The Spread of HIV-1 Subtypes B and CRF01_AE Among Injecting Drug Users in Bangkok, Thailand

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Summary: The HIV epidemic among injecting drug users (IDUs) in Bangkok was initially dominated by HIV subtype B and later by the recombinant CRF01_AE. The present study investigates the distribution of the 2 variants in time and how it is affected by changes in injecting risk behavior and treatment. A mathematic model describing the spread of HIV subtype B and CRF01_AE among IDUs was developed, and data from the AIDSVAX B/E cohort of IDUs in Bangkok were used. From the model, it was calculated that during 1999 to 2003, the annual incidence of HIV was around 0.6 and 2.7 to 3.9 infections per 100 person-years for subtype B and CRF01_AE, respectively. Of the new infections, 18% and 72% are first infections with subtype B and CRF01_AE, respectively, and 9% are superinfections. With increases in risk behavior, the fraction of superinfections rises. If treatment reduces the infectivity of CRF01_AE more than that of subtype B, the fraction of subtype B infections should increase. Subtype B should remain prevalent in a small but considerable fraction of the population for a long time. Changes in risk behavior and the introduction of treatment may alter the distribution of subtypes, but CRF01_AE should remain dominant.

Key Words: dual infection, HIV-1 subtypes, injecting drug users, mathematic models, superinfection, Thailand, treatment

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The first HIV outbreak among injecting drug users (IDUs) in Bangkok in the late 1980s was mainly attributed to HIV-1 subtype B.[1,2] Later, increasing numbers of infections with CRF01_AE (previously designated as subtype E) were documented, and it was estimated that between 1995 and 1998, 79% of new infections were with CRF01_AE.[3,4] This turnover in the distribution of the 2 HIV variants might be explained by a difference in their infectivity. Viral load during primary HIV infection is higher for CRF01_AE than for subtype B, although no significant differences during chronic HIV infection have been observed.[5] Consequently, infectiousness during primary HIV infection for individuals infected with CRF01_AE may be higher than for those infected with subtype B.[6] Currently, the incidence of both HIV variants remains high,[4] and superinfections of one of these variants after the other have also been documented.[7] How the HIV epidemic is likely to develop in subsequent years is an open question. In this study, we developed a mathematic model that describes the spread of HIV subtype B and CRF01_AE. Data from an IDU cohort in Bangkok were used. We studied the difference between the incidence of subtype B and that of CRF01_AE and explored how the distribution of the 2 variants is affected by changes in injecting risk behavior and treatment. How protective immunity against superinfections affects the distribution of first and secondary infections was examined.

METHODS

Model

A model is considered that describes the spread of HIV subtype B and CRF01_AE. HIV infection is divided into 3 stages. The first stage consists of the first few months after infection, during which HIV viremia and infectivity are high.[8,9] The second stage is the asymptomatic chronic HIV infection, with lower viral load and infectivity. This stage ends with the development of AIDS or the initiation of highly active antiretroviral therapy (HAART). Allowing for treatment failure and compliance, HAART can reduce infectivity and increase survival to AIDS.[10,11] In that case, individuals with chronic HIV infection progress to the third stage of treated HIV infection. Individuals depart from the population because of factors not related to HIV; for instance, death from other causes or end of injecting career. Those infected remain in the population for a shorter time because of AIDS. Dual infections have been documented, resulting from infection with subtype B and CRF01_AE simultaneously (double infections) or at different time points (superinfections).[7,12,13] This means that infection with one of the HIV variants does not offer complete immunity

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to infection with the other variant. Therefore, in the model, we included a level of protection against superinfection and varied this level from 0% to 100% protection. Persons dually infected can transmit subtype B, CRF01_AE, or both. Persons infected with one of the HIV variants who are superinfected with the other variant during primary or chronic HIV infection go through the first stage of dual infection. If a treated person is superinfected, the viral load of the second infection remains suppressed; therefore, the person moves to the class for treated persons with dual infection. Mixing between IDUs, injecting behavior, and the biologic properties of HIV are rather similar for male and female IDUs; therefore, the population was not stratified according to gender. The model is described by a system of differential equations, as given in the Appendix, and a schematic diagram is shown in Figure 1.

AIDSVAX B/E Cohort

In 1999, a phase 3 trial to evaluate the efficacy of AIDSVAX B/E (a preventive HIV-1 candidate vaccine) was initiated in Bangkok, Thailand. The study design, recruitment, and screening are described in detail elsewhere.[14] Between March 1999 and August 2000, 4943 IDUs were screened and 2546 of them were enrolled. Participants received vaccine or placebo at a 1:1 ratio. At baseline and every 6 months, a questionnaire was administered regarding drug use, sexual behavior, beliefs, and incarceration. Follow-up was terminated on June 5, 2003. Until then, there were 230 HIV-1 infections, of which 33 were subtype B, 182 were CRF01_AE, and the remaining were not typed or were untypable.[15] HIV-1 infection was determined using the Genetic Systems-Biorad enzyme-linked immunosorbent assay (ELISA) and Western blot kits (Redmond, WA); HIV-1 subtype was determined from amplified full-length gp120 using reverse transcriptase (RT; First Strand cDNA Synthesis kit; Amersham Biosciences, Piscataway, NJ) polymerase chain reaction (PCR; Sigma-Aldrich, St. Louis, MO) by Phylogenetic Analysis Using Parsimony (Sinauer Associates, Sunderland, PA). Subtyping was performed once, and double infections or superinfections could not be determined. The methods for determining seroconversion and assigning subtypes are described in detail elsewhere.[15]

