Morbidity and Mortality in South African Gold Miners: Impact of Untreated Disease Due to Human Immunodeficiency Virus

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A cohort of 1792 human immunodeficiency virus (HIV)–positive and 2970 HIV-negative South African miners was observed for 12 months starting in February 1998. All-cause hospitalizations and deaths were significantly associated with HIV infection (respective unadjusted incidence rate ratios, 2.9 and 9.2; respective 95% confidence intervals, 2.5–3.4 and 5.5–16.0). Tuberculosis (TB), bacterial pneumonia, cryptococcosis, and trauma were the major causes of admission for HIV-positive patients, whereas *Pneumocystis carinii* pneumonia was an uncommon cause (respective admission rates, 8.5, 6.9, 2.2, 6.0, and 0.53 admissions per 100 person-years). Enteritis, bronchitis, urinary tract infections, and soft-tissue infections were also significantly associated with HIV infection. Cryptococcosis caused 44% of deaths among HIV-positive patients. Trauma was the main hazard for HIV-negative men, causing 42% of admissions and 60% of deaths. A broad range of infectious conditions is significantly associated with HIV infection in South African miners. Identification and implementation of effective prophylactic regimens are urgently needed.

In 7 countries in the southern region of Africa, the estimated prevalence of HIV infection among adults was ⩾20% by the end of the year 2000 [1], which inevitably translated into a huge increase in the need for health care. Despite the gravity of the situation, research into the clinical aspects of HIV infection in southern Africa has not been prioritized, and the natural history of HIV infection in the region remains poorly characterized [2]. A clear understanding of how HIV affects the frequency and etiology of common illnesses facilitates good clinical management, points the way to interventions likely to reduce HIV infection–associated morbidity and mortality rates, and provides a firm basis for advocacy and planning.

We report a prospective cohort study that compared hospitalization and mortality rates between HIV-positive and HIV-negative South African gold miners. During follow-up, the prevalence of HIV infection was 24% in the workforce evaluated [3], which primarily included male migrant workers living in single-sex hostels. Rates of trauma, sexually transmitted disease (STD), and silica-associated occupational disease are high [4, 5]. In recent years, the incidence of tuberculosis (TB) has increased to extremely high rates (figure 1) as a result of the combined effects of the HIV epidemic and the exposure to silica dust [8, 9]. The main aims of the study were to quantify the impact of HIV infection on the incidence and spectrum of diseases leading to hospitalization or death and to assess the scope for preventive interventions in this population.

Received 17 September 2001; revised 4 December 2001; electronically published 5 April 2002.

Financial support: Wellcome Trust, United Kingdom.

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Clinical Infectious Diseases 2002; 34:1251–8

1058-4838/2002/3409-0013$03.00

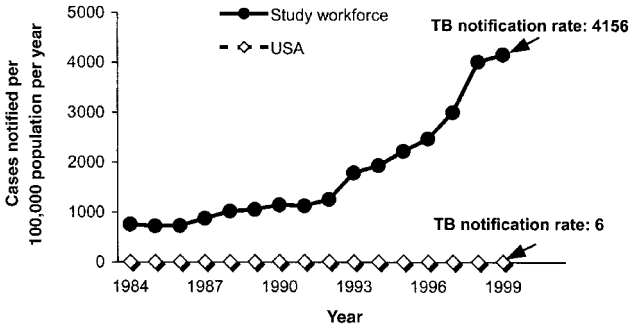

Figure 1. Time trend in tuberculosis (TB) case notification rates among the study workforce of South African gold miners, compared with the rates for the general population of the United States. Figures for the United States are from the World Health Organization [6]. Workforce TB figures are from the Chamber of Mines, South Africa [7].

