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Estimation of HIV incidence in San Francisco

Susan Scheer, Chi-Sheng Chin, Anthony Buckman and Willi McFarland

The Centers for Disease Control and Prevention recently released the first direct national estimate of HIV incidence. Local jurisdictions have begun to apply this methodology. The national and local estimates have been higher than assumed. When applied to San Francisco, there were 935 new HIV infections [95% confidence interval (CI) 658–1212] during 2006. We compared this incidence estimate to an estimate produced in San Francisco in 2006 by a panel of HIV researchers using an iterative Delphi method. Results were similar. Further corroboration of the new method in local areas would strengthen interpretation and identify HIV risk variations.

The Centers for Disease Control and Prevention (CDC) recently released the first direct estimate of HIV incidence in the United States [1]. Drawing data from 22 states that participated in a national surveillance system during 2006, HIV incidence was calculated using the BED HIV-1 capture enzyme immunoassay (BED) that distinguishes recent from long-standing infection among new diagnoses and a statistical adjustment for frequency of HIV testing and then extrapolated to the United States [1,2]. The calculation estimated that 56 300 (95% CI 48 200–64 500) persons were newly infected in the United States in 2006. The figure was similar to that produced by a method of back calculation from AIDS cases, estimating 55 400 (95% CI 50 000–60 800). The same methodology was applied to New York City and the resulting estimate was 4762 – three times higher than the national rate [3]. Both the national and the New York City estimates were higher than many public health officials assumed.

San Francisco was participating in the CDC-funded HIV incidence surveillance system during 2006. However, the State of California did not implement name-based HIV case reporting until April 2006. As such, data from California was not included in the 22 states from which the national incidence estimate was derived. However, of the 593 newly diagnosed and reported HIV cases in San Francisco, California in 2006, only 17 were originally reported before name-based HIV was implemented in April 2006 and 14 of these were re-reported later in 2006 by name. As a result, 590 cases (99.5%) are included in San Francisco's 2006 HIV case registry, and all were subject to the same scrutiny regarding checking for duplication and accuracy of date of diagnosis, for example, that cases reported in other name-based reporting systems.

After release of the national HIV estimate, CDC released the methodology [2] and accompanying SAS computer programs [4], so that individual incidence surveillance sites could calculate their local estimate. We, therefore, report here the 2006 HIV incidence estimate for San Francisco.

Table 1 provides the available data used for the HIV incidence estimation in San Francisco. Ninety cases were classified as recently infected with HIV out of a total of 590 new HIV diagnoses reported in 2006. On the basis of the CDC adjustment and extrapolation methods, we estimate that there were 935 new HIV infections (95% CI 658–1212) in San Francisco during 2006. We used the same 20-fold multiple imputation process that CDC used to calculate the national estimate because HIV testing history and BED results were not available for all cases in 2006. For the population of men who have sex with men (MSM) [including MSM who inject drugs (MSM-IDU)], the estimate was 716 (95% CI 489–944). No other risk population met the criterion of having a minimum of 200 new HIV diagnoses needed for reasonable precision.

For comparison, a HIV incidence number was produced for San Francisco in 2006 by the HIV Epidemiology Section of the San Francisco Department of Public. The HIV Epidemiology Section periodically examines all known local data and consults with experts in the HIV/AIDS field to arrive at a 'consensus' estimate of HIV incidence [5]. Data include studies using different methods to estimate HIV incidence in diverse risk populations, including longitudinal cohorts and clinical trials, the less sensitive assay, trends in new HIV diagnoses, trends in sexually transmitted infections and risk behavior and repeat testing histories [6]. An iterative Delphi method is used by an expert panel to arrive at the most plausible estimate and upper and lower bounds. The final estimate is adopted into the Epidemiological Profile of the city's HIV Prevention Plan and used for programme planning. Using this approach, the estimated number of people acquiring a new HIV infection in San Francisco in 2006 was 975 adults (upper and lower plausible bounds, 801 and 1082, respectively). For MSM (including MSM-IDU), the corresponding figure is 851 (732–1023).