Parameter Values

The model equations were solved numerically from 1999 onward, with the parameter values given in the Appendix and Table 1. To account for uncertainty in some parameter estimates, a range of values was assigned to them. Using Latin Hypercube Sampling,[16] 1000 sets of values were sampled from these ranges and the model equations were solved with each of them. For a specific outcome of interest, means and 95% confidence intervals (CIs) were calculated from the 1000 results. The lower and upper limits of the CIs were $m \pm 1.96s/\sqrt{1000}$, where m is the mean and s is the standard deviation of the 1000 results. The incidence of subtype B and that of CRF01_AE were calculated from the model and from data from the AIDSVAX B/E cohort. We used various levels of frequency of sharing of injecting equipment and compared the resulting incidences from the model with those from the data. From this, we obtained a range of frequencies that provided the best match between model and data incidences.

RESULTS

Incidence in the AIDSVAX B/E Cohort

From the seroconverters of the cohort, we calculated the incidence of each subtype separately and in total. The incidence of subtype B varied between 0.2 and 0.7 infections per 100 person-years (PYs) in the years 1999 to 2003, and that of CRF01_AE varied between 2.1 and 3.5 per 100 PYs. The

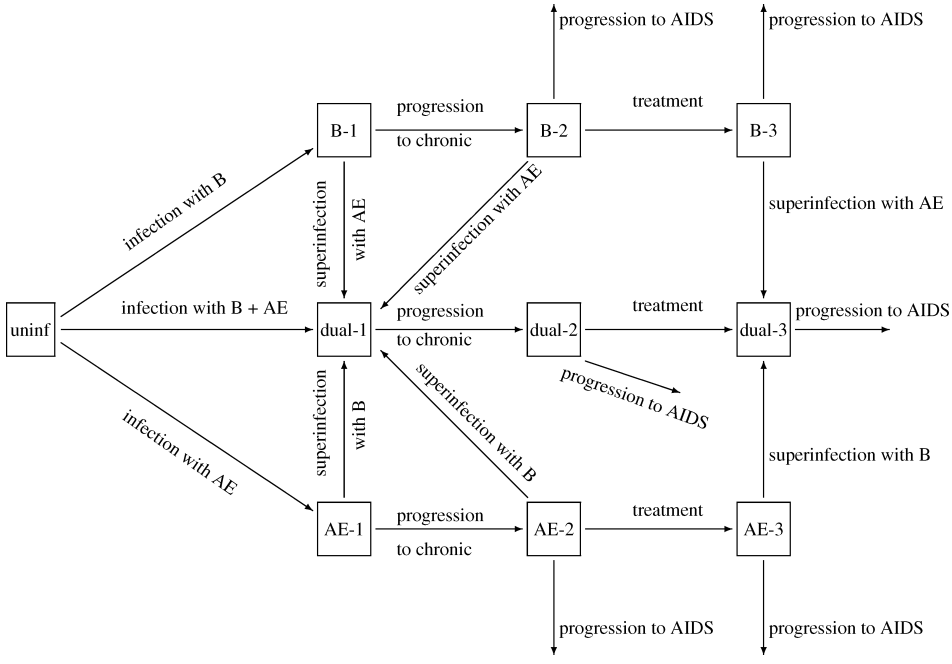

FIGURE 1. Flow diagram of model for the transmission of HIV subtypes B, CRF01_AE, and dual infections. There are 10 groups of individuals: uninfected (uninf); infected only with subtype B in the first, second, or third stage of infection (B-1, B-2, and B-3, respectively); infected with CRF01_AE (AE-1, AE-2, and AE-3 in the 3 stages of the infection); and dually infected with subtype B and CRF01_AE (dual-1, dual-2, and dual-3). The arrows denote transitions of individuals between these groups because of infection, superinfection, progression to chronic HIV (from stage 1 to stage 2), treatment (from stage 2 to stage 3), and progression to AIDS (from stage 2 or 3). There is also import of uninfected individuals and natural death (causes not related to HIV/AIDS) for all individuals, which are not shown in the diagram (see text and Appendix for details).