METHODS

Study population and cohort selection. In South Africa, gold miners are provided with private medical care at company-funded hospitals and clinics. In the study hospital (Ernest Oppenheimer Hospital; Welkom), HIV testing has been offered, since 1991, to all patients presenting with HIV-associated conditions; consent is obtained from all miners, and pre- and posttest counseling is available. Hospital laboratory and payroll records were used to identify all current employees who had been tested for HIV since 1991. All men who had tested positive for HIV were included in the study, as were men who had tested negative for HIV because of an STD in 1994 or later. The cutoff date was imposed because of the increasing cumulative risk of new HIV infection as time passed after a negative HIV test result was obtained. Additional HIV testing to confirm negative status was not performed because of logistic and financial constraints. However, miners who presented with HIV-associated conditions during follow-up were asked to consent to retesting. Miners provided informed consent and received pre- and posttest counseling; they were excluded from the final analysis if they were subsequently found to be HIV positive. Participants who declined retesting were assumed to have remained HIV negative.

Cohort follow-up. Cohort subjects were observed for 12 months, starting in February 1998; we assessed admission to the study hospital and/or death. Admissions to other facilities were identified when emergency transfers were requested. However, because the town in which the study took place (Welkom) was geographically isolated, and because the hospital was the only source of free health care and sickness benefits, use of other inpatient facilities was minimal. Hospitalized participants were interviewed and examined according to a standardized protocol, and they were observed until discharge from the hospital or death. HIV-positive participants were asked to provide consent for measurement of their $CD4^+$ T lymphocyte count.

Gold miners who left employment or died were periodically identified by review of payroll, death benefit, and mortuary records. Routine heart and lung postmortem examinations for occupational diseases were performed for men who died in the hospital or in the vicinity of the mine. Postmortem findings were reviewed by the senior histopathologist at the National Centre for Occupational Health (Johannesburg).

Laboratory methods. $CD4^+$ T lymphocyte counts were measured by flow cytometry (FACScan; Becton Dickinson). Microscopic evaluation for TB was performed with auramine staining of concentrated specimens. Mycobacterial culture was performed using Lowenstein-Jensen slopes for sputum specimens and BACTEC (Becton Dickinson) liquid media for other specimens. *Mycobacterium tuberculosis* was identified with a colorimetric ribosomal RNA hybridization test (AccuProbe *M. tuberculosis* complex probe kit; Gen-Probe). Bacterial pathogens were identified by Gram staining and biochemical testing done after culture was performed with conventional media. Fungal identification was done by use of India ink contrast staining and microscopic evaluation, culture with Sabouraud media, and, for diluted blood or CSF specimens, latex agglutination testing for cryptococcal antigens. *Pneumocystis carinii* infection was diagnosed by microscopic evaluation of specimens stained with Grocott-Gomori methenamine–silver nitrate.

Case definitions. The main reason for admission to the hospital was determined for each patient on the basis of predefined case definitions (not detailed here) that incorporated clinical, radiologic, laboratory, and, if relevant, postmortem findings. The 1993 Centers for Disease Control and Prevention case definition for AIDS was followed, except that CD4 cell count criteria were not used [10].

Ethical considerations. The study was approved by the ethics committees of the London School of Hygiene and Tropical Medicine (London) and the Ernest Oppenheimer Hospital (Welkom, South Africa). To maintain confidentiality, consent to participate in the study was obtained from hospitalized patients before their HIV test results were referenced. Additional testing and counseling were freely available.

Data analysis. Data were analyzed with Stata software, version 7.0 (Stata Corporation). Patient records were expanded into person-year follow-up records, according to each patient's age and reason for hospital admission. For all gold miners, separate records were created for each period between entry into the cohort and first admission (where relevant), between any subsequent hospital admissions, and then from last event to the end of the follow-up period. Poisson regression was used to calculate univariate incidence rate ratios (IRRs) from the expanded data set. For analyses in which multiple events were possible, random rate multipliers (assumed to follow a γ distribution) were used to adjust rate ratio and 95% CI estimates for individual "frailty" effects, because rehospitalization rates

were significantly greater than predicted by the Poisson distribution alone. Otherwise, IRRs were not adjusted.

For variables with >2 categories, tests for trend were calculated using likelihood-ratio tests. The Mann-Whitney test was used to test differences in $CD4^+$ T lymphocyte counts for significance between subgroups of HIV-positive patients, according to admission and outcome categories.