Both methods of estimating HIV incidence have their limitations. The CDC methodology extrapolates from a relatively small number of new HIV diagnoses (590),

Table 1. Available data and estimated HIV incidence using the BED assay and Centers for Disease Control and Prevention extrapolation methods, San Francisco, 2006.

Data or estimate	Number of cases
Number of persons newly diagnosed with HIV in 2006[a]	590
Number of persons with HIV testing history	586
Number of persons with concurrent HIV and AIDS diagnoses[b]	106
Number of persons with BED result available	251
Number of persons with long-standing infection by BED assay	125
Number of recent HIV infections by BED assay	90
Total estimated HIV incidence number (95% CI)	935 (658–1212)

CI, confidence interval.
[a]Includes all newly diagnosed and reported HIV cases.
[b]Includes cases with and without a BED result.

total BED tests (251) and recent HIV infections on BED testing (90) to the entire population of testers and nontesters in San Francisco. However, we more than fulfilled the methodological requirements that the dataset includes 200 new HIV diagnoses, 40 BED tests and 10 recent tests. We also met these requirements among the MSM subpopulation. The consensus estimate, on the contrary, is an indirect summary of available data sources with each having its own potential biases and limited ability to extrapolate outside of their respective study populations.

When independent methods reach similar conclusions, confidence in the findings is bolstered. Although we may never have a gold standard to which we can compare the new method to estimate HIV incidence, the similarity of results from the new CDC approach and our synthesis of local data corroborate our current understanding of epidemic using different data, methods and other information. Further corroboration of the new method in local areas would strengthen interpretation and identify variations in HIV risk.

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San Francisco Department of Public Health, HIV Epidemiology Section, San Francisco, California, USA.

Correspondence to Dr Susan Scheer, San Francisco Department of Public Health, 25 Van Ness Avenue, Suite 500, San Francisco, CA 94102, USA.
E-mail: susan.scheer@sfdph.org

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Clinical course of classic Kaposi's sarcoma in HIV-negative patients treated with the HIV protease inhibitor indinavir

Paolo Monini[a], Cecilia Sgadari[a], Maria Gabriella Grosso[a], Stefania Bellino[a], Antonio Di Biagio[b], Elena Toschi[a], Ilaria Bacigalupo[a], Michela Sabbatucci[a,c], Giulia Cencioni[a], Emanuela Salvi[a], Patrizia Leone[a], Barbara Ensoli[a], for the Concerted Action on Kaposi's Sarcoma

HIV protease inhibitors have been shown to exert antiangiogenic and antitumor actions independently from their antiretroviral effect. Based on these studies, HIV-seronegative patients with classic Kaposi's sarcoma were treated with indinavir and followed for clinical evolution, drug pharmacokinetics and Kaposi's sarcoma biomarkers. A favorable clinical course was associated with high drug plasma levels, reduced production of basic fibroblast growth factor, lower numbers of circulating endothelial cells, and a decrease in antibody titers against human herpesvirus 8.

Kaposi's sarcoma onset is associated with $CD8^+$ T-cell activation and T-helper 1 (Th1) polarization leading to production of inflammatory cytokines, in particular, γ-interferon (γ-IFN), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) [1]. These cytokines reactivate human herpesvirus 8 (HHV8) infection and trigger the production and release of angiogenic factors, particularly basic fibroblast growth factor (bFGF) [1–7], which stimulate angiogenesis and Kaposi's sarcoma growth and invasion through the activation of matrix metalloprotease type 2 (MMP-2) [2,3,5–8].

