The incidence of human immunodeficiency virus type 1 (HIV-1) infection among opiate users was determined in a retrospective cohort of 436 patients with multiple admissions to the only inpatient drug treatment program in northern Thailand between October 1993 and September 1995. During 323.4 person-years of follow-up, 60 patients presenting for detoxification acquired HIV-1 infection, for a crude incidence rate of 18.6 per 100 person-years (95% confidence interval 14.4-23.9). All seroconverters were male. HIV-1 incidence varied by the current route of drug administration: 31.3 per 100 person-years for injectors and 2.8 per 100 person-years for noninjectors (smoking and ingestion). Significant differences were found by ethnicity: HIV-1 incidence was 29.3 per 100 person-years for Thai lowlanders and 8.5 per 100 person-years for hilltribes. Multivariate relative risk estimates showed that injecting opiates (vs. use by other routes), being unmarried, being under age 40 years, being a Thai lowlander, having a primary and secondary education, and being employed in the business sector were each independently associated with human immunodeficiency virus seroconversion. This HIV-1 incidence rate is double that reported for Bangkok and suggests that prevention and control programs for drug users need to be expanded throughout Thailand. Improved availability of more-effective treatment regimens and increased access to sterile injection equipment are needed to confront the HIV-1 epidemic among opiate users in northern Thailand. Am J Epidemiol 1999; 149:558-64.

drug utilization; ethnic groups; HIV-1; incidence
To our knowledge, no studies on HIV incidence or risk factors among opiate users in Thailand, outside of Bangkok, have been reported. The six upper-northern provinces comprise only 12 percent of the nation’s population but account for approximately half of all reports of acquired immunodeficiency syndrome to the Ministry of Public Health (11). As this area borders Burma and Laos, completing the infamous “Golden Triangle,” the source of much of the world’s production of raw opium, it is critical to determine the burden of HIV-1 infection among drug users to plan for public health needs (12). In addition, this region is home to the many hilltribes, some of whom have a long history of opium cultivation as well as the use of unprocessed opium by inhalation (smoking) (13), and many have been affected by the drug interdiction efforts of both Thai and Western governments.

MATERIALS AND METHODS

Study population

The Department of Medical Services of the Royal Thai Ministry of Public Health administers regional comprehensive detoxification and drug treatment facilities in Thailand. The Northern Drug Treatment Center (the Center) in Mae Rim (Chiang Mai Province) is the referral center for the 17 northern provinces. Treatment is provided free of charge to patients who present voluntarily. The Center has a census of 185 patients who undergo detoxification in a 21-day treatment regimen. Staff estimate that relapse occurs among 90 percent of treated patients. Of a total of 2,980 patients (4,196 admissions) seen for a first admission during the 2-year study period, 436 (14.6 percent) were admitted two or more times during the study period. We report data on HIV-1 incidence among a retrospective cohort of 436 patients (382 with two admissions, 44 with three admissions, six with four admissions, one with five admissions, and three with six admissions) admitted to the Center between October 1993 and September 1995.

Incidence of HIV-1 Infection

Patients are screened routinely for antibodies to HIV-1 on admission to the Center. All patients with negative HIV-1 antibody test results on enzyme-linked immunosorbent assay formed the study cohort. Those who had a subsequent admission during that 2-year period after their initial seronegative admissions were tested again for HIV-1 infection. Patents whose sera were repeatedly reactive on enzyme-linked immunosorbent assay from two manufacturers were considered to have seroconverted to HIV-1 infection; confirmation of enzyme-linked immunosorbent assay results by Western blot was not routinely performed.