RESULTS

The final cohort comprised 1792 HIV-positive men (38%) and 2970 HIV-negative men (62%). Baseline characteristics and cohort events are shown in table 1. The rate of leaving employment was significantly higher among HIV-positive employees than it was among HIV-negative employees (18.4 and 15.3 persons left employment per 100 person-years, respectively; IRR, 1.2; 95% CI, 1.03–1.4), but there were no significant differences in age or duration of employment.

Hospitalization rates among HIV-negative gold miners. There were 363 admissions to the hospital among HIV-negative men, for a rate of 14 hospitalizations per 100 person-years. Information about the hospitalizations is listed in table 2, and the main causes are illustrated in figure 2. Most admissions were related to trauma. Of the patients included in the final analysis, all of those with pneumonia and enteritis and all but 2 with TB (who declined additional testing) were confirmed to be HIV negative at admission.

Hospitalization rates among HIV-positive miners. For HIV-positive men, there were 599 admissions to the hospital. The overall rate was significantly higher than that for HIV-negative men (40.0 admissions to the hospital per 100 person-years; IRR, 2.9; 95% CI, 2.5–3.4). Infectious diseases were responsible for 70% of admissions to the hospital for HIV-positive men, as opposed to 30% of the admissions for HIV-negative men ($P < .001$). Incidence rates and rate ratios are shown in table 2, and the main causes are illustrated in figure 2.

The most frequent reasons for hospitalization of members of the HIV-positive cohort were TB (8.5 hospitalizations per 100 person-years), acute pneumonia (6.9 per 100 person-years), cryptococcosis (2.2 per 100 person-years), and trauma (6.0 per 100 person-years). *P. carinii* pneumonia (PCP) was uncommon, and there was only 1 diagnosis of HIV wasting syndrome. Admissions to the hospital because of TB, acute pneumonia, bronchitis, enteritis, soft-tissue infections, urinary tract infections, cryptococcosis, PCP, or conditions due to viral infections were each significantly associated with HIV infection (table 2).

$CD4^+$ T lymphocyte counts are shown, according to cause and outcome of admission, in figure 3. Not all HIV-positive men consented to provide additional blood samples to allow us to test for $CD4^+$ T lymphocyte counts. $CD4^+$ T lymphocyte counts in HIV-positive men with TB were significantly higher ($P < .01$) than were counts for patients with cryptococcal disease or other AIDS-defining diagnoses, but they did not differ significantly from the $CD4^+$ T lymphocyte counts for patients with pneumonia or enteritis. The highest $CD4^+$ T lymphocyte counts were in trauma and surgical patients.

Table 1. Baseline characteristics of South African gold miners and events that occurred during follow-up.

Characteristic or event	HIV-positive patients (n = 1792)	HIV-negative patients (n = 2970)
Age, mean years ± SD	37.9 ± 7.2	37.7 ± 7.1
Time employed as a miner, mean years ± SD	14.4 ± 7.8	14.5 ± 7.5
No. of person-years (mean no. per subject)	1498 (0.84)	2590 (0.87)
Admission to the hospital	453 (25)	311 (10)
⩾2 hospitalizations during follow-up	108 (6)	40 (1.3)
Death	82 (5)	15 (0.5)
Left employment[a]	275 (15)	395 (13)

NOTE. Data are no. (%) of patients, unless otherwise indicated. No. of patients reflects cohort selection methods.

[a] For reasons other than death.

Rehospitalizations. Rehospitalization rates were significantly higher than the incidence rate for first admissions (for HIV-positive men with and without a previous admission during the study, 75 and 35 rehospitalizations per 100 person-years, respectively; IRR, 2.18; 95% CI, 1.8–2.6). Infections were again the predominant cause (106 [70%] of 151 rehospitalizations and 317 [70%] of 448 first admissions), but pneumonia, rather than TB, was the most common cause among HIV-positive men (38 [25%] and 12 [8%] of the 151 recurrent admissions, respectively).

