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HIV population-level adaptation can rapidly diminish the impact of a partially effective vaccine

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ABSTRACT

Background: Development of an HIV vaccine might be essential to ending the HIV/AIDS pandemic. However, vaccines can result in the emergence and spread of vaccine-resistant strains. Indeed, analyses of breakthrough infections in the HIV phase 3 vaccine trial RV144 identified HIV genotypes with differential rates of transmission in vaccine and placebo recipients. We hypothesized that, for HIV vaccination programs based on partially effective vaccines similar to RV144, HIV adaptation will rapidly diminish the expected vaccine impact.

Methods and findings: Using two HIV epidemic models, we simulated large-scale vaccination programs and, critically, included HIV strain diversity with respect to the vaccine response. We show here that rapid population-level viral adaptation can lead to decreased overall vaccine efficacy and substantially fewer infections averted by vaccination, when comparing scenarios with and without viral evolution (with outcomes depending on vaccination coverage, vaccine efficacy against the sensitive allele, and the initial resistant allele frequency). Translating this to the epidemic in South Africa, a scenario with 70% vaccination coverage may result in 250,000 infections (non-averted by vaccination) within 10 years of vaccine rollout that are due solely to HIV adaptation, all else being equal.

Conclusions: These findings suggest that approaches to HIV vaccine development, program implementation, and epidemic modeling may require attention to viral adaptation in response to vaccination.

1. Introduction

Despite concerted global effort and the existence of effective methods for prevention, HIV continues to be a public health crisis. The need for an HIV vaccine remains paramount. The phase 3 RV144 HIV vaccine trial is the only trial of an HIV vaccine to show modest success in preventing infection [1]. RV144 resulted in an estimated 31% vaccine efficacy (VE) at 3.5 years post-vaccination ($p = .04$, modified intent-to-treat analysis). The vaccine was partially protective but not therapeutic; i.e. vaccinated individuals had decreased rates of infection, but breakthrough infections were not associated with differences in early HIV plasma viral loads, post-infection CD4+ T cell counts, or HIV disease progression rates, when comparing vaccine and placebo recipients [2]. The RV144 results spurred the development of the recently initiated HVTN

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702, a large phase 3 HIV vaccine trial in South Africa that aims to replicate the RV144 findings in a different study group, with regimen and schedule that follow from RV144 (with several modifications, including a vaccine insert specific to HIV subtype C, the most common subtype in South Africa).

Partially effective vaccines have been of enduring scientific, clinical, and theoretical interest. For HIV, two decades of mathematical modeling studies suggest that partially effective vaccines, whether protective or therapeutic, can have a substantial impact on the HIV pandemic [3–15]. More recently, HIV epidemic models were used to predict the impact of a partially effective (protective) vaccine similar to RV144 in terms of VE and duration. Models were used to assess the impact of vaccination programs with 30% and 60% population coverage of sexually active adults, with subsequent vaccine rollouts at 1- to 5-year intervals [16]. Results were consistent across several model and epidemic types, e.g., multiple vaccination rounds, at 60% coverage, were predicted to prevent 5–15% of new infections over 10 years [17–24]. The expected impact of vaccination programs depended on vaccination coverage, VE, and the duration of vaccine protection [25].

However, the potential for HIV adaptation at the population-level in response to vaccination was not considered in these modeling studies. The requirements for adaption (via natural selection) are few: there must be phenotypic variation in a population, this variation must be heritable (linked to genetic variation), and this variation must be related to fitness (differential reproduction) [26]. Evidence from RV144 follow-up studies suggest that, with respect to a partially effective protective vaccine, HIV meets these requirements. Namely, genetic sieve analyses of RV144 breakthrough infections showed that sequences from infected vaccine recipients differed from those isolated from infected placebo recipients. Two signatures were identified in the Env V2 region: in the vaccine recipients, K169X mutations were more frequent (34% vs. 17%) and 181I was more conserved (91% vs. 71%). VE against viruses matching the vaccine at position 169 was 48% (95% confidence interval (CI) 18% to 66%), whereas VE against viruses mismatching the vaccine at position 181 was 78% (CI 35% to 93%) [27,28]. Thus, heritable (genetic) variation in HIV can be associated with differential infection rates in a vaccinated population, making viral adaptation a potential outcome.

We hypothesized that HIV population-level adaptation after vaccine rollout will result from selection acting on a viral locus containing an allele that confers resistance to the vaccine response; i.e., viruses not blocked by a vaccine-elicited immune response will spread in the HIV-infected population. Our goal was to predict the public health impact of this viral evolution, under varying VE, population vaccination coverage, and initial frequency of vaccine-resistant genotypes. We quantified this impact in terms of the resistant genotype frequency, the overall VE, and the cumulative HIV infections averted by vaccination.