TABLE 1. Parameter Definitions and Their Values or Ranges

	Parameter	Value/Range	Source
n	Initial population size	36,000	28
μ	Rate of departing from the population (μ per capita) and rate at which uninfected individuals enter the population (constant μn)	0.04 per year	29
ϕ	Frequency of sharing of injecting equipment	6–14 times per year	*
p_{bj}	Probability of transmission of HIV subtype B from a person infected only with this subtype at stage j = 1,2,3 per injecting act	p_{b2}, 0.001–0.01 $p_{b1} = f_p p_{b2}$, $p_{b3} = f_\tau p_{b2}$	6, 30
p_{ej}	Probability of transmission of CRF01_AE from a person infected only with this variant at stage j = 1,2,3 per injecting act	$p_{e1} = f_s p_{b1}$, $p_{e2} = p_{b2}$, $p_{e3} = p_{b3}$	5, 6
f_τ	Reduction in infectivity of stage 2 attributable to treatment ($p_{b3} = f_\tau p_{b2}$)	0.01–0.5	10, 31
f_p	Relative infectivities primary versus chronic HIV infection, $f_p = p_{b1}/p_{b2}$	5–35	8, 9
f_s	Relative infectivities CRF01_AE:B, $f_s = p_{e1}/p_{b1}$	1–4	5, 6
q_{ij}	Probability of transmission of HIV subtype B, CRF01_AE, or both (i = b,e,d, respectively) from a person with dual infection at stage j = 1,2,3	$q_{bj} = p_{bj}(1-p_{ej})$, $q_{ej} = p_{ej}(1-p_{bj})$, $q_{dj} = p_{bj}\, p_{ej}$	
γ_i	Progression rate from stage 1 to stage 2, i = b,e,d	4–12 per year	32
δ_i	Progression rate from stage 2 to stage 3, i = b,e,d	0.14–0.33 per year	
θ_{i2}	Progression rate from stage 2 to AIDS, i = b,e,d	0.083–0.125 per year	33
θ_{i3}	Progression rate from stage 3 to AIDS, i = b,e,d	0.04–0.07 per year	34
σ_{ij}	Protection from infection with HIV subtype i = b,e, against superinfection with the other subtype if infective at stage j = 1,2,3	50%–100%	

*Estimated from the cohort data (see text).

total incidence was 2.6 to 4.2 per 100 PYs. The analyses were not stratified by participants who received vaccine versus placebo, because the distributions of CRF01_AE and subtype B in the 2 groups were similar.[15]

Incidence and Prevalence From the Model

Figure 2 shows the incidence of subtype B and that of CRF01_AE, as calculated from our model for the years 1999 to 2003. Incidence of subtype B remained stable at around 0.6 per 100 PYs, whereas that of CRF01_AE varied between 2.7 and 3.9 infections per 100 PYs. The total number of all first infections (ie, excluding superinfections) was 3.2 to 4.6 per 100 PYs. The incidence of subtype B superinfections after CRF01_AE infections was 0.4 per 100 PYs, which is comparable to the incidence of first subtype B infections. The incidence of CRF01_AE superinfections was 2.0 to 3.1 per 100 PYs, which is also comparable to the incidence of first CRF01_AE infections. The fact that the incidence of first and the incidence of second infections are almost the same also agrees with data from the preparatory cohort of IDUs in Bangkok during 1995 to 1998.[7]

Incidence of CRF01_AE Versus Subtype B

Figures 3A and B show the difference between the incidence of CRF01_AE and the incidence of subtype B in 2003 and how it depends on the infectiousness of the 2 variants and the duration of primary HIV infection. The difference was calculated as the ratio between the incidence of CRF01_AE and that of subtype B. The probability of transmission of CRF01_AE from a person infected only with CRF01_AE at the first stage of infection was assumed to be 1 to 4 times higher than that of subtype B, whereas the infectivity of CRF01_AE and that of subtype B at stage 2 were equal and the rates of infectivity at stage 3 also were equal (see Table 1). The duration of primary infection was 1 to 3 months. With each combination of the uncertain parameters, the model equations were solved, resulting in a set of values for the ratio of incidence of CRF01_AE to subtype B in 2003. These values are plotted against the ratio of infectivity of CRF01_AE to subtype B in Figure 3A and against the duration of primary infection in Figure 3B. If infectivity of CRF01_AE is 1 to 2 times higher than that of subtype B, the incidence of CRF01_AE is 1 to 5 times higher than that of

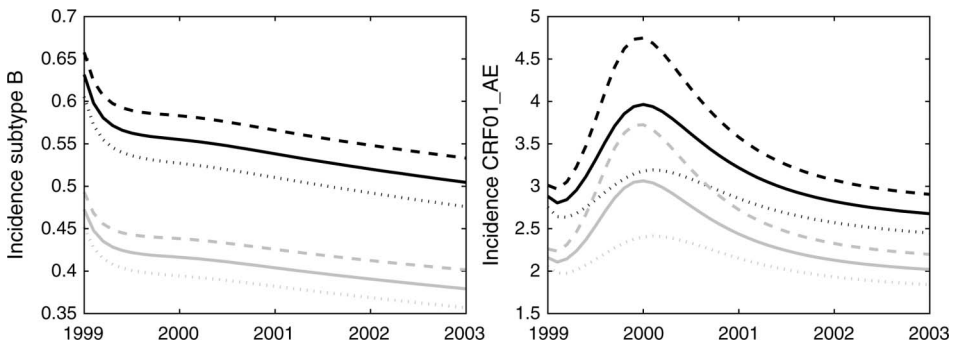

FIGURE 2. Incidence of HIV subtype B (left) and of CRF01_AE (right), as calculated from the model. Black lines are first infections, and gray lines are superinfections. For each case, a set of 3 lines is shown: mean (solid lines) and lower and upper limits of the 95% CIs (dotted and dashed lines, respectively). Incidence is presented as the number of infections per 100 PYs.