The incidence of Kaposi's sarcoma has greatly reduced in HIV-infected individuals since the introduction of the highly active antiretroviral therapy (HAART), and early-stage Kaposi's sarcoma often resolves and/or regresses upon therapy [9]. Previous studies indicated that HIV protease inhibitors (HIV-PIs) inhibit the development of angioproliferative Kaposi's sarcoma-like lesions in mice and block angiogenesis induced by bFGF and/or vascular endothelial growth factor due to inhibition of MMP-2 proteolytic activation [9,10]. Further, HIV-PIs have been shown to induce an anti-inflammatory response that may be key in controlling reactive, early-stage Kaposi's sarcoma in treated patients [9]. These data prompted us to treat HIV-seronegative individuals with classical Kaposi's sarcoma (C-KS) with the HIV-PI indinavir (ClinicalTrials.gov NCT00362310). The rareness of C-KS as well as ethical reasons precluded the inclusion of drug-dose or control groups. Therefore, the study was designed to determine the relation between the clinical course of Kaposi's sarcoma and plasmatic levels of indinavir and surrogate markers of Kaposi's sarcoma, including angiogenesis, immune activation, inflammation, Th1 or Th2 polarization, and HHV8 infection.

Twenty-eight patients with early-stage Kaposi's sarcoma (stage I or II, 14 patients) or late-stage Kaposi's sarcoma (stage III or IV, 14 patients) [11] were enrolled. Most individuals (19 patients) had Kaposi's sarcoma-associated complications such as edema, lymphorrea, lesion ulceration, bleeding and pain, and a history of previous therapy failure. The treatment schedule was 800 mg of indinavir twice daily for 12 months. The results refer to the late interim analysis conducted when 26 out of the 28 enrolled patients were evaluated for clinical course, pharmacokinetic parameters, and safety, and 22 out of 28 also for biological markers.

A favorable clinical course upon treatment was experienced by 16 out of 26 (61.5%) of the patients. In particular, a complete remission was observed in one patient, partial regression in two, improved disease in five, and stabilization of progressive disease (PD) in eight [12]. Nine of these patients had early-stage Kaposi's sarcoma (56.3%) and seven late-stage Kaposi's sarcoma (43.7%). In six of these patients, Kaposi's sarcoma relapsed and progressed after a median favorable course of 19 weeks (range 14–40 weeks). Relapse was significantly associated with late-stage Kaposi's sarcoma (Fisher's exact test; $P = 0.0350$).

A nonfavorable clinical course upon treatment was observed in 10 out of 26 (38.5%) patients, mostly with late-stage Kaposi's sarcoma (seven out of 10; 70%). In particular, three patients were stable and remained so (stable disease) and seven continued to progress (PD) [12].

Surprisingly, having progressive Kaposi's sarcoma at study entry (i.e., appearance of new lesions within 3 months prior to enrollment [11]) was significantly associated with a favorable clinical outcome upon treatment (Fisher's exact test; $P = 0.0152$). The clinical course was not significantly predicted by Kaposi's sarcoma stage, presence of confluent tumor masses, number of lesions, or Kaposi's sarcoma complications (ulceration, bleeding, lymphorrea, and/or pain).

The 10 patients showing a durable favorable clinical course had a significantly higher plasmaic indinavir C_{max} and drug area under curve (AUC) at week 4 of treatment, as compared with the patients with transient favorable course or unfavorable clinical evolution (analysis of variance; C_{max}, $P = 0.0313$; AUC, $P = 0.0124$). Further, patients whose C_{max} values were always below the mean value of the patient population (patients with 'low C_{max}') clustered in the group having unfavorable clinical course, whereas patients with one or more C_{max} values above the mean value of the patient population (patients with 'high C_{max}') clustered in the group experiencing a favorable clinical evolution (Fisher's exact test; $P = 0.0256$) (Fig. 1a). Patients with 'low C_{max}' and those with unfavorable course showed a significant increase of bFGF plasmatic levels upon treatment (analysis of covariance; $P = 0.0270$ and $P = 0.0290$, respectively) as compared with patients with 'high C_{max}' and with those with a favorable clinical outcome ($P = 0.0542$ and $P = 0.0584$, respectively) (Fig. 1b). These data are consistent with antitumor and antiangiogenic effects of indinavir [10] and are further supported by a significant decrease of circulating endothelial cells [13] in patients with a favorable clinical course ($P = 0.0019$), which, however, was not significant as compared to patients with unfavorable course.