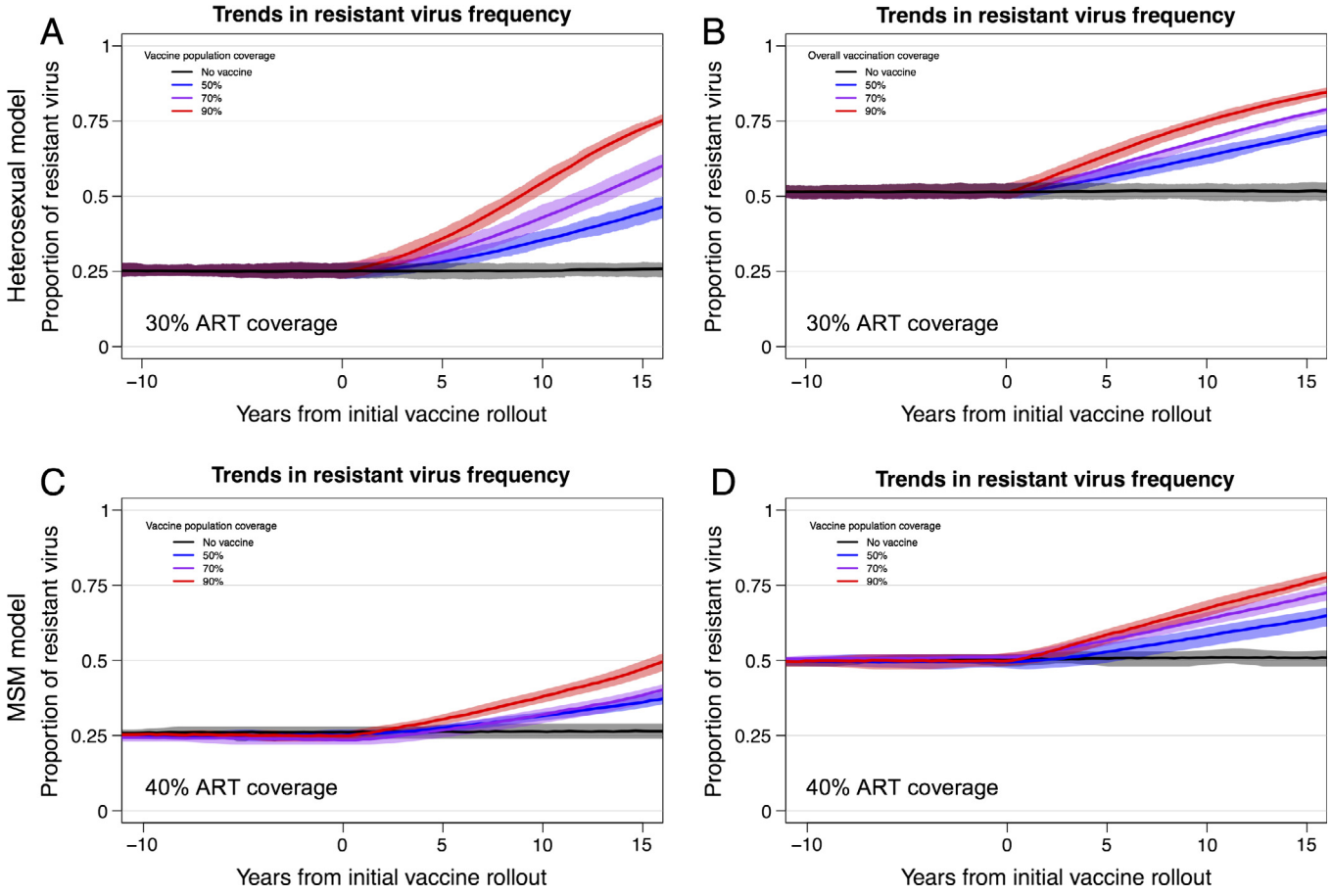

Fig. 1. Trends in the proportion of HIV strains that are resistant to a vaccine-driven immune response. Trends in the proportion of resistant strains among all HIV strains (with interquartile ranges) for 20 replicate HIV epidemic simulations from heterosexual (panels A and B) and MSM (panels C and D) models. Panels A and C depict results from epidemic scenarios that included an initial resistant strain (VE = 0.0) at a proportion = 0.25 and a sensitive virus (VE = 0.75). Panels B and D depict results from scenarios with initial resistant strain proportion = 0.50 and a sensitive virus VE = 0.90. Background population ART coverage was at 30% for the heterosexual model and 40% for the MSM model. (See Fig. S1 for equivalent results from heterosexual model scenarios in which a high-risk subgroup is preferentially targeted for vaccination, which leads to substantially decreased overall vaccination coverage but results in similar effects of HIV adaptation on resistant virus frequency.)

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