and whether zidovudine was taken) were included in logistic-regression analyses.

When a dichotomous variable had data missing among both case patients and controls, health care workers with missing data were not excluded from the logistic-regression analyses; instead, "missing" was considered a third response category for that variable. A missing-value indicator variable (assigned a value of 1 if missing and a value of zero otherwise) was created and forced into the model, and the missing value was recorded as zero. Thus, we maximized the number of health care workers in the analysis and assessed the potential confounding influence of missing values on the estimated effects of the other risk factors.

Data were analyzed with the Statistical Analysis System (SAS Institute, Cary, N.C.). All P values are two-tailed.

RESULTS

The study population included 33 case patients (23 from the United States, 5 from France, 3 from the United Kingdom, and 2 from Italy) and 679 controls (from 190 of the U.S. health care facilities involved in the CDC Needlestick Study). There was no significant difference between case patients and controls with respect to the year of exposure ($P = 0.84$). Of the injuries sustained by the case patients, 30 (91 percent) were needle sticks (all with hollow-bore needles) and 3 (9 percent) involved other sharp objects. Of the injuries sustained by controls, 620 (91 percent) were needle sticks (594 with hollow-bore needles and 26 with suture needles) and 59 (9 percent) involved other sharp objects.

Univariate analysis revealed that HIV transmission was significantly associated with injuries with a large-diameter needle (a gauge of less than 18), deep injury, visible blood on the device, procedures involving a needle placed in the source patient's vein or artery, emergency procedures, and terminal illness in the source patient (Table 1). No significant difference in risk was found between exposure involving a hollow-bore needle and that involving a suture needle. By univariate analysis, there was no significant difference between case patients and controls in the use of zidovudine after exposure (9 of 33 case patients, or 27 percent, vs. 247 of 679 controls, or 36 percent; odds ratio = 0.7; $P = 0.35$). There was no evidence that case patients were more or less likely than controls to be offered zidovudine. Twenty-five case patients (76 percent) and 500 controls (74 per-

TABLE 1. CHARACTERISTICS OF INJURIES SUSTAINED BY CASE PATIENTS AND CONTROLS.

RISK FACTOR	CASE PATIENTS		CONTROLS		CRUDE ODDS RATIO (95% CI)*	P VALUE†
	NO. OF PATIENTS‡	% WITH RISK FACTOR	NO. OF PATIENTS‡	% WITH RISK FACTOR		
Large-gauge (<18) hollow-bore needle	27	15	488	1.2	14 (4.9–39)	0.001
Deep injury	33	52	675	6.8	15 (8.0–26)	<0.001
Visible blood on device	32	84	632	35	10 (4.6–23)	<0.001
Procedure involving needle in artery or vein	33	73	669	31	5.9 (2.9–12)	<0.001
Emergency procedure	33	12	661	2.4	5.6 (2.0–16)	0.012
Use of gloves	32	78	679	78	1.0 (0.4–2.4)	1.0
AIDS in source patient	33	82	676	70	1.9 (0.8–4.6)	0.18
Terminal illness in source patient§	27	48	349	16	4.8 (2.3–10)	<0.001
Postexposure use of zidovudine	33	27	679	36	0.7 (0.3–1.4)	0.35

*CI denotes confidence interval. Odds ratios are for the odds of seroconversion after exposure in workers with the risk factor as compared with those without it.

†P values were determined by the two-tailed Fisher's exact test.

‡The numbers are the numbers of subjects for whom data were available.

§Terminal illness was defined as disease leading to the death of the source patient from AIDS within two months after the health care worker's exposure.

cent) were exposed during 1990 to 1994, when postexposure use of zidovudine had become more common.[1] Among the 23 of these 25 case patients for whom information was available, 19 (83 percent) had been offered the drug (11 of 13 U.S. case patients and 8 of 10 European case patients). From September 1990 through August 1994, 268 of 338 controls (79 percent) had been offered zidovudine ($P = 1.0$). Among health care workers who were known to have been offered zidovudine, 9 case patients (47 percent) and 172 controls (64 percent) took the drug ($P = 0.15$).