Rate and main causes of death. The rate of death was significantly higher among HIV-positive men than it was among HIV-negative men (5.5 and 0.6 deaths per 100 person-years, respectively; IRR, 9.2; 95% CI, 5.5–16.0). Cause of death, according to HIV infection status, is illustrated in figure 4. The most common causes of death were cryptococcal disease, in HIV-positive men, and trauma, in HIV-negative men. Postmortem examination was performed for 51 (62%) of 82 HIV-positive patients who died and for 14 (93%) of 15 HIV-negative patients who died. HIV-positive men who died after being admitted to the hospital or within 2 weeks of discharge (defined as a fatal outcome for that admission) had significantly lower $CD4^+$ T lymphocyte counts than did those with nonfatal outcomes (respective median $CD4^+$ T lymphocyte counts, 36 and 209×10^6 cells/L; $P < .001$). Overall, 7.7% of HIV-positive patients and 3.6% of HIV-negative patients admitted to the hospital died ($P = .01$).

Disease-specific microbiologic data and clinical presentation. Data regarding relevant isolates recovered from patients

Table 2. Impact of HIV infection on rates of admission to the hospital for different conditions.

Condition	No. of admissions		Admission rates per 100 person-years		IRR (95% CI)[a]
	HIV-positive patients	HIV-negative patients	HIV-positive patients	HIV-negative patients	
Mycobacterial disease					
Tuberculosis	128	15	8.5	0.58	14.8 (8.7–25.2)
Mycobacterium kansasii disease[b]	3	3	0.20	0.12	1.7 (0.3–8.6)
Bacterial infection					
Acute pneumonia[c]	103	5	6.9	0.19	35.9 (14.5–89.0)
Enteritis	27	7	1.8	0.27	6.7 (2.9–15.5)
Traumatic wound infection	19	19	1.3	0.73	1.7 (0.9–3.4)
Bronchitis[d]	17	7	1.1	0.27	4.2 (1.7–10.1)
Urinary tract infection	14	2	0.93	0.08	12.1 (2.6–56.6)
Perianal abscess	13	10	0.87	0.39	2.3 (0.9–5.8)
Spontaneous soft-tissue infection[e]	12	7	0.80	0.27	3.0 (1.2–7.5)
Ear, nose, and throat infections	10	12	0.67	0.46	1.4 (0.6–3.5)
Other[f]	5	4	0.33	0.15	2.2 (0.6–8.0)
Fungal infection					
Cryptococcosis	33	0	2.2	0	∞ (—)[g]
Pneumocystis carinii pneumonia	8	0	0.53	0	∞ (—)[g]
Esophageal candidiasis	1	0	0.07	0	∞ (—)[h]
Other infection					
Parasitic[i]	6	12	0.40	0.46	0.8 (0.3–2.5)
Viral[j]	15	6	1.0	0.23	4.3 (1.6–11.5)
Self-limiting fever	2	1	0.13	0.04	3.5 (0.3–38.1)
Other AIDS-defining diagnoses[k]	3	0	0.20	—	— (—)
Other medical causes	49	56	3.3	2.2	1.5 (0.9–2.5)
Traumatic injury					
Occupational	38	78	2.5	3.0	0.8 (0.6–1.2)
Nonoccupational	39	47	2.6	1.8	1.4 (0.9–2.2)
Later complications[l]	14	25	0.93	0.97	1.0 (0.5–1.9)
Other surgical causes	30	45	2.0	1.7	1.2 (0.7–1.9)
Total[m]	599	363	40.0	14.0	2.9 (2.5–3.4)

NOTE. IRR, incidence rate ratio.

[a] Adjusted for overdispersion if recurrent admissions were possible (see the data analysis subsection in the Methods section).

[b] All pulmonary *M. kansasii* disease, which is associated with mining in South Africa.

[c] Includes 16 admissions to the hospital for recurrent pneumonia in 14 HIV-positive men.

[d] Distinguished from pneumonia by absence of radiographic changes.

[e] Includes cellulitis, erysipelas, and a single case of necrotizing fasciitis.

[f] Includes intra-abdominal sepsis, chancroid, gastritis due to *Helicobacter* species, and neurosyphilis.