Risk factors for HIV-1 seroconversion

Upon first admission during the study interval, patients were interviewed by a social worker about their sociodemographic background (age, gender, ethnicity, education, occupation, and religion) and drug use history (principal drug of choice and usual route of administration). Two types of opiates were assessed—heroin and unprocessed opium. The routes of drug administration were by injection and noninjection (smoking or ingestion). Patients were classified as heroin users upon reporting heroin use regardless of whether they said they had used opium. Similarly, patients were classified as injectors once they reported injecting drugs regardless of whether they had also used other routes of administration. Ethnicity was assessed at baseline, and patients were classified as Thai lowlanders (ethnic Thais) or as one of several ethnic minorities, commonly referred to as “hilltribes” based on self-identified culture or language. These groups include the Shan and Karen (of Burmese origin); the Hmong and Yao (migrants from southwest China and Laos); Akha, Lisu, and Lahu (highland agriculturalists); and Yunnanese (Han Chinese immigrants). Ethnicity was analyzed as a dichotomy (Thai lowlanders vs. hilltribes) due to the small number of persons followed.

While men comprise the majority of drug users and treated patients, some women also seek treatment for opiate use. Age was stratified by decade (≤19, 20–29, 30–39, and ≥40 years). Religious affiliation was categorized as Buddhist and others (comprising animism, Christianity, Islam, and others). Marital status was categorized into two groups: married and unmarried (never married, separated, divorced and widowed). Educational attainment was classified in three groups: no formal education, primary and secondary education, and vocational schools and university. Finally, employment status was categorized into three groups: students and civil servants; laborers, including those in agriculture and the seasonally unemployed; and persons employed in the business sector. Students and civil servants represent higher education and social status and were therefore combined. Information on sexual behavior, history of sexually transmitted diseases, and condom use practices was not available.

Statistical analysis

Incidence rates of HIV-1 infection were compared among groups classified according to route of drug administration and type of drug as well as ethnicity.
We used Poisson regression analysis, in which time was measured in days between entry into the study and first readmission, when HIV-1 seroconversion was detected. Person-days of exposure were then accumulated over the cohort and converted to person-years of observation. The assigned date of seroconversion was the midpoint between the last HIV-negative antibody test and the date of the first HIV-positive antibody result. Incidence rates of HIV-1 seroconversion were then calculated per 100 person-years of observation. We used Poisson regression to calculate adjusted rate ratios and 95 percent confidence intervals, which were estimated from the profile likelihood of the Poisson regression model for each drug-use variable (14, 15).

RESULTS

During the 323.4 person-years of follow-up (mean = 0.79 years and 0.44 years for HIV seronegatives and seroconverters, respectively), 60 individuals seroconverted to HIV-1 infection. The crude incidence rate was 18.6 per 100 person-years (95 percent confidence interval (CI) 14.4–23.9). The crude incidence rate for men was 20.8 per 100 person-years (95 percent CI 16.2–26.8); there were no seroconversions identified among women during the study period. All remaining analyses were therefore performed only for the male patients. The HIV incidence rates by route of opiate administration were 31.3 per 100 person-years (95 percent CI 24.1–40.6) and 2.8 per 100 person-years (95 percent CI 0.9–8.8) for injectors and noninjectors, respectively. The ethnicity-specific crude HIV-1 incidence rates were 29.3 per 100 person-years (95 percent CI 22.2–38.6) and 8.5 per 100 person-years (95 percent CI 4.6–15.8) for Thai lowlanders and hilltribes, respectively.

Those aged 20–29 and 30–39 years had more than twice the incidence as did those age 40 years and over (table 1). Buddhists experienced HIV-1 seroconversion five times more frequently than did persons avowing other religious preferences, although religion is confounded with ethnicity in this sample. Virtually all lowland Thais are Buddhist, while many hilltribes practice other religions. Compared with persons who were married, those who were unmarried were more than twice as likely to seroconvert to HIV-1 infection during the follow-up period. Finally, compared with patients who reported no formal education, drug users who reported completing primary (compulsory) or secondary education were more than three times as likely to be HIV-1 seroconverters. Individuals with a vocational or university education had a slightly higher seroconversion experience than did those with no education, but the rate ratio was not statistically significant.