Logistic-Regression Model

The final logistic-regression model, which included 33 case patients and 665 controls (14 controls were eliminated because of missing values), identified several risk factors that were associated with HIV transmission: deep injury, injury with a device that was visibly contaminated with the source patient's blood, procedures involving a needle placed in the source patient's vein or artery, and terminal illness in the source patient (Table 2). After control for these factors, no differences were detected in the rates at which case patients and controls were offered postexposure prophylaxis with zidovudine (odds ratio = 0.92, $P = 0.90$). However, case patients were significantly less likely to have taken zidovudine than controls (odds ratio = 0.19, $P = 0.003$). This is a classic example of confounding, since the adjusted odds ratio differed from the crude odds ratio (0.7) because zidovudine use was more likely among both case patients and controls after exposure characterized by one or more of the four risk factors in the model. These risk factors were more prevalent among case patients than among controls, indicating that the case patients had more serious exposure than the

TABLE 2. LOGISTIC-REGRESSION ANALYSIS OF RISK FACTORS FOR HIV TRANSMISSION AFTER PERCUTANEOUS EXPOSURE TO HIV-INFECTED BLOOD.

RISK FACTOR	U.S. CASES*	ALL CASES†
	adjusted odds ratio (95% CI)‡	
Deep injury	13 (4.4–42)	15 (6.0–41)
Visible blood on device	4.5 (1.4–16)	6.2 (2.2–21)
Procedure involving needle in artery or vein	3.6 (1.3–11)	4.3 (1.7–12)
Terminal illness in source patient§	8.5 (2.8–28)	5.6 (2.0–16)
Postexposure use of zidovudine	0.14 (0.03–0.47)	0.19 (0.06–0.52)

*All risk factors were significant ($P<0.02$).

†All risk factors were significant ($P<0.01$).

‡CI denotes confidence interval. Odds ratios are for the odds of seroconversion after exposure in workers with the risk factor as compared with those without it.

§Terminal illness was defined as disease leading to the death of the source patient from AIDS within two months after the health care worker's exposure.

TABLE 3. POSTEXPOSURE USE OF ZIDOVUDINE AMONG CASE PATIENTS AND CONTROLS, ACCORDING TO THE NUMBER OF RISK FACTORS PRESENT.*

NO. OF RISK FACTORS	CASE PATIENTS		CONTROLS		UNADJUSTED ODDS RATIO
	TOTAL	POSTEXPOSURE ZIDOVUDINE USE	TOTAL	POSTEXPOSURE ZIDOVUDINE USE	
	number (percent)				
0	0	—	128 (40)	40 (31)	—
1	3 (11)	0	124 (39)	51 (41)	0.20
2	11 (41)	2 (18)	55 (17)	33 (60)	0.15
3	8 (30)	1 (12)	12 (4)	7 (58)	0.10
4	5 (19)	5 (100)	1 (0.3)	0	33
Total	27 (100)	8 (30)	320 (100)	131 (41)	0.61

*Case patients and controls with missing values for one or more risk factors in Table 2 were excluded from the analysis. The Cochran–Mantel–Haenszel estimate of the odds ratio for postexposure use of zidovudine among these case patients and controls, with adjustment for the number of risk factors present, is 0.21 ($P=0.002$), whereas the estimate of the crude (unadjusted) odds ratio is 0.61 ($P=0.31$).

controls; hence, the crude odds ratio for zidovudine use was severely confounded.

In a separate analysis performed after we excluded case patients and controls with missing values for one or more of the risk factors and stratified subjects according to the number of risk factors present, the adjusted odds ratio for zidovudine use (0.21) obtained by Cochran–Mantel–Haenszel techniques was similar to the adjusted odds ratio calculated with the logistic-regression model (0.19) (Table 3). A significant ($P<0.05$) protective effect of zidovudine use was also observed after control for the influence of any two of the four risk factors.