[g] $P = .001$.

[h] $P = .16$.

[i] Includes malaria, neurocysticercosis, and urinary schistosomiasis.

[j] Includes chickenpox, shingles, acute hepatitis B virus infection, genital warts, and genital herpes.

[k] Includes 1 patient with cerebral space-occupying lesion that did not respond to toxoplasmosis treatment, 1 with HIV encephalopathy, and 1 with HIV wasting syndrome.

[l] Does not include wound infections.

[m] Includes admissions to the hospital for an additional 10 HIV-positive and 2 HIV-negative patients not categorized above (2 admissions for palliative care for progression of cryptococcal disease, and 10 admissions for episodes of suspected tuberculosis that did not meet the study case definitions).

with TB, cryptococcosis, pneumonia, and enteritis, according to the patient's HIV infection status, are shown in table 3. The most frequently identified pathogens in HIV-positive men were *M. tuberculosis*, pneumococcus, and *Cryptococcus* species.

Seroconversion in the HIV-negative group. As detailed in the Methods section, the interval between the date that a negative HIV test result was obtained and the start of the study was as long as 5 years for some men, so that some men had become

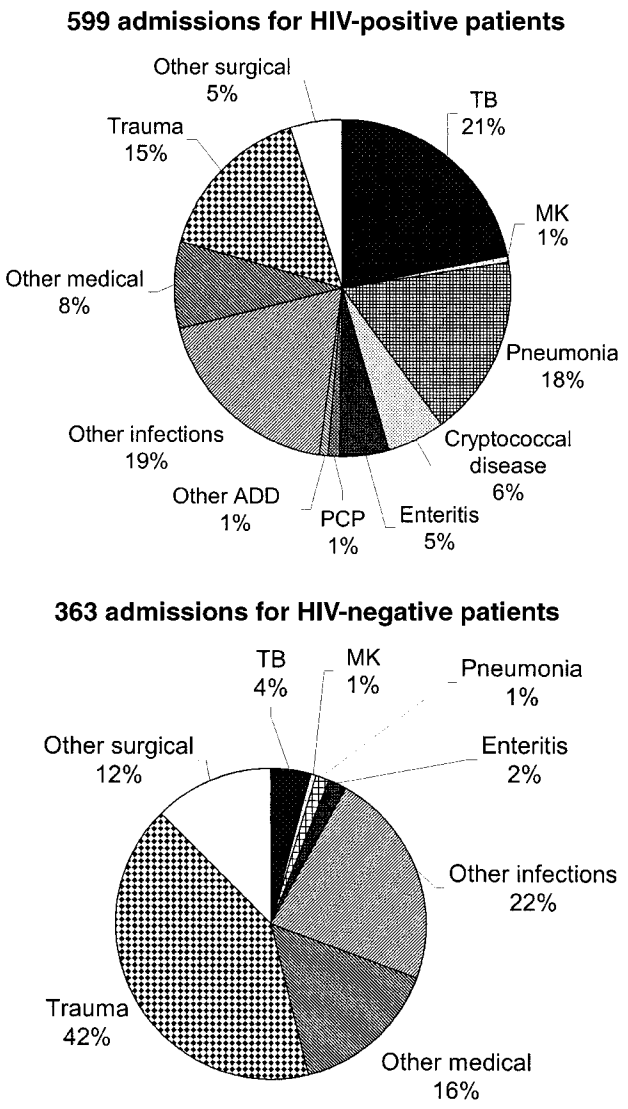

Figure 2. Causes of hospitalization, according to HIV infection status. See table 2 for numbers of admissions and incidence rates. ADD, AIDS-defining diagnoses; MK, *Mycobacterium kansasii* disease; PCP, *Pneumocystis carinii* pneumonia; TB, tuberculosis.

HIV infected during this interval. As discussed in the Methods section, the admission and person-years data from men who were initially included in the HIV-negative arm of the cohort, but who were subsequently found to be HIV positive, were excluded from the final analysis. Altogether, 201 men (6% of the 3172 men initially selected into the HIV-negative cohort) and 187 (7% of a total of 2777 person-years observed for the initially selected HIV-negative cohort) were excluded because of a positive HIV test result obtained during the study period.