An estimate of the independent contribution of the risk factors found to be associated with HIV-1 seroconversion in univariate analysis was obtained using Poisson regression analysis (table 2). Variables that continued to be significant in this analysis were occupation, marital status, and route of drug administration (table 2). All injectors (n = 264) were heroin users, and noninjectors (n = 129) were opium users, except for three patients who reported having smoked heroin.

To assess the extent to which individuals with more than one admission might represent a biased sample, we compared the baseline data for patients with multiple admissions with those who had a single admission during the study interval to estimate the possible bias in our incidence estimates (table 3). No differences were seen by gender or marital status. However, more patients in the age group 30–39 years were readmitted, and fewer were age less than 20 or 40 or more years. In addition, those with multiple admissions were more likely to be Thai lowlanders, to have a higher level of education, and to inject heroin. Thus, hilltribes, who more commonly were opium smokers, agrarian-based, and poorly educated, were less likely to return to the Center.

DISCUSSION

The HIV-1 incidence in this cohort is much higher than that reported for Bangkok, although it is lower than the incidence rate during the peak of the 1988 epidemic, when a rate of 50 per 100 person-years was reported (10). The seroconversion rate for lowland Thai drug users appears to be associated with the risk of parenteral exposure, presumably reflecting higher probability of exposure to HIV-contaminated injection equipment. In multivariate analysis, injection (vs. noninjection) was the strongest predictor of incident HIV-1 infection. The lower HIV-1 incidence among the hilltribes is probably due to their more frequent use of opiates by smoking or ingestion. This inference is substantiated by the independent risks in multivariate analysis associated with both injection (vs. noninjection) and heroin (vs. opium) use (data not shown). A recent report on HIV prevalence among hilltribes (16) shows widely varying rates: Villages that experienced higher prevalence of HIV infection had more drug use, involvement of women in sex work, and men reporting visits to brothels. Importantly, we found no case of HIV-1 seroconversion among women. The fact that no seroconversions were detected among the 43 women with multiple admissions may be a reflection of low prevalence (5.9 percent among women compared with 20.0 percent among men) (17) and the small number in the study population. Another risk in this sample was being unmarried, a risk factor also found to be associated with the sexual transmission of HIV-1 infection in
TABLE 1. Incidence rates, rate ratios, and 95% confidence intervals for risk factors for incident HIV-1* among opiate users readmitted to the Northern Drug Treatment Center, Chiang Mai, Thailand, 1993–1995