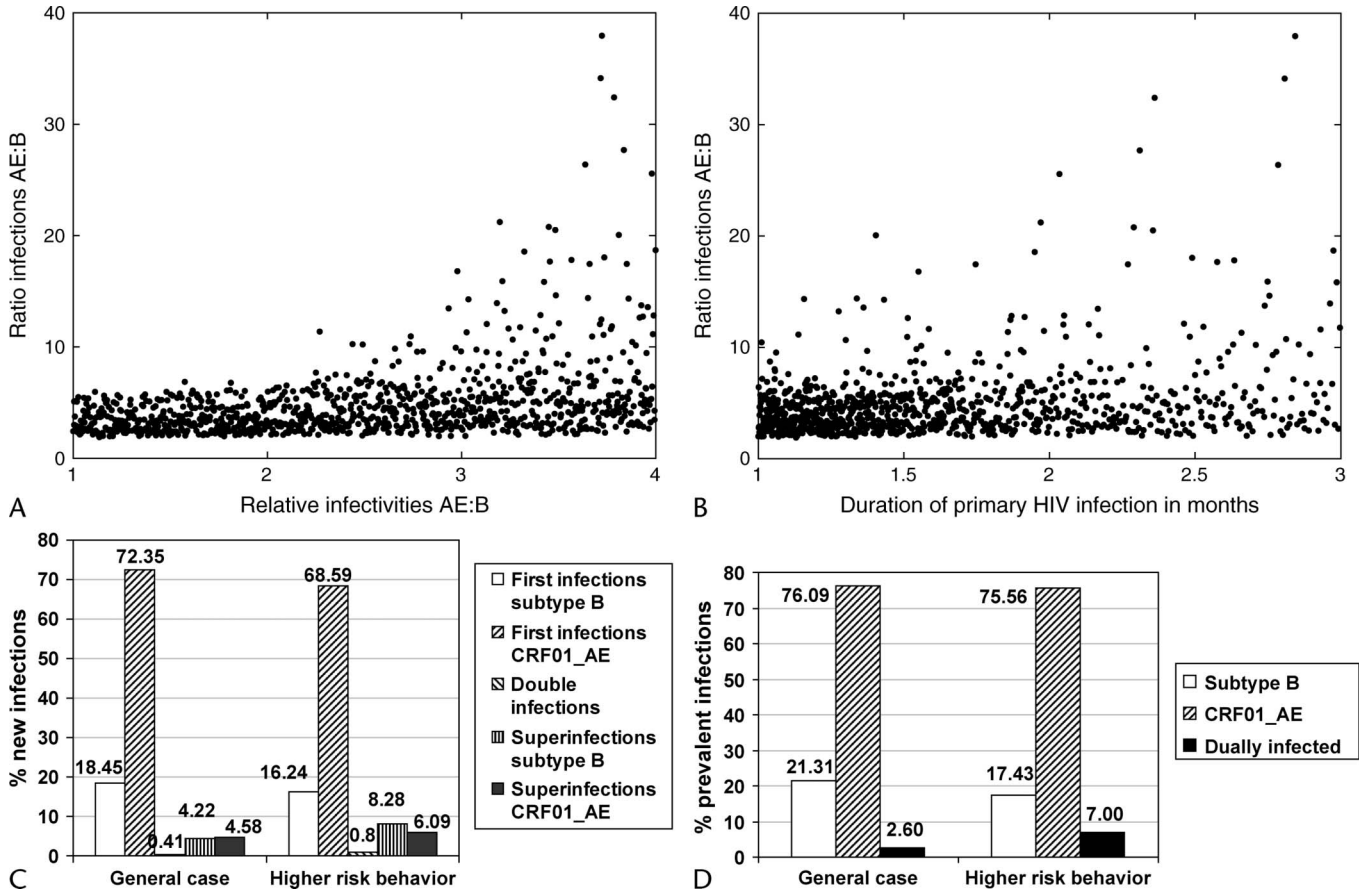

FIGURE 3. The ratio of new infections with CRF01_AE compared with new infections with subtype B, in 2003, plotted against the ratio of infectivity of CRF01_AE compared with infectivity of subtype B (A) and the duration of primary HIV infection in months (B). Distribution of new infections (C) and distribution of prevalent infections (D) in 2003. In each bar plot, 2 cases are shown: the general case, with parameters as in Table 1, and a case with higher risk behavior (the frequency of sharing of injecting equipment was doubled). Dually infected individuals are those infected with subtype B and CRF01_AE at the same (double infections) or different (superinfections) time points.

subtype B. As the difference between the 2 infectivity levels increases, the difference between the respective incidences becomes larger but also more variable. Also, if primary infection lasts longer, the incidence of CRF01_AE is even higher compared with the incidence of subtype B (see Fig. 3B). This results from the assumption that the infectivity of CRF01_AE is greater than that of subtype B only during primary infection; hence, the duration of this highly infectious stage is important for the difference between the 2 incidences.