In most cases (123 [61%] of 201), the indication for additional HIV testing was for a symptomatic STD, and retesting was performed during outpatient clinic visits. For the remaining 78 patients (39%), however, the indication for retesting was because of admission to the hospital with an HIV-associated condition. Men with previously unidentified seroconversion to HIV-positive status accounted for 16 pneumonia admissions, 26 TB admissions, and 3 cryptococcal disease admissions. If we assume that hospitalization for HIV-associated diseases occurred at the same rate as that for the HIV-positive cohort, then the admission data from excluded men can be used to provide estimates of the total HIV prevalence for men in the initially selected HIV-negative cohort. For example, if the rate of admissions for cryptococcal disease was 2.2 admissions per 100 person-years for all HIV-positive miners, then 136 HIV-positive person-years of follow-up would be required to produce the 3 persons admitted from the initially selected HIV-negative cohort. This allows us to estimate that 5% (136 of 2777 person-years of observation) of the initially selected HIV-negative cohort was, in fact, HIV positive. Equivalent calculations for TB and pneumonia give estimates of HIV prevalence of 11% (306 of 2777 person-years) and 10% (275 of 2777) in the initially selected HIV-negative cohort. Because 6% of the initially selected HIV-negative cohort and 7% of the person-years of observation were identified as being HIV positive and were excluded from the final analysis, then the aforementioned

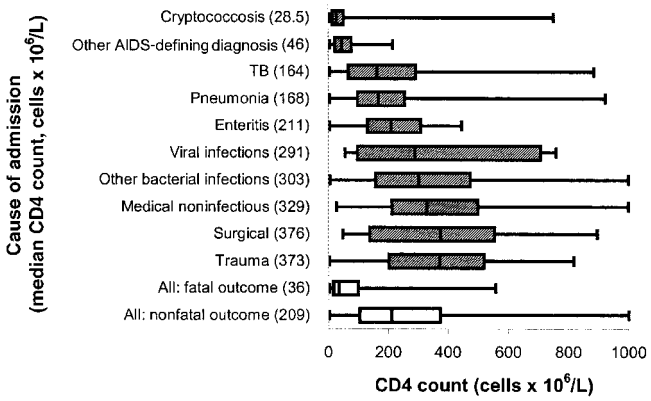

Figure 3. Box-and-whisker plot showing median and range of $CD4^+$ T lymphocyte counts, according to cause and outcome of admission. Lower and upper line bars show the minimum and maximum $CD4^+$ T lymphocyte counts recorded for each admission category, up to a maximum of 1000×10^6 cells/L. The lower, middle, and upper points on the solid bars denote the 25th percentile, median, and 75th percentile, respectively. Median values are also shown in parentheses after the admission categories. Values were based on $CD4^+$ T lymphocyte counts recorded at admission to the hospital for 114 patients with tuberculosis (TB; 89%); 96 patients with pneumonia (93%); 28 patients with cryptococcal disease (85%); 23 patients with enteritis (85%); 10 patients with other AIDS-defining conditions (83%); 47 patients with other bacterial infections (52%); 7 patients with viral infections (47%); 33 patients with other medical conditions (67%); 32 patients with trauma (42%; not including complications); 11 patients with other surgical conditions (37%); and patients who were admitted to the hospital who had fatal (33 patients [72%]) and nonfatal (395 patients [71%]) outcomes, respectively.

