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Predicting the level of vaccine-induced cross-immunity necessary to eliminate HIV epidemics composed of multiple subtypes

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HIV; multiple subtypes; mathematical model; vaccine; elimination; coexistence

In a very interesting study, Kiwanuka *et al.* [1] report significant differences in the rates of transmission associated with different HIV-1 subtypes in Rakai, Uganda. Controlling for other factors, they find the transmission rate of subtype A to be nearly double that of subtype D. The authors suggest that differential transmission rates among subtypes are important for: (i) HIV vaccine development and testing, (ii) understanding the dynamics of HIV-1 epidemics in different geographical regions and (iii) projections of the pandemic.

Over a decade ago, we constructed a mathematical model of an HIV epidemic composed of multiple co-circulating subtypes that differed on the basis of transmissibility [2]. We constructed this subtype model because preliminary data, collected in the mid 1990's, indicated that HIV subtypes might exhibit differences in transmission efficiency [3,4]. We used our model to predict temporal trends in prevalence of co-circulating subtypes and the potential impact of prophylactic vaccines. Specifically, we investigated (theoretical) vaccines that would provide a degree of protection against infection by one subtype and induce cross-immunity against infection by another subtype. As the focus of our modeling work is so closely in line with the implications of [1], we now reexamine our subtype model using the remarkable data of Kiwanuka *et al.* in order to gain insights into current epidemiological patterns and predict the long-term outcome of mass vaccination against HIV in Uganda.

In [2], we used the model to calculate basic reproductive numbers (R_0) for each of the co-circulating subtypes. R_0 represents the expected number of secondary infections caused by the introduction of one infectious individual into a completely susceptible population, and hence is a measure of fitness. Our modeling showed that, in the absence of vaccination, the subtype with the largest R_0 will eventually outcompete and eliminate the other subtype. However, we found elimination would take over 100 years to occur and that the prevalence of the less-fit subtype could remain high for several decades. If subtype D emerged before subtype A in Uganda, our results could explain why the less-fit subtype D is currently more prevalent than subtype A and is slowly decreasing (71 to 63% from 1994 to 2002), whereas the prevalence of subtype A is slowly increasing (15 to 20% from 1994 to 2002) [5].

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As Kiwanuka *et al.* point out, it is important to develop vaccines that are effective against several subtypes in order to control HIV epidemics. Our previous modeling has shown that mass vaccination could result in several long-term outcomes: (i) elimination of both subtypes, (ii) elimination of only one subtype, and (iii) persistence of both subtypes [2]. We showed that which outcome would occur depends on the R_0 's, the vaccine coverage level, and three characteristics of the vaccine: take (i.e. the fraction of individuals for which the vaccine produces a protective immune response), degree of protection against one subtype, and the level of cross-immunity (i.e. degree of protection against the second subtype) [2].

The model was originally formulated to reflect transmission of HIV in a community of men who have sex with men. However, the model can be parameterized to reflect heterosexual transmission in Uganda because no significant differences between male-to-female and female-to-male transmission were observed in [1]. Doing so, we assume that the transmissibility of subtype A is approximately double that of subtype D [1] and that the average time to develop AIDS is 8 and 6.5 years, for subtypes A and D, respectively [6].

Figure 1 shows the long-term outcomes of mass vaccination given different levels of vaccine-induced cross-immunity, vaccine take and coverage. Calculations were made assuming the vaccine would provide an 80% degree of protection against infection by subtype A. It may be seen that even using this highly effective vaccine, HIV elimination will only be possible if a high fraction of the population is effectively vaccinated (Figure 1). For example, even if the vaccine take is 75%, it would be necessary to vaccinate over 90% of the population and for the vaccine to induce more than 30% cross-immunity against subtype D. If the level of cross-immunity is too low, elimination would not be possible and the less-fit subtype D could outcompete subtype A (Figure 1). This occurs when the vaccine's protection renders subtype A less fit than subtype D.

Our findings indicate that the presence of multiple subtypes will make HIV elimination more difficult and that mass vaccination campaigns may produce surprising results.

Sincerely Dr. David J. Gerberry and Professor Sally Blower

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Fig. 1.

Predicted long-term outcomes of a vaccination policy in Uganda using a vaccine with an 80% degree of protection against infection from subtype A. The fraction effectively vaccinated is calculated as the product of take and population coverage (e.g. if the vaccine induces a protective immune response in 50% of the 90% of the population that is inoculated, then the fraction effectively vaccinated would be 45%). In this figure, the basic reproductive number (R_0) is assumed to be 2.25 and 1.25 for subtypes A and D, respectively.