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Repeat visits</th>
<th>Person-years</th>
<th>HIV-1 seroconversion</th>
<th>HIV-1 sero-incidence rate†</th>
<th>Rate ratio</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>436</td>
<td>323.4</td>
<td>60</td>
<td>18.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>393</td>
<td>288.1</td>
<td>60</td>
<td>20.8</td>
<td>2.06</td>
<td>0.48–8.98</td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
<td>35.4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤19</td>
<td>38</td>
<td>26.9</td>
<td>5</td>
<td>18.6</td>
<td>2.06</td>
<td>0.48–8.98</td>
</tr>
<tr>
<td>20–29</td>
<td>129</td>
<td>90.0</td>
<td>22</td>
<td>24.4</td>
<td>2.71</td>
<td>1.00–9.18</td>
</tr>
<tr>
<td>30–39</td>
<td>161</td>
<td>115.6</td>
<td>28</td>
<td>24.2</td>
<td>2.69</td>
<td>1.02–8.90</td>
</tr>
<tr>
<td>≥40</td>
<td>65</td>
<td>55.5</td>
<td>5</td>
<td>9.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Religion‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Buddhism</td>
<td>337</td>
<td>242.2</td>
<td>58</td>
<td>23.9</td>
<td>5.49</td>
<td>1.45–46.4</td>
</tr>
<tr>
<td>Other</td>
<td>56</td>
<td>45.9</td>
<td>2</td>
<td>4.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status‡</td>
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<tr>
<td>Unmarried</td>
<td>203</td>
<td>140.8</td>
<td>43</td>
<td>30.5</td>
<td>2.64</td>
<td>1.48–4.94</td>
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<tr>
<td>Married</td>
<td>190</td>
<td>147.3</td>
<td>17</td>
<td>11.5</td>
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<td>Education‡</td>
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<td>115</td>
<td>91.2</td>
<td>8</td>
<td>8.8</td>
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<tr>
<td>Primary/secondary</td>
<td>229</td>
<td>163.0</td>
<td>46</td>
<td>28.2</td>
<td>3.32</td>
<td>1.50–8.8</td>
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<tr>
<td>Other</td>
<td>49</td>
<td>33.8</td>
<td>6</td>
<td>17.7</td>
<td>2.02</td>
<td>0.58–6.66</td>
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<tr>
<td>Occupation‡</td>
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<td>Student/civil servant</td>
<td>34</td>
<td>23.2</td>
<td>2</td>
<td>8.6</td>
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<tr>
<td>Laborer</td>
<td>328</td>
<td>243.9</td>
<td>49</td>
<td>20.1</td>
<td>2.33</td>
<td>0.61–19.78</td>
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<tr>
<td>Business</td>
<td>31</td>
<td>20.3</td>
<td>9</td>
<td>43.0</td>
<td>4.99</td>
<td>1.03–47.33</td>
</tr>
<tr>
<td>Ethnicity‡</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Hilltribes</td>
<td>146</td>
<td>117.4</td>
<td>10</td>
<td>8.5</td>
<td></td>
<td>Reference</td>
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<tr>
<td>Thai lowland</td>
<td>247</td>
<td>170.7</td>
<td>50</td>
<td>29.3</td>
<td>3.44</td>
<td>1.72–7.80</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heroin</td>
<td>334</td>
<td>234.0</td>
<td>60</td>
<td>25.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opium</td>
<td>59</td>
<td>54.1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route of administration‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninjection</td>
<td>129</td>
<td>105.9</td>
<td>3</td>
<td>2.8</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Injection</td>
<td>264</td>
<td>182.1</td>
<td>57</td>
<td>31.3</td>
<td>11.05</td>
<td>3.59–55.09</td>
</tr>
</tbody>
</table>

* HIV-1, human immunodeficiency virus type 1; CI, confidence interval.
† HIV-1 seroincidence rate: per 100 person-years.
‡ Restricted to men only.

northern Thailand, presumably reflecting a greater number of different sexual partners (18, 19). The high risk associated with being employed in the business sector reflects relatively greater income, frequently indicates urban residence (where drugs are more available and more drug users are found), and reflects greater mobility.

The high incidence of HIV-1 infection among drug injectors, particularly Thai lowlanders, in northern Thailand may reflect the later introduction of the HIV-1 epidemic among drug users in the north. The HIV-1 incidence in this population of drug users is much higher than that in most epidemics among drug users studied in Europe and the Americas (20–28), with the exception of an early report of an incidence rate of over 30 percent in Italy in the mid-1980s (29).

HIV-1 isolates were first characterized among injection drug users in Bangkok in the mid-1980s and were nearly all subtype B (30). However, six of nine drug users in northern Thailand were infected with subtype E (31) at the time when the sexually transmitted HIV-1 epidemic was rapidly expanding in the north (1, 32). Persons who had only sexual risks for HIV infection from anywhere in Thailand have been consistently shown to be infected mostly with HIV-1 subtype E (31). A study of the molecular epidemiology of drug users from the Center recently showed that 19 of 21 HIV-1-infected drug users had subtype E (17).
Although these preliminary findings are consistent with an inference that some infections may be due to sexual transmission rather than to injection practices, the high proportion of HIV-1 subtype E among injectors in this population suggests that subtype E also may be efficiently transmitted through parenteral inoculation.