No significant interactions were found among the risk factors in the model or between the risk factors and the missing-value indicators forced into the model (for visible blood on the device and terminal illness in the source patient). When all health care workers with missing values were excluded, all factors remained significant, with similar adjusted odds ratios but slightly larger confidence intervals. All factors in the model also remained significant when the analysis was restricted to case patients from the United States (Table 2).

Postexposure Zidovudine Regimens

Among the health care workers who took zidovudine, 67 percent of controls and 89 percent of case patients had their first dose within four hours after exposure ($P=0.28$). Sixty-six percent of controls and 44 percent of case patients continued postexposure prophylaxis for at least four weeks ($P=0.28$); 78 percent of controls and 75 percent of case patients took at least 1000 mg of zidovudine per day ($P=1.0$).

The degree of susceptibility of HIV strains from most source patients to zidovudine is unknown. Information about antiretroviral drugs taken by source patients at the time of exposure was available for 7 case patients and 124 controls who took zidovudine. In the case of 5 (71 percent) of the case patients and 87 (70 percent) of the controls, the source patients were receiving zidovudine at the time of the health care workers' exposure.

DISCUSSION

In this study, the risk of HIV transmission to a health care worker after percutaneous exposure to HIV-infected blood appeared to be influenced by several factors. Increased risk was associated with three factors that were probably indirect measures of the quantity of blood transferred in the exposure: deep injury, injury with a device that was visibly contaminated with the source patient's blood, and a procedure that involved a needle placed in the source patient's vein or artery, which means that the needle probably contained undiluted blood. When the logistic-regression analysis was restricted to needle sticks with hollow-bore needles, large-diameter needles were weakly associated with an increased risk of seroconversion ($P=0.08$), supporting the premise that the volume of blood involved is important. The risk of HIV transmission was also increased if a health care worker was exposed to blood from a source patient in the terminal stage of AIDS. This association is probably due to the higher titer of HIV in the blood of patients late in the course of AIDS, but it could possibly be due to other factors, such as syncytium-inducing HIV strains in these patients.[7,8]

After controlling for other factors associated with the risk of HIV transmission, our model indicated that the odds of HIV infection among health care workers who took zidovudine prophylactically after exposure were reduced by approximately 81 percent (95 percent confidence interval, 48 to 94 percent). Because it is difficult to control for known and unknown factors that contribute to HIV transmission, a retrospective case–control study is not the optimal design for assessing the efficacy of zidovudine; however, a prospective, placebo-controlled trial has not been possible.[1,5]

The apparent efficacy of postexposure prophylaxis with zidovudine in this study is consistent with data from other sources. In a prospective trial, administration of zidovudine to HIV-infected pregnant women and their infants reduced perinatal transmission by 67 percent[9]; a direct prophylactic effect on the fetus or infant was suggested, since only a small portion of the protective effect of zidovudine was due to a reduction of the HIV titer in maternal blood.[10]

Studies of antiretroviral chemoprophylaxis in animals have yielded mixed results, and their applicability to humans has been difficult to assess, but prophylaxis has prevented or ameliorated infection in several studies.[11,12]

Zidovudine is beneficial in the treatment of acute HIV infection in humans,[13] and its efficacy for postexposure prophylaxis would be consistent with a new understanding of HIV pathogenesis in which the virus is cleared by the human immune system while the immune system is still intact.[14] At least 13 instances of failure of postexposure prophylaxis with zidovudine in health care workers have been documented worldwide, indicating that any protection provided is not absolute.[15-17]

This study has several potential limitations, primarily because it was a retrospective review of surveillance data obtained from different sources and the number of case patients is relatively small. Reporting bias may have resulted if health care workers preferentially reported exposure that they believed was more likely to result in HIV transmission or for which they wanted zidovudine treatment (or both). This tendency would presumably be similar, however, among case patients and controls. Ascertainment bias may have affected some data, particularly subjective variables such as the severity of injury, because information for controls was obtained prospectively soon after exposure, whereas for some case patients, information was obtained after HIV seroconversion. However, for most variables there was objective documentation from incident reports and medical records.

