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Jing Wu, University of Tennessee, Knoxville
The R5 to X4 Coreceptor Switch: A Dead-End Path, or a Strategic Maneuver?
Lessons from a Game Theoretic Analysis

Sharon Bewick · Jing Wu · Scott C. Lenaghan · Ruoting Yang · Mingjun Zhang · William Hamel

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Abstract In this paper, we show how a game theoretic analysis can provide a model to explain the interdependence of host produced APOBEC3G levels and virus encoded Vif levels. We then use the relationship between these two opposing proteins in order to predict the success of two different HIV-1 viral variants, R5 and X4. From our analysis, we show that when APOBEC3G strongly favors mutation from an R5 strain to an X4 strain, it can be optimal for HIV-1 to suppress transmission of the X4 variant, despite the loss of X4 fitness potential. This is particularly true when the X4 strain significantly interferes with the host adaptive immune response, when Vif production is limited, or when host APOBEC3G targets the X4 strain more severely than the R5 strain. Using the proposed game theoretic analysis, we show that transmitting only R5 viruses has two advantages so far as HIV-1 is concerned. First, it allows for an increased R5 viral load due to immune interference caused by the X4 strain, and second, it forces the host to down-regulate APOBEC3G production, which is automatically favorable to the virus. APOBEC3G down-regulation, which is predicted in our model for a wide range of parameter values, may offer an explanation for the observed low level of APOBEC3G transcription and translation in hosts infected with HIV-1.

Keywords HIV-1 · Coreceptor switch · Game theory · Nash equilibrium

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S. Bewick · J. Wu · S.C. Lenaghan · R. Yang · M. Zhang (✉) · W. Hamel
Biomedical Engineering Program, Department of Mechanical, Aerospace and Biomedical Engineering, University of Tennessee, Knoxville, TN 37996, USA

e-mail: mjzhang@utk.edu
1 Introduction

Human immunodeficiency virus type 1 (HIV-1) enters target cells through a set of sequential interactions between receptors on the host cell surface, and glycoprotein gp120 on the viral envelope. The first step in this entry process is the interaction between gp120 and the cellular receptor CD4. While interaction between CD4 and gp120 are necessary to initiate viral binding to the target cell, the fusion of the virus to the cell membrane and subsequent viral access to the host cell itself requires an additional interaction between gp120 and a coreceptor on the host cell surface. Although 12 potential coreceptors have been observed in vitro, in vivo HIV-1 appears to be primarily restricted to the coreceptors CCR5 and CXCR4 (Doms and Trono 2000; Skrabal et al. 2007; Schmidtmaierova et al. 1998; Fouchier et al. 1996; Bjorndal et al. 1997).

Coreceptor usage by HIV-1 is strain specific. Viruses which use CCR5 to gain access to host cells are known as R5 variants, while those which use CXCR4 are known as X4 variants. Interestingly, since CCR5 and CXCR4 coreceptors are differentially expressed on the surfaces of target cells in the host system, R5 and X4 viruses exhibit differing tropism. Typically, CCR5 coreceptors are found on activated T-cells, monocytes, macrophages, and dendritic cells (DC), while CXCR4 coreceptors are found on naive T-cells, B-cells, and macrophages (Shields and Adams 2002). As well, X4 viruses appear to have faster replication kinetics (Van’t Wout et al. 1998; LeGuern et al. 1993) than their R5 counterparts, while R5 viruses appear to have better ability to transmit between hosts. One of the most puzzling aspects of the relationship between R5 and X4 viruses is the unusual and yet predictable time course for their respective appearances during HIV-1 progression. In almost all cases, R5 HIV-1 accounts for the primary infection, independent of the route of transmission (Connor et al. 1997; Long et al. 2002; Pope and Haase 2003; Schuitemaker et al. 1992). Despite the early predominance of the R5 variant, however, emergence of an X4 strain occurs in ~50% of patients who go on to develop the clinical symptoms of AIDS (Panos and Nelson 2007; Ho et al. 2007; Koot et al. 1993). In several studies, X4 viruses have been found in HIV-infected individuals at all stages of infection, suggesting that X4 viruses may be transmitted along with R5 viruses, but may initially replicate at lower levels (Groenink et al. 1991). Other studies, however, indicate that X4 emerges through mutation of the infecting R5 strain (Van Rij et al. 2000).

While X4 variants do not appear in all patients prior to the development of AIDS, detection of X4 in the bloodstream is typically associated with a poorer prognosis and a faster disease progression (Richman and Bozzette 1994; Connor et al. 1997). As a result, there is a significant interest in understanding the driving forces which lead to emergence of viral strains capable of using CXCR4 coreceptors. Most hypotheses proposed to date fall into three categories. According to the transmission mutation hypothesis (Vignuzzi et al. 2006), R5 viruses are selectively transmitted, and evolve into X4 strains once infection in the host has been established. An alternate explanation, known as the target-cell-based hypothesis, assumes that both R5 and X4 viruses are transmitted, but that their relative populations change over the course of the infection in response to a gradual shift in the availability of host cells expressing CCR5 and CXCR4. Finally, the immune-system based hypothesis suggests that X4 viruses
are selectively targeted by the host immune system, and thus only have a chance to 
emerge after the immune system has been sufficiently degraded by HIV infection. 
Obviously, these hypotheses are not mutually exclusive. Indeed, while each offers 
a partial explanation for the unusual time profile of HIV variants during an infec-
tion, none of the three can independently account for all observations associated with 
the R5 to X4 coreceptor switch. Significant effort is currently being focused on de-
termining exactly when X4 restriction occurs and exactly what aspects of infection 
pathology and immune defense lead to reduction in X4 transmission and/or replica-
dation during the early stages of HIV infection.