Distribution of Infections per Subtype

The distributions of new and prevalent infections according to infecting subtype in 2003 are shown in Figures 3C and D, respectively. In each bar plot, the general case and a case with higher risk behavior (the frequency of sharing of injecting equipment was doubled) are shown. In the general case, the percentage of new infections with subtype B was 18.4%, ranging from 2.4% to 31.2%. Further, 72.3% of infections were with CRF01_AE (range, 52.8%–91.1%), and 0.4% were dual infections (range, 0.0011%–4.1%). Superinfections accounted for 8.8% of incidence, ranging from 2.5% to 34.0%. It is important to note that in the whole range of parameter values examined here, CRF01_AE accounted for most new infections (minimum value = 52.8%) and dual infections accounted only for a minor fraction (maximal value = 4.1%). The contribution of subtype B, however, varied from a small fraction (2%) up to a third of new infections. Among infected individuals, 76.1% (range, 62.9%–93.3%) were infected only with CRF01_AE, 21.3% (range, 0.6%–33.8%) were infected only with subtype B, and 2.6% (range, 0.2%–18.7%) were dually infected. If risk behavior increases, the incidence of all variants increases, but the distribution of new and prevalent infections changes. The proportion of superinfections increases and, together with double first infections, constitutes 15.2% of all new infections. Superinfections with subtype B become slightly more incident than superinfections with CRF01_AE, whereas the opposite is true in the general case. Among those infected, the fraction dually infected increases to 7% and the fraction infected with subtype B decreases to 17.4%.

Protection Against Superinfection

Because little is known about the level of protection that infection with a specific HIV variant offers against a second

infection, we examined how it affects the distribution of subtypes. Figure 4 shows the fractions of infections with subtype B and CRF01_AE plotted against the protection level. As the protection decreases, the fractions of superinfections increase and the fractions of first infections decrease but the results become more variable. With 80% to 100% protection, 0% to 30% and 60% to 100% of infections are first infections with subtype B and CRF01_AE, respectively, whereas 0% to 10% and 0% to 7% are superinfections with subtype B and CRF01_AE, respectively. With 0% to 20% protection, 5% to 35% and 30% to 90% of new infections are first infections with subtype B and CRF01_AE, respectively, whereas 0% to 30% and 0% to 15% are subtype B and CRF01_AE superinfections, respectively.

Effect of Treatment

Figure 5 shows the effect of HAART, which was introduced in 2003. The percentage change in incidence compared with the value that incidence would have been at that point if HAART had not been introduced is shown in Figures 5A and B, and the distribution of new infections in 2013 is shown in Figure 5C. If HAART has the same effect on CRF01_AE and subtype B (see Figs. 5A, C), the incidence of both variants is reduced by the same percentage. The reduction in incidence increases over time, as more and more infected individuals initiate HAART. This shows that the magnitude of the impact of HAART rises over time. Ten years after the initiation of HAART, the fraction of first infections with CRF01_AE should have increased to 78%, that of subtype B should be 18%, and that of superinfections should be 4%. Further, to investigate whether treatment can alter the distribution of subtypes, we examined a hypothetic scenario, wherein HAART reduces the infectivity of CRF01_AE more than that of subtype B (the former was half of the latter for those treated). In that case, CRF01_AE incidence is reduced more than the incidence of subtype B, the fractions of first and second infections with CRF01_AE decrease, and the fractions of first and second infections with subtype B increase.