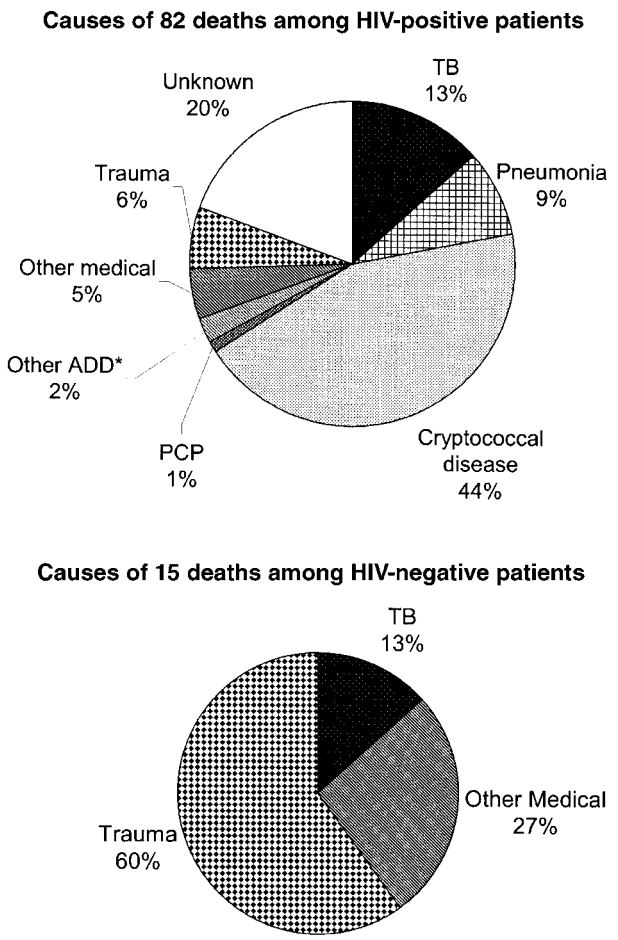

Figure 4. Cause of death, according to HIV infection status. ADD, AIDS-defining diagnoses; PCP, *Pneumocystis carinii* pneumonia; TB, tuberculosis.

estimated range of HIV prevalence of 5% to 11% suggests that most of the HIV-positive men were identified during the study year.

DISCUSSION

This study describes the impact of HIV infection on the incidence and spectrum of disease in South African gold miners. HIV infection greatly increased rates of hospitalization and death as a result of significantly increased rates of a range of different infectious diseases. TB was the single most common cause of hospitalization for the HIV-positive cohort. The grave consequences of the HIV epidemic on TB control at the workforce level are shown in figure 1 [6, 7]. Bacterial pneumonia, cryptococcal disease, and acute enteritis were also important HIV-associated opportunistic infections, with cryptococcal disease being the most common cause of death.

There are both similarities to and differences with other studies of HIV-associated disease in Africans [2, 11–24]. Greatly increased rates of TB and bacterial pneumonia are consistently associated with HIV disease in Africa, although there is an extra occupational component to TB in gold miners because of their exposure to silica dust [9], and rates of pneumococcal disease in newly recruited miners were high even before the HIV epidemic [25]. Rates of acute pneumonia as variable as 9.3 [19], 3.0 [23], and 1.8 [18] cases per 100 person-years were observed in the placebo arms of 3 randomized, controlled trials involving HIV-positive Africans. Two of these trials investigated treatment with cotrimoxazole in Abidjan, Cote d'Ivoire [18, 19], and the other trial studied pneumococcal vaccination in Ugandans [23]. Important differences in ascertainment are likely to have existed, however, because 2 of the studies included outpatients [19, 23], whereas the study with the lowest rate of acute pneumonia included hospitalized patients only [18].

Acute enteritis was the most common gastrointestinal com-

Table 3. Disease-specific microbiologic findings, according to HIV infection status.

Disease and isolate	HIV-positive patients	HIV-negative patients
Tuberculosis		
No. of cases	128	15
Smear and culture negative	9 (7)	0 (0)
Smear positive, culture negative, or not done	20 (16)	3 (20)
Smear negative, culture positive	23 (18)	1 (7)
Smear and culture positive	76 (59)	11 (73)
Cryptococcosis		
No. of cases	33	0
Culture positive	26 (79)	—
Antigen positive, culture negative	4 (12)	—
Biopsy or postmortem diagnosis	3 (9)	—
Pneumonia		
No. of cases	103	5
Pneumococcus	32 (31)	1 (20)
Haemophilus influenzae	8 (8)	0 (0)
Klebsiella species	5 (5)	0 (0)
Pseudomonas species	2 (2)	0 (0)
Staphylococcus aureus	1 (1)	0 (0)
Escherichia coli	1 (1)	0 (0)
None	54 (52)	4 (80)
Enteritis		
No. of cases	27	7
Salmonella species	5 (19)	0 (0)
Shigella species	3 (11)	1 (14)
Cryptosporidia	1 (4)	0 (0)
None	18 (67)	6 (86)