In agreement with the key role of HHV8 in Kaposi's sarcoma burden and progression [1], antilytic HHV8 antibody titers [14,15] decreased significantly in both patients with 'high C_{max}' and those with a favorable clinical evolution (analysis of covariance; $P = 0.0224$ and $P = 0.0145$, respectively), although the variation of titers in these patients was not significantly different as compared to that in patients with 'low C_{max}' and in patients with unfavorable outcome. As previously reported [16,17], unfavorable clinical course showed a trend toward CD4 losses ($P = 0.0642$), which, however, was not related to drug pharmacokinetics.

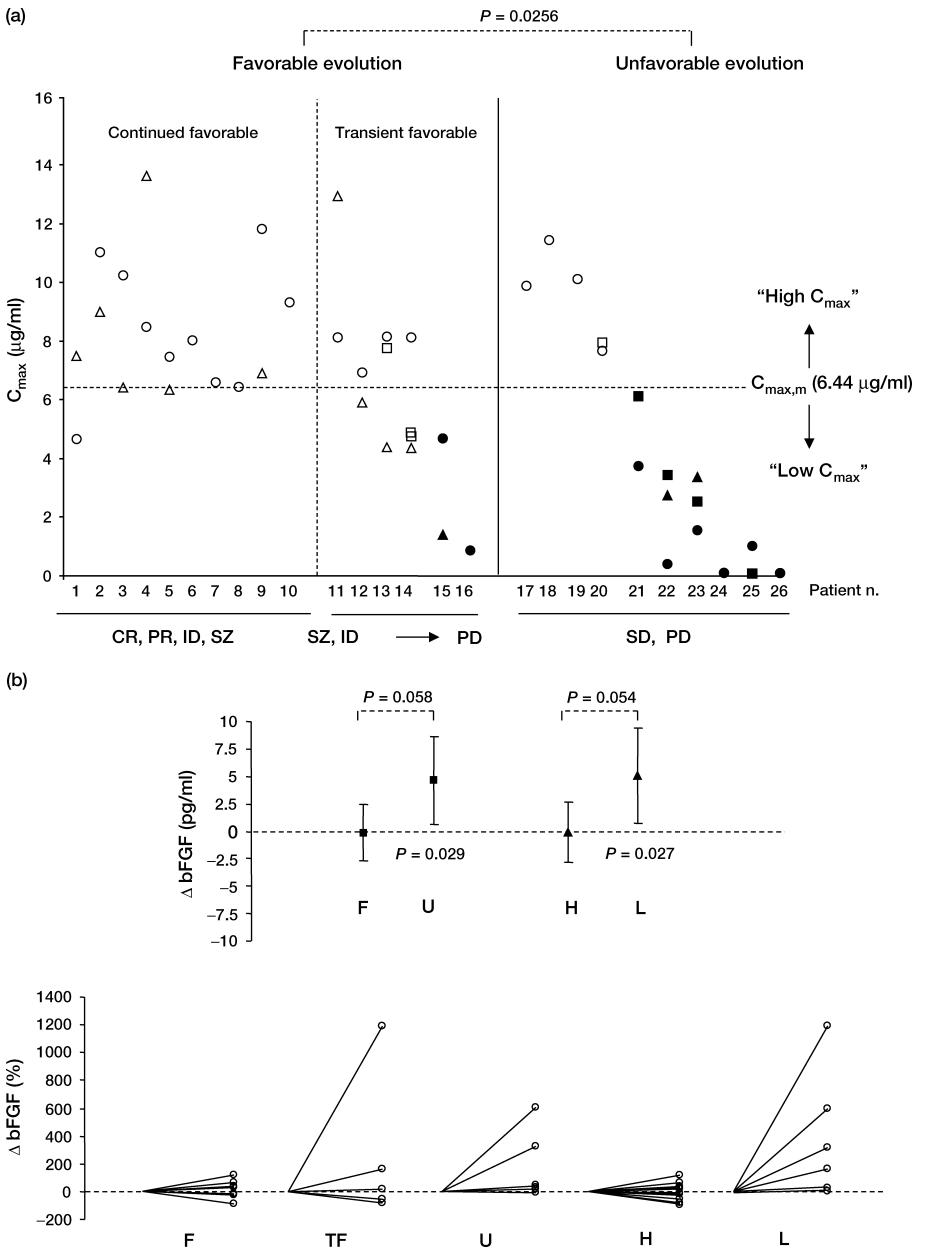

Fig. 1. Relation of clinical evolution, indinavir pharmacokinetics, and bFGF plasma levels in treated patients. (a) Distribution of C_{max} values in patients showing a continued or transient clinical course and patients having an unfavorable evolution. C_{max} values determined at week 4 (circles) or week 12 (triangles) of treatment, or at nonscheduled time points (squares), were plotted as a function of the clinical course. 'High C_{max}' or 'low C_{max}' values are above or below the mean population value ($C_{max,m}$, dashed line), respectively. Filled symbols identify patients whose C_{max} values were always below $C_{max,m}$ (patients with 'low C_{max}'). The association between favorable/unfavorable clinical course and high/low C_{max} was assessed using the Fisher's exact test. CR, complete remission; ID, improved disease; PD, progressive disease; PR, partial remission; SD, persistent stable disease; SZ, stabilization of