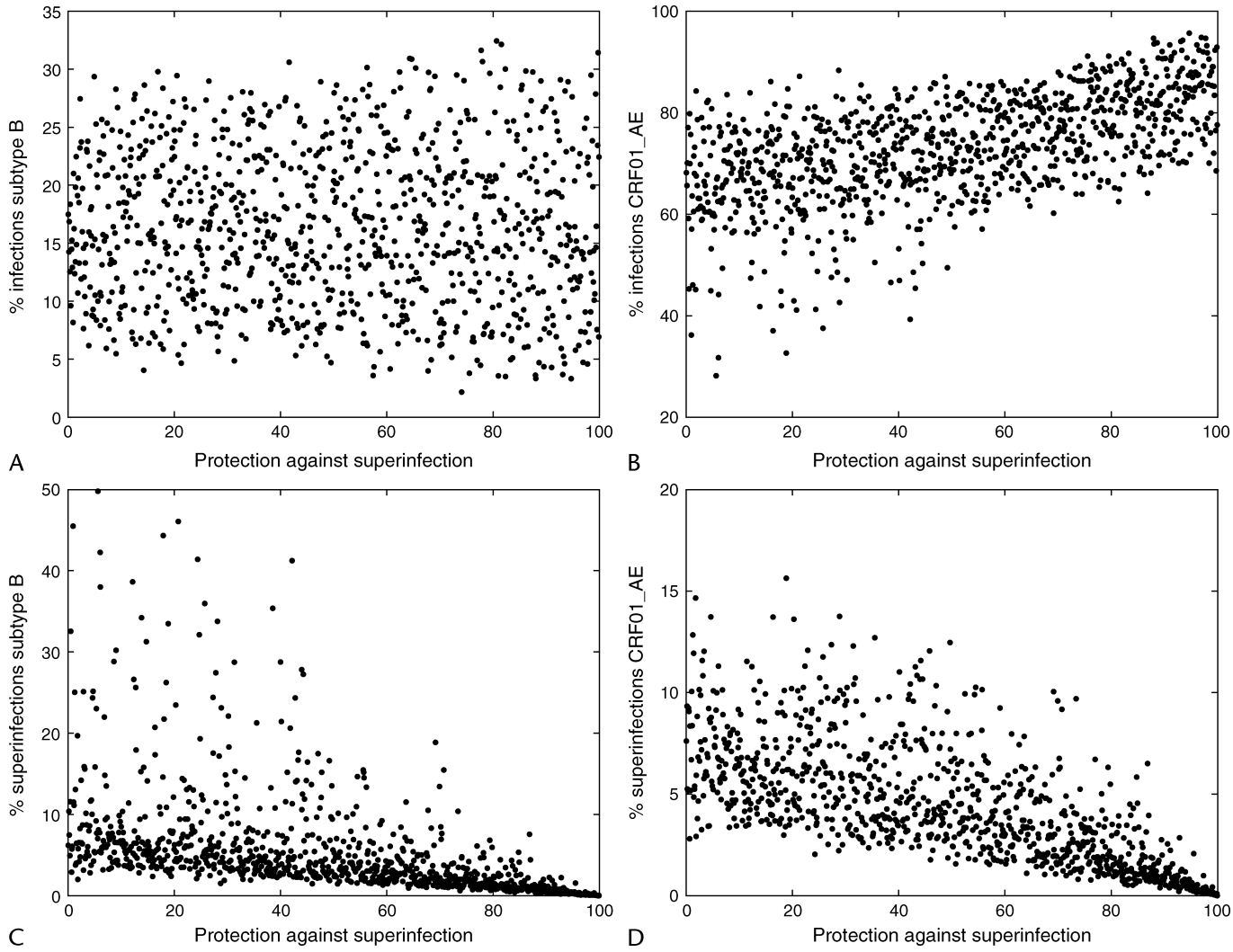

FIGURE 4. Fractions of first and second infections with subtype B and CRF01_AE, in 2003, plotted against the level of protection against superinfections (100% protection means that superinfection is not possible).

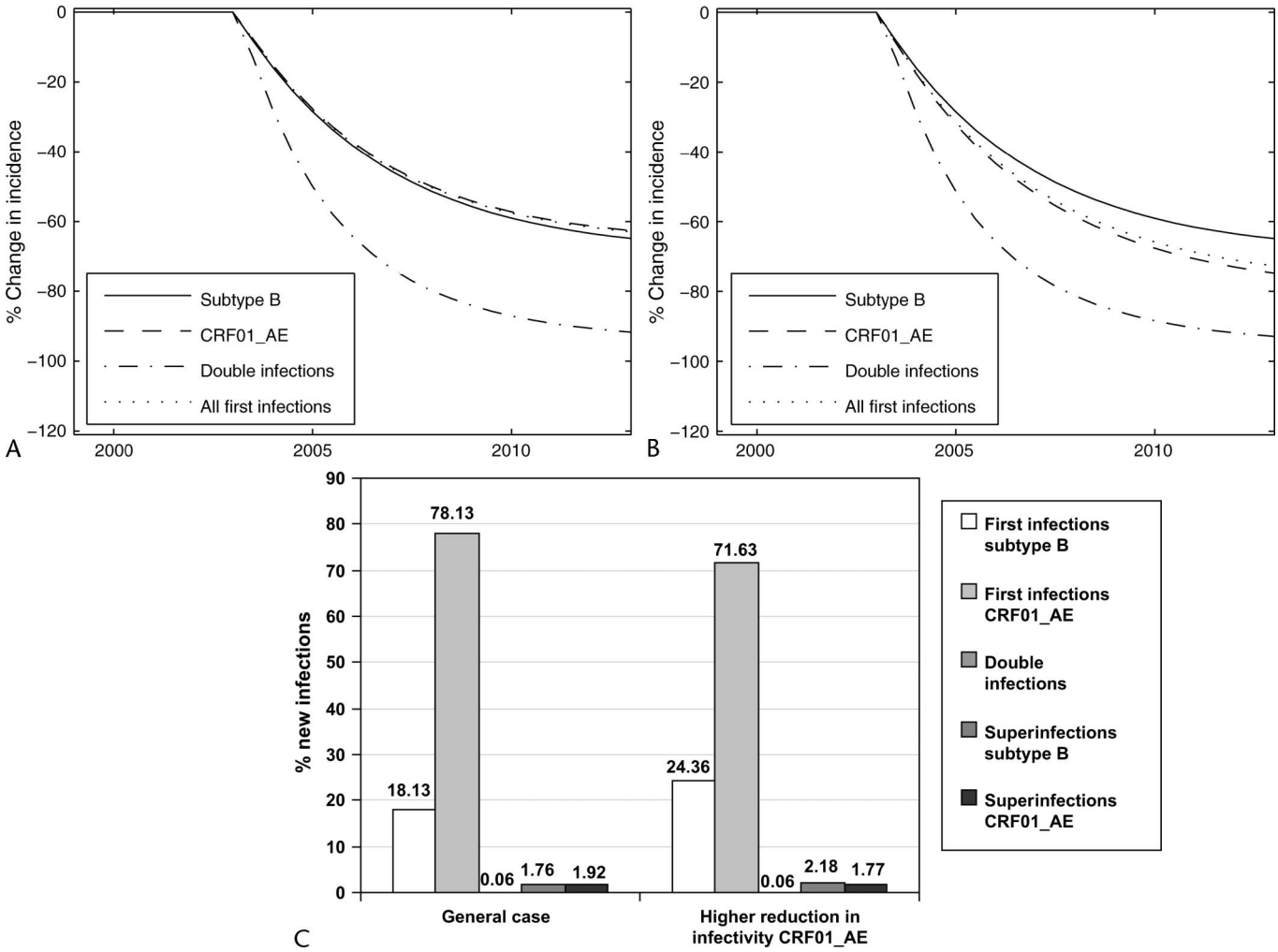

FIGURE 5. Effect of treatment. Percentage change in incidence attributable to treatment compared with the value that incidence would have had at that point if treatment had not been introduced, for the general case with parameters as given in Table 1 (A) and for a case in which HAART reduces the infectivity of CRF01_AE more than that of subtype B (infectivity of CRF01_AE was half of that of subtype B) (B). C, Distribution of new infections for the cases (A) and (B) in 2013.