The incidence rate we found in these drug users is nearly an order of magnitude higher than HIV-1 incidence rates seen among young men who acquired HIV-1 sexually; the HIV-1 seroconversion rate among military conscripts from the same provinces who denied ever using drugs was 2.4 per 100 person-years during 1991-1993 (18). Other studies in northern Thailand have reported incidence rates of 2-4 per 100 person-years (33-35); while the exact mechanism of transmission of HIV is unknown, presumably most of these persons were infected by sexual transmission. The high HIV-1 incidence found here suggests that parenteral inoculation may be more efficient in transmitting HIV-1 than by sexual exposure.

The utilization of administrative data such as those used here for constructing a retrospective cohort has a number of shortcomings. First, the HIV-1 incidence we report may not be reflective of the HIV seroconversion rates among drug users who do not seek drug treatment. Most (86 percent) of the patients presenting to this treatment center had only one admission during the 2-year study interval. Since the incidence of HIV might have been different in the latter population than in those who had multiple admissions, higher-risk patients might have been more likely to need or request drug treatment services. If true, our sampling scheme might have selected for a higher incidence subgroup, and the incidence rates calculated may be biased upward. Facility-based studies are inherently limited in this regard. Nevertheless, methadone maintenance treatment is not available in northern Thailand, and most patients are quite poor, reside in rural areas, and cannot afford other health care services.

Second, we have no data on sexual risk factors for HIV-1 incidence. Other studies from populations in this region have shown that sexual risk factors for HIV-1 infection include homosexual behavior, incident sexually transmitted diseases, and visits to female sex workers (18, 19, 36, 37). We also have no information on specific drug-related risk factors, such as needle sharing and reuse, and disinfection practices, which have been shown to be important risk factors for HIV-1 infection in other studies of Thai drug users (9). Finally, our data on drug of choice and route of administration are based on the most frequently used drugs.
and usual route of administration. There could be some misclassification, since some injectors may sometimes be smokers and some opium users may occasionally inject heroin. A study of drug users in Bangkok found that "mixing" drugs and routes of administration led to HIV incidence rates lower than those of exclusive injectors but higher than those of smokers (10). We cannot determine with confidence the proportion of incident infections due to parenteral transmission and those that are sexually acquired.

A final limitation is that this cohort was composed of only drug users with more than one admission for treatment during the relatively short study period. Several selection biases could be operating. Most important, readmitted patients may have sought drug treatment after notification of HIV test results conducted elsewhere. We have no evidence that this occurred, although HIV testing is widely available. In addition, all patients were readmitted to the same facility, reflecting an inability to remain drug free, limited choices of alternative treatment in the private sector, or other factors. There also was a possibility of being in the window period of seroconversion among those who were seronegative at the immediate previous admissions. However, only six of the 60 seroconverting patients and 14 of 376 patients who remained uninfected had two visits within 60 days.

To our knowledge, this is the first large study of incident HIV-1 infection among Thai drug users outside of Bangkok. The data suggest that the burden of the drug-related epidemic is being experienced by Thai lowlanders who are heroin injectors. Internationally recognized prevention/harm reduction programs for injection drug users include education and behavior change (38), needle disinfection and needle exchange programs (39), the provision of needles and syringes either through outreach or by decriminalizing sales (40), and expanding drug treatment, predominantly with methadone maintenance (41, 42). Few of these control strategies have yet to be mounted in a systematic fashion in northern Thailand, although the Department of Medical Services is expanding drug treatment services. The only reported Thai trial of methadone maintenance versus detoxification of opiate users in Bangkok demonstrated that individuals randomized to methadone maintenance were more likely to complete a 45-day course of treatment and less likely to have used heroin on the last day of treatment (43).

This high HIV-1 incidence suggests that this population might be suitable for studies of HIV vaccines to determine whether adequate follow-up can be obtained at the level necessary to conduct a rigorous trial. Such a trial could be conducted with significantly fewer volunteers than in populations with lower HIV incidence rates, e.g., 2–3 per 100 person-years. Retaining drug users in follow-up and recognizing that some (breakthrough) infections are likely to occur before all vaccine doses could be provided are two principal challenges to this effort.

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