NOTE. Data are no. (%) of episodes of respective disease, unless otherwise indicated.

plaint and was significantly associated with HIV infection. Chronic diarrhea, wasting syndrome, and enteric fever–like illness due to nontyphoidal *Salmonella* species are among the most common serious illnesses noted in studies of HIV infection from other parts of Africa [11, 13, 15, 18–20], but this was not the case in the present study. The relative scarcity of gastrointestinal symptoms in the current study may reflect regional differences, or it may indicate that sanitation and water supplies in gold mines are unusually good for Africa. PCP and pulmonary Kaposi's sarcoma both occurred, albeit at low rates, and other AIDS-defining conditions, such as cerebral toxoplasmosis, cytomegalovirus disease, and disseminated *Mycobacterium avium intracellulare,* were notable for their absence, despite the availability of appropriate diagnostic facilities and expertise.

Overall mortality rates and the relative risk of death for HIV-positive gold miners in this study were within the range observed in other African cohorts [15, 21, 22, 24, 26], but at the lower end. The high proportion of deaths due to cryptococcosis is noteworthy. Although there are no other regional incidence estimates, a high risk of cryptococcal disease appears to be a general feature of HIV in southern Africa [27–30] that is not shared throughout the continent. Absolute incidence rates of cryptococcosis were <1 case per 100 person-years, and cryptococcosis was responsible for a much lower proportion of hospital admissions and deaths in both of the Abidjan cotrimoxazole trial cohorts [18, 19] and in rural Uganda [20].

The main strengths of this study are its unusually large size, inclusion of both HIV-positive and HIV-negative cohorts, and unusually good diagnostic facilities plus a high coverage of postmortem examinations. These factors have enabled us to develop an unusually detailed description of the situation, with the impact of HIV infection clearly distinguished from that of HIV-negative disease. The main limitations of our report are the unusual population studied, which may well have altered the spectrum of disease seen, and the reliance on routine clinical services. We estimate that 6%–9% of the HIV-negative patients in our study had acquired HIV infection after their initial HIV test, but not all of these patients were identified and excluded during follow-up. This may have artificially increased our estimated rates of disease among HIV-negative patients, thereby underestimating the impact of HIV infection, although the potential for this was minimized by the high consent rates to retesting of patients with strongly HIV-related conditions. There is likely to have been a substantial "healthy worker" effect in our HIV-positive cohort, because the rate of leaving employment increased once workers became symptomatic, leading to reduced disease rates. On the other hand, our HIV-positive cohort was made up of prevalent (rather than incident) cases, including individuals identified through symptomatic HIV disease as well as STDs, resulting in an opposing bias toward inclusion of individuals with more-advanced HIV disease.

HIV prevalence in the study workforce was 24% by 1999 [3]. Our observed rates of hospital admission and death imply that, by 1999, general workforce death rates had tripled as a consequence of the HIV epidemic, and the rates of hospital admission had increased 1.5-fold. The scale of the impact of untreated HIV infection at such a high prevalence, and the huge toll from preventable opportunistic infections, such as TB [31], bacterial infections [18, 19], and cryptococcosis [32], greatly exceed the level of uncertainty surrounding these estimates. After completion of this study, routine outpatient clinics offering isoniazid and cotrimoxazole prophylaxis have been started, and provision of additional therapies, including highly active antiretroviral drugs and prophylactic fluconazole, is now being considered. Increased access to the means of HIV diagnosis and treatment is urgently required throughout southern Africa.

Acknowledgments

We acknowledge the contributions of Edison Zulu and Themba Moyake, for translation and counseling, and the cooperation of the ward nurses.

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