DISCUSSION

Among the participants of the AIDSVAX B/E vaccine trial in the years 1999 to 2003, the incidence of CRF01_AE remained much higher than that of subtype B. Our results from the model indicate that CRF01_AE should remain dominant in the subsequent years and that the fraction of subtype B infections should decline over time. Subtype B is not likely to die out for a long time, however, and considerable fractions of the IDU population are likely to be infected with 1 of the 2 variants or both. The fraction of CRF01_AE infections is even larger if CRF01_AE is more infectious or the duration of primary HIV infection is longer. It is also interesting that if risk behavior increases, the incidence of superinfections increases more than the incidence of first infections and dual infections become more prevalent. Conversely, if infection with HIV offers a high level of protection against superinfections, superinfections should become rarer. Finally, the introduction of HAART can induce large reductions in the incidence of both HIV variants. The reductions should increase over time; therefore, treatment should considerably limit the epidemic.

The results are in agreement with those from epidemiologic and modeling studies. The incidence rates of subtype B and CRF01_AE in the preparatory IDU cohort in Bangkok in the years 1995 to 1998 were 1.2 and 4.3 infections per 100 PYs, respectively.[4] These are slightly higher than our estimates of incidence from the 1999–2003 cohort (see Fig. 2), which can be explained by lower risk behavior or better risk reduction counseling in this cohort or by a decline in the incidence of both variants. Furthermore, in the preparatory cohort, the incidence of subtype B and CRF01_AE superinfection was 1.5 and 3.9 per 100 PYs, respectively.[7] These incidences are also comparable to those found from our model for the years 1999 to 2003 (unfortunately, no data on double infections or superinfections from the 1999–2003 cohort were available). The distributions of new and prevalent infections per subtype are also in agreement with the data (see Figs. 3C, D).[4,14] The spread of 2 viral strains leading to infection with 2 infectious stages without

superinfection has been studied by Xiridou et al.[17] It has been shown that treatment may alter the outcome of the competition between the 2 strains, such that the strain that dies out after the introduction of treatment is the one that would have prevailed if treatment had not been introduced (see other modeling studies investigating the spread of multiple HIV subtypes[18–22]).

A limitation of this study is that several assumptions were made regarding dual infections, because limited empiric evidence is available. Specifically, caution is needed for the assumption that superinfections can occur after primary infection and the assumption that, in that case, both strains go through the primary phase. It has been argued that superinfections can occur only in a short window phase after infection. Even if they can occur during asymptomatic HIV infection, the depletion of target cells after the primary phase would imply that these "late" superinfections continue to the asymptomatic phase and do not go through the primary phase.

The model can be extended to account for the introduction of additional HIV variants and of recombination. This issue was beyond the scope of this article, but it would be interesting to investigate how a third HIV variant would change the current distribution of subtypes. Drug resistance was also not modeled here, but the model could be extended to account for its effect on the spread of the 2 HIV variants. Drug resistance may decrease the effect of treatment in reducing infectivity and prolonging survival. Therefore, the distribution of the 2 variants may be different, and the reductions in incidence might be smaller.[23] Another task for future studies is the modeling of heterogeneity in injecting behavior, such as different levels of sharing, lending, cleaning of injecting equipment, patterns of mixing between subgroups, and partnership networks.[24,25]

It is possible that a part of the increase in CRF01_AE can be explained by the interaction of IDUs with non-IDUs, mainly by means of sexual contact. Most HIV infections among heterosexuals in Bangkok are with CRF01_AE.[26] Therefore, any importation of HIV into the IDU population should with CRF01_AE. Nevertheless, the authors have observed that the introduction of new IDUs into the population is small in recent years (because fewer individuals initiate injecting), and thus expect the import of infection to be small. In addition, in the preparatory cohort, sexual behavior was not associated with increased risk for HIV infection;[4] therefore, sexual infections of IDUs were also considered to be limited.

The results of the present study suggest that the dominance of CRF01_AE over subtype B could be explained by a difference in their infectivity during primary HIV infection, even if infectivities in the latter phase of the infection are equal. Our findings also indicate that subtype B is declining but that subtype B and CRF01_AE should remain circulating in the population for many years. This information is crucial for the design of vaccines to ensure that the vaccine viruses match the circulating ones. Also, the result that increases in risk behavior may increase the fraction of superinfections should receive special attention, because individuals with dual infection can transmit both variants. Finally, it should be stressed that the introduction of public health interventions, such as wide availability of treatment, can have an enormous impact on the epidemic but that it may take a long time until their full effect is observed. In addition, they may alter the distribution of subtypes, thus giving the advantage to the variants that are currently underrepresented or on the decline. These findings are crucial for the design of intervention measures and highlight the need for strategies that can combat the bivalent epidemic in this population.