progressive disease. (b) Variations of patients' bFGF plasma levels. Upper panel: mean pre-therapy–post-therapy changes in plasma bFGF concentration (Δ bFGF) adjusted for baseline values in patients with favorable (continued or transient) (F) or unfavorable (U) clinical course (filled squares) and in patients with 'high C_{max}' (H) or in patients with 'low C_{max}' (L) (filled triangles); bars: confidence intervals. Lower panel: Percentage changes from baseline of bFGF plasma concentration (Δ bFGF %) for single patients are shown. F, continued favorable course; TF, transient favorable course. Statistical analysis was performed by the analysis of covariance (ANCOVA) model.

Although the patients in this study were of advanced age (median age 68 years, range 51–82), adverse events were occasional and modest. The most frequent adverse events were a self-reported mild-to-moderate asthenia or arthralgia and nonspecific skin manifestations such as erythema, rash, or itching. Indinavir is known to form

drug precipitates in the kidney [18]; however, such responses were also modest and successfully managed with hydration.

On the basis of these data, it is tempting to conclude that high indinavir plasma levels exerted therapeutic effects in our setting through antiangiogenic effects. Although this conclusion should be taken with caution, given the frequent indolent course and spontaneous regression of C-KS, particularly in early-stage [11], it is worth noting that favorable clinical evolution was significantly associated with progressive behavior at study entry, which has no obvious relation with spontaneous regression.