We could not rule out, but did not identify, biases related to the use of zidovudine. If controls were more likely to have been offered zidovudine or more strongly encouraged to take it, the use of the drug might have been statistically associated with the absence of HIV seroconversion, even if the drug was not truly protective. Controls did not appear more likely than case patients to have been offered zidovudine, but it was impossible to assess whether controls may have been more strongly encouraged to take the drug. There was no difference in the rate of zidovudine use between the controls and health care workers who reported exposure to HIV in the hospitals participating in the CDC Needlestick Study but who did not complete the six-month follow-up.

The absence of statistically significant interaction terms in the logistic-regression model implies that the effect of zidovudine use was the same for all types of exposure and that the odds of HIV transmission after exposure was the product of the odds associated with each of the risk factors present. However, the small number of case patients made it very unlikely that we would find significant interactions in the analysis. There were no significant differences between zidovudine regimens (i.e., daily dose, duration of treatment, and interval between exposure and the initial dose) used by controls and case patients; however, the small number of case patients who took zidovudine limited our ability to detect such differences. Finally, in the case of approximately 70 percent of the case patients and controls who took zidovudine, the source patients were taking zidovudine at the time of the health care workers' exposure. If exposure to zidovudine-resistant virus was more common among case patients than controls, the efficacy of the drug after exposure to a sensitive virus may be even higher than we estimated.

The results of this study have important implications for the counseling and treatment of a health care worker after exposure to HIV and for public health. We estimate that the risk of transmission for exposure involving relatively large quantities of blood, particularly when the source patient's viral load is probably high, is higher than the average risk of 0.3 percent. This type of exposure should be a particular focus of preventive measures[18] and postexposure prophylaxis. Interviews of exposed health care workers should elicit information about factors associated with an increased risk of HIV transmission. Risk assessment should take into account the specific risk factors identified in this study, but it should be recognized that these factors are probably surrogates for an increased volume of blood and an increased viral load. Other factors, such as injection of blood or exposure involving a hollow-bore rather than a solid needle, may also be important but either were not assessed in this study or may not have been statistically significant because of the small number of cases involved.

In part on the basis of the results of this study, the Public Health Service and the International AIDS Society have recommended chemoprophylaxis after certain types of occupational exposure to HIV.[19-21] The decision to recommend prophylaxis and the drug used depend on the type of exposure; the likelihood of drug resistance in the source patient's HIV strain or strains is also a factor in drug selection. Since chemoprophylaxis should be initiated promptly after exposure, implementation of these recommendations requires rapid, confidential mechanisms for evaluating exposed health care workers, ascertaining the HIV status of source patients, and starting prophylaxis, if appropriate.[22,23] Although the current recommendations of the Public Health Service are limited to occupational exposure, others have extended these recommendations to include exposure related to sexual contact.[24] It is unclear, however, whether the extent of the protective effect of postexposure prophylaxis after percutaneous exposure to HIV-infected blood would be similar for other types of exposure.

Finally, the results of this study may interest expert review panels that determine which jobs are

appropriate for HIV-infected health care workers.[25] Although our study does not address this topic directly, it provides more precise documentation than was previously available regarding the influence of the volume of blood and stage of HIV infection on the risk of transmission after exposure to HIV-infected blood. The finding that the stage of AIDS of the source patient was an important predictor of the risk of HIV transmission suggests that previous estimates, which did not take into account the stage of HIV disease in infected health care workers, may have overestimated the risk to patients who were exposed to blood from health care workers in earlier stages of HIV infection.[26]

A major problem in developing recommendations for postexposure prophylaxis is the relatively limited amount of data on the safety and tolerability of new antiretroviral drugs in exposed, uninfected persons, most of whom would not become infected even without prophylaxis. To increase the amount of information available, health care providers in the United States are encouraged to enroll all workers who receive chemoprophylaxis in a national registry (without personal identifiers) at the following telephone number: 888-737-4448 (888-PEP-4HIV).

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