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APPENDIX

Let Y_{b1}, Y_{b2}, Y_{b3} denote the numbers of individuals infected only with subtype B in stage $j = 1,2,3$ of the infection (primary, chronic, and treated, respectively). Similarly, let Y_{e1}, Y_{e2}, Y_{e3} denote the numbers of individuals infected only with CRF01_AE, and let Y_{d1}, Y_{d2}, Y_{d3} denote the numbers of individuals dually infected. The term *HIV subtype i*, with $i = b,e,d$, refers to subtype B, CRF01_AE, and dual infection, respectively. Let X be the number of uninfected individuals, and let $N = X + \Sigma_{i,j}\, Y_{ij}$ be the total population size. The parameters and their values are shown in Table 1.

For the infectivity of dual infections, no data were found in the literature; therefore, the following assumptions were made. We assumed that $q_{bj} = p_{bj}(1-p_{ej})$ so as to account for transmission of subtype B but not of CRF01_AE. Similarly, we assumed that $q_{ej} = p_{ej}(1-p_{bj})$ and that $q_{dj} = p_{bj}\, p_{ej}$ so as to account for transmission of both subtypes. This means that (1) the total transmission of an HIV variant from persons with dual infection is equal to that from persons with a single infection with that same variant: $q_{bj} + q_{dj} = p_{bj}$ and $q_{ej} + q_{dj} = p_{ej}$ and (2) the total infectivity of persons with dual infection is $q_{bj} + q_{ej} + q_{dj} = p_{bj} + p_{ej} - p_{bj}p_{ej}$. Define $F_i = \phi\, \Sigma_j (p_{ij}\, Y_{ij} + q_{ij}\, Y_{dj})/N$, for $i = b,e$, and define $F_d = \phi\, \Sigma_j\, q_{dj}\, Y_{dj}/N$ as the per capita force of infection for those uninfected, using a simple mass action term for the mixing between the subgroups. Then, uninfected individuals get infected with subtype B, CRF01_AE, or both at the rates $F_b\, X$, $F_e\, X$, and $F_d\, X$, respectively. Persons infected with subtype B get superinfected during primary or chronic infection with CRF01_AE at the rates $\sigma_{b1}\, Y_{b1}\, F_e$ and $\sigma_{b2}\, Y_{b2}\, F_e$, respectively, and they then move to class Y_{d1}. Treated IDUs infected with subtype B (class Y_{b3}) get infected with CRF01_AE at the rate $\sigma_{b3}\, Y_{b3}\, F_e$, and they then move to class Y_{d3}. Those infected only with CRF01_AE are superinfected with subtype B at the rate $\sigma_{ej}\, Y_{ej}\, F_b$; those untreated move to class Y_{d1}, and those treated move to class Y_{d3}. The model is described by the following equations, with $i,k \in \{b,e\}$ and $k \neq i$:

$$\frac{dX}{dt} = \mu n - \mu X - X \sum_{j=b,e,d} F_j$$

$$\frac{dY_{i1}}{dt} = XF_i - \sigma_{i1}\, Y_{i1} F_k - (\mu + \gamma_i)\, Y_{i1}$$

$$\frac{dY_{i2}}{dt} = \gamma_i\, Y_{i1} - \sigma_{i2}\, Y_{i2} F_k - (\mu + \delta_i + \theta_{i2})\, Y_{i2}$$

$$\frac{dY_{i3}}{dt} = \delta_i\, Y_{i2} - \sigma_{i3}\, Y_{i3} F_k - (\mu + \theta_{i3})\, Y_{i3}$$

$$\frac{dY_{d1}}{dt} = XF_d + (\sigma_{b1}\, Y_{b1} + \sigma_{b2}\, Y_{b2})F_e + (\sigma_{e1}\, Y_{e1} + \sigma_{e2}\, Y_{e2})F_b - (\mu + \gamma_d)\, Y_{d1}$$

$$\frac{dY_{d2}}{dt} = \gamma_d\, Y_{d1} - (\mu + \delta_d + \theta_{d2})\, Y_{d2}$$

$$\frac{dY_{d3}}{dt} = \delta_d\, Y_{d2} + \sigma_{b3}\, Y_{b3} F_e + \sigma_{e3}\, Y_{e3} F_b - (\mu + \theta_{d3})\, Y_{d3}$$

Since 2000, the government of Thailand has expanded its antiretroviral program. Until 2003, however, only a small number of individuals with HIV/AIDS were under treatment.[27] Therefore, we assumed that HAART was introduced in 2003 and that individuals are treated since then 3 to 7 years after the beginning of chronic infection (the progression rate, δ_i, from stage 2 to stage 3 was 0 up to 2003 and in the range from 0.14–0.33 per year after 2003; for all, $i = b,e,d$). In 1999, the prevalence of HIV was 35%, and 76% of those who were HIV-positive were infected with CRF01_AE.[14] These fractions were taken in the ranges from 25% to 45% and from 66% to 86%, respectively, for the initial conditions (year 1999) in the numeric results presented here.