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Members of the Concerted Action on Kaposi's Sarcoma. Istituto Superiore di Sanità, Rome, Italy: G. Barillari, G. Moracci; Preventive Medicine Center, Gubbio, Italy: L. Carratelli; Infectious Diseases Clinic, University of Genoa, S. Martino Hospital, Genoa, Italy: G. Gatti; Institute of Dermatological Sciences, University of Milan, Ospedale Maggiore, Mangiagalli e Regina Elena, Milan, Italy: L. Brambilla, M. Brambati, S. Ferrucci; Istituto Dermopatico dell'Immacolata - IRCCS (IDI), Rome, Italy: O. De Pità, M.A. Pilla; Istituto Dermatologico S. Gallicano, Rome, Italy: A. Di Carlo, M. Giuliani; Dermatology Clinic, University of Sassari, Italy: F. Cottoni, M.A. Cuccuru; Dept. of Dermatological/ Venereal Diseases and Plastic Surgery, University 'La Sapienza', Rome, Italy: S. Calvieri, R. Clerico, C. Potenza; Dept. of Medical Oncology, Centro di Riferimento Oncologico (CRO), Aviano, Italy: U. Tirelli, C. Simonelli, F. Martellotta; Dermatology Clinic, Ospedale S. Anna, Ferrara, Italy: R. Strumia, A. Borghi; Dept. of Internal Medicine, University of Cagliari, Italy: S. Del Giacco, L. Moi and G. Piludu; Dept. of Clinical Medicine, Laboratory of Immunology, University 'La Sapienza', Rome, Italy: M.C. Sirianni, M. Campagna; Institute of Infectious Diseases, University of Tor Vergata, Rome, Italy: L. Sarmati, M. Andreoni; II Medical Clinic, Nephrology Division, Hospital 'Umberto I', Rome, Italy: G. Bianchini; Dept. of Molecular Biology, Hospital Carlos III, Madrid, Spain: J. Sheldon; Institute of Virology, Hannover Medical School, Hannover, Germany: J. Milzer, T. Schulz.

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[a]*National AIDS Center, Istituto Superiore di Sanità, Rome,* [b]*Infectious Diseases Clinic, University of Genoa, S. Martino Hospital, Genoa, and* [c]*Department of Cell Biology and Neurosciences, Istituto Superiore di Sanità, Rome, Italy.*

Correspondence to Dr Barbara Ensoli, National AIDS Center, Istituto Superiore di Sanità, V.le Regina Elena 299, 00161 Rome, Italy.
Tel: +39 06 49903209; fax: +39 06 49903002;
e-mail: barbara.ensoli@iss.it

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HIV seroconversion among injection drug users in detention, Tehran, Iran

Mohammad R. Jahani[a], Parastoo Kheirandish[b], Mostafa Hosseini[c], Hadi Shirzad[d], Seyed A. Seyed-Alinaghi[b], Nazli Karami[b], Pegah Valiollahi[b], Minoo Mohraz[b] and Willi McFarland[e]

Jails may foster the spread of HIV, particularly among drug users. In 2006, male injection drug users ($n = 499$) detained in Tehran consented to HIV testing at intake and discharge. HIV prevalence at intake was 24.4%. Nine of those who were HIV negative at intake were positive at discharge (annualized incidence rate 16.8%), including one p24 antigen positive. Jails may be contributing to the rapid spread of HIV in Iran and should be major points for prevention interventions.

Injection drug users (IDU) account for a substantial proportion of HIV infections worldwide and are the predominant risk population in many countries of Eastern Europe, Central Asia, and the Middle East [1]. Iran, in particular, is experiencing a growing HIV epidemic among IDU that is fueled by a high and rising number of opioid users [2,3]. In response, Iran has adopted harm-reduction measures, including needle exchange programs (NEP), methadone maintenance, and, on a limited basis, NEP in jails [3]. Jails, prisons, and other detention institutions may play an important role in the HIV epidemic, particularly among drug users, as they constrain the use of clean syringes. Studies document that HIV is more prevalent among prisoners than the general population in part because prisons contain a high proportion of IDU [4–6]. However, fewer data are available to document the risk that HIV is acquired while under detention [7–10]. Such data may help advocate for expansion of jail-based NEP and other prevention measures. We, therefore, conducted a serological study of male IDU incarcerated in Tehran, Iran, from February to April 2006.

