



Cornering HIV: Taking advantage of interactions between selective pressures

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Summary Adaptive immune responses, cellular restrictive factors and antiretroviral drugs, target multiple regions in the Human Immunodeficiency Virus (HIV) proteome, imposing diverse pressures to viral adaptation. However, the virus is remarkably able to escape from these pressures as mutations are selected. In many cases these mutants have diminished viral fitness. We propose that the concerted action of strategically placed agents and pressures in a host can limit HIV variation capacity while inhibiting its replication. These mechanisms would corner HIV by selecting conflicting adaptive mutations, each having a disadvantage in face of another selective pressure. This would keep the virus unable to efficiently escape the suppressive effects of selective pressures. Cornering between antiretroviral drugs and cytotoxic T lymphocytes may explain recent observations, and can be predicted and used in viral control strategies. This idea can be extended to numerous other identified sites in the viral genome that confer selective pressures. We describe these other sites and how they could be induced to interact in prophylactic or therapeutic cornering strategies, as well as their experimental verifications. Cornering would control HIV infection better than current strategies, focused on few, albeit important, sites in the HIV genome.
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Introduction

The variation and extraordinary evolutionary capabilities of the Human Immunodeficiency Virus (HIV) have seriously compromised all the prophylactic and therapeutic approaches proposed so far to control its infection [1–4]. Variation in the virus renders immune responses ineffective as escape mutants emerge [5], and it limits the duration of treatments with the appearance of viruses resistant to antiret-

roviral (ARV) drugs [6]. Further complicating this picture, the main human selective pressure acting on the virus, the cytotoxic T lymphocyte (CTL) response, is also highly polymorphic, increasing HIV variability at the individual as well as the population level [7]. Thus, vaccine strategies making use of highly conserved sites as immunogens have found important limitations [8]. Similarly, successful highly active antiretroviral therapy (HAART), based on the use of various antiretroviral (ARV) drugs that suppress viral replication, does not eliminate the possibility of eventual virologic failure due to the possible accumulation of drug-resistance mutations [6]. However, HIV variability is not unlimited, due to

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the small size of its genome and functional restrictions determined by viral viability and fitness. Moreover, natural and artificial selective pressures such as the immune response, intracellular restrictive factors and ARV therapy determine restrictions for HIV variation, which in conjunction to intrinsic variability restrictions in the viral genome may in principle be used to overwhelm HIV capabilities of adaptation through the accumulation of mutants. We hereby propose an approach that could make current HIV control strategies more efficient, based on cornering the virus by limiting its adaptation possibilities in the context of multiple selective pressures. As the nature of these multiple variation restrictions becomes better understood, the possible outcomes of the interactions between different selective pressures become predictable, thus allowing its use to improve control strategies. Furthermore, these predictions of potentially useful selective pressure interactions for HIV control can be tested experimentally.

Hypothesis

Given that CTL responses and ARV therapy act in concert as evolutionary selective pressures on HIV, we propose that, in given individuals and conditions, there are specific sites in the HIV genome under the simultaneous influence of these two suppressive factors (immune and pharmacological). Each mechanism would select for an adaptive

mutation with a disadvantage in the presence of the other selective pressure. The simultaneous presence of the restrictive factors will keep the virus incapable of efficiently escaping the suppressing effects (Fig. 1b). This cornering strategy would be designed by determining an individual's HLA alleles, which would allow to predict the main targeted CTL epitopes, and whether they include ARV resistance mutations.

Generalizing this idea, if two or more selective pressures are made to act simultaneously on HIV, they would facilitate the accumulation of mutations in different positions of the genome that would render the virus particularly unfit, and therefore less pathogenic (Fig. 2). HIV could thus be cornered by particular sets of selective pressures.

We propose that this approach would increase the probability of success in the development of immunogens for vaccines, as well as in the individualization of treatments, compared to current strategies based on targeting specific conserved sites in the viral genome.

Fundamentals, case predictions, and implications

Cytotoxic T Lymphocytes are a predictable, multiple selective pressure

It is well known that cytotoxic T lymphocytes (CTLs) constitute a main factor in the control of HIV infec-

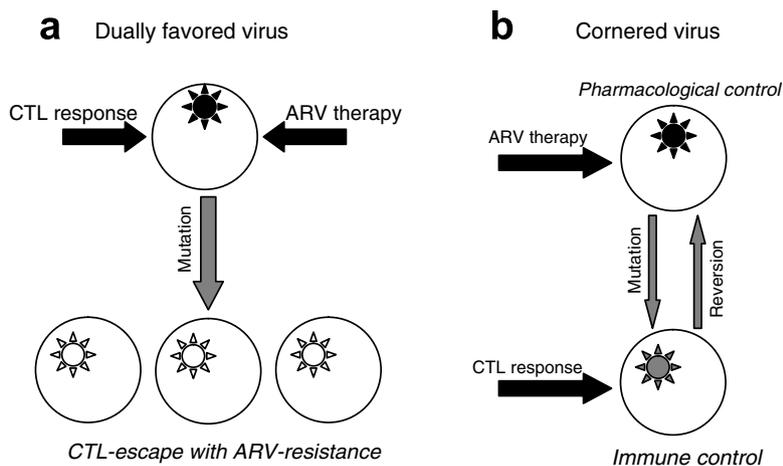


Figure 1 Two ways in which selection by cytotoxic T lymphocytes (CTLs) and selection by antiretrovirals (ARV) may concur in a site in HIV pol gene products. (a) A particular CTL escape mutation also confers resistance to ARV drugs. An individual able to select such mutation (by targeting CTL epitopes comprising the possible mutation site), would favor the predominance of the mutation during ARV treatment. Under these conditions, the mutation would confer a double advantage to the virus. (b) A particular CTL epitope comprises an amino acid in HIV reverse transcriptase or protease that corresponds to a drug-resistance mutation. In this case, the selection of the drug resistance mutation during ARV treatment would favor the presence of such an epitope and its further recognition and control by CTLs. Either variant would be controlled by antiretroviral drugs or host's CTLs. The virus would thus be cornered.

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