Study individuals were male IDU arrested by police during a geographically comprehensive police 'sweep' in Tehran. Men determined to be IDU by urine test and physical examination for injection marks by a physician were sent to mandatory detoxification and rehabilitation for 3 months. As part of a study approved by the Ethics Committee of Tehran University Medical School, we offered HIV counseling and testing to inmates upon intake and discharge. Records were kept separate from the jail system, and referrals for treatment and care were given through the University medical center. After providing written consent, blood specimens were collected for HIV ELISA antibody testing (Biotest AG, Dreieich, Germany). Positive ELISA results were confirmed by western blot (Diagnostic, Berlin, Germany). Upon release, those who were HIV negative on entry were offered repeat HIV antibody test. HIV incidence or the rate of seroconversion was estimated as the number of IDU testing HIV negative at intake who tested HIV positive at release divided by the number testing HIV negative at intake. HIV incidence was annualized by converting the 3-month seroconversion rate to a 12-month rate. We, additionally, assessed whether the seroconversions were recent using p24 antigen testing (Biomerieux, Nurtingen, Germany). Of note, neither

condoms nor clean needles were dispensed during the detention period.

Of 499 offered, 459 (92.0%) male IDU agreed to participate in HIV testing. At intake, 112 (24.4%) had HIV antibodies. Of 347 HIV-negative men, 214 (61.7%) accepted to retest upon release. Of these, nine were HIV positive. HIV incidence according to these antibody results was 16.8% per year [95% confidence interval (CI) 7.6–31.6]. Of the nine putative seroconverters, eight were p24 antigen negative and one was p24 antigen positive.

We note that it is possible that some of the HIV seroconverters may have been in the antibody window period at the time of intake. However, the finding of a p24 antigen-positive inmate strengthens the conclusion that some men were infected, while incarcerated. We also note the limitation of not having conducted p24 antigen testing at intake. Additionally, the rate of refusal to retest (38.3%) may affect the incidence rate estimation.

At present, only a small number of countries have NEP in jails. Although some jails in Iran have NEP, the current reach and coverage is limited. The situation in Iran creates a special need, as there are many persons who smoke opium and upon incarceration may resort to injection to satisfy their addiction as clandestine smoking is nearly impossible [4,11]. Additionally, male–male sex may pose a risk for transmission while in jail, particularly given sex may be exchanged for drugs [12].

Both the Iranian and United States Centers for Disease Control and Prevention (CDCs) agree that HIV-prevention services be made available to inmates of correctional facilities. They recommend that voluntary HIV counseling and testing be provided upon entry into prison, before release, and be made available periodically during incarceration. Prison-testing programs provide an opportunity for inmates to learn their HIV serostatus and protective behavior to reduce the risk of acquiring and transmitting HIV while incarcerated and after release [13]. Such programs provide potentially great benefit to inmates and wider society. Our study suggests a very high rate of HIV acquisition while in jail. Harm-reduction programs within jails, such as NEP, are more controversial, but may also provide benefits to inmates and society by preventing a substantial number of infections. We recognize, however, availability of clean needles and syringes in prison is no guarantee for complete elimination of needle and syringe-sharing behavior [4]. In the Iranian context, arrested opium smokers may be mixing the first time with injectors who have a high prevalence of HIV coming into jail. Therefore, the question arises whether the mandatory detention for detoxification is causing more harm than good.

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[a]Department of Medicine, Baghiyat-Allah University, [b]Iranian Research Center for HIV/AIDS (IRCHA), Department of Infectious and Tropical Diseases, Tehran University of Medical Sciences, [c]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, [d]Research Center-Head Quarter of Police Force Medicine, Tehran, Iran; [e]CAPS and the Institute for Global Health, University of California, San Francisco, California, USA.

Correspondence to SeyedAhmad SeyedAlinaghi, MD, Iranian Research Center for HIV/AIDS (IRCHA), Imam Khomeini Hospital, Keshavarz Blvd., Tehran, Iran.
Tel/fax: +98 21 66 94 79 84;
e-mail: s_a_alinaghi@yahoo.com

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