Despite ongoing efforts to elucidate the nature of early selection forces against 
HIV-1 X4 variants, few studies have considered the question of why HIV-1 would 
generate an X4 variant in the first place. We believe, however, that answers to this 
question will lead to new insight into X4 transmission and HIV-1 biology in general. 
In particular, we note that while the X4 strain may exhibit more effective within-host 
replication during the later stages of HIV, its between-host fitness (Coombs et al. 
2007; Gilchrist and Coombs 2006), at least under the transmission mutation hypoth-
esis, is remarkably limited. Without being transferred to an alternate host, X4 viral 
variants necessarily represent a ‘dead-end’ path. It is unusual then that X4 viruses 
should consistently appear in approximately half of all AIDS patients, and yet never 
evolve an improved capacity to spread beyond their current host. While this may 
represent a biological constraint, the presence of dual-tropic strains which could po-
tentially infect host cells present during both early and late stages of AIDS argues 
against such limits.

Focusing on the transmission mutation hypothesis, we propose an alternate 
explanation—that the limited transmission of X4 viral variants may be required as 
part of a strategic maneuver to undermine host immune defenses. This hypothesis 
is in keeping with the recently proposed cooperative aspects of quasi-species viral 
populations in general (Vignuzzi et al. 2006), and suggests that emergence of the X4 
strain may represent more than antigenic escape. It may, in fact, be part of an elab-
orate strategy which allows for more HIV-1 replication and transmission than would 
be possible with populations of either R5 or X4 viruses alone. Using game theoretic 
models, we show that the ability to mutate from one coreceptor usage to another 
has the potential to benefit HIV-1 both through immune interference and through the 
‘threat’ of a penalty cost associated with increased host defense. Provided that these 
advantages are significant, the optimal HIV-1 strategy is to maintain a population of 
viruses with the potential for co-receptor switching. When X4 viruses are incapable 
of reverting back to R5 variants, maintaining such a population necessarily implies 
limiting X4 transmission.

Mathematical models (Wodarz and Nowak 1998; Callaway et al. 1999; Wodarz et 
al. 1999; Wodarz and Krakauer 2000; Ho et al. 1995; Chao et al. 2004; Perelson et 
al. 1996; Wiegel and Perelson 2004) have been developed in the previous literature. 
Mathematical models of HIV dynamics have proven valuable in understanding the 
mechanisms of many of the observed features of the progress of the HIV infection. In 
Ribeiro et al. (2006), a model of R5 to X4 switching, based on the hypothesis that X4 
and R5 viruses have a preferential tropism for naïve and memory T-cells, respectively. 
In Biebricher and Eigen (2005), HIV-1 infected individuals show heterogeneous viral
populations described as viral quasi-species. In this paper, we will modify the model form (Wodarz 2006), and allow for the R5–X4 coreceptor switch.

Since it is the interplay between the host defense and the viral offense that determines HIV-1’s optimal strategy, we choose to formulate the problem using a game theoretical approach, since game theory allows us to simultaneously consider the actions taken by both the virus and the host. Game theory has been employed previously to biological systems (Smith 1982), and to pathogens specifically (Bremermann and Pickering 1983). In Bremermann and Pickering (1983), for example, game theory was used to predict pathogen virulence based on a model that considered competition between different viral strains within a single host. Game theory does not, however, appear to have found wide stream application as a tool for analyzing the particular strategies and their resulting outcomes in the context of battle between infectious agents and the immune system. We suggest, however, that a game theoretic approach may greatly aid in our understanding of the progression of certain diseases because: (1) the optimal nature of a certain viral offensive strategy can only be appreciated in the context of the host defense against it, (2) the optimal nature of a certain host defensive strategy can only be appreciated in the context of the viral offense toward it, (3) assuming the virus does adopt an optimal offensive strategy, this strategy can only be predicted with reference to the host defensive strategy that it must overcome, (4) assuming the host does adopt an optimal defensive strategy, this strategy can only be predicted with reference to the viral offensive strategy that it must defeat. In other words, we expect that, in most cases, an understanding of host and virus behavior will require careful consideration of the highly intertwined optimization problems faced by the two parties in the context of each others actions.

2 The Basic Model of Host and Viral Dynamics

Rather than focus on the details of viral and immune cell dynamics, which have been considered elsewhere (Nowak and May 2000), we chose a model capable of capturing the effects responsible for driving the viral invasion strategy and the immune system response. Following Wodarz’s analysis of heterologous antigen stimulation (Wodarz 2001, 2006), we wrote a set of four ordinary differential equations describing the two viral variants and their corresponding immune responses. Table 1 gives a summary of the variables described in the model, while Table 2 gives a summary of parameters in the model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>( v_{R5} )</td>
<td>Viral load of R5 variant</td>
<td>Virions mm(^{-3})</td>
</tr>
<tr>
<td>( v_{X4} )</td>
<td>Viral load of X4 variant</td>
<td>Virions mm(^{-3})</td>
</tr>
<tr>
<td>( c_{R5} )</td>
<td>Adaptive immune response against R5 variant</td>
<td>Cells mm(^{-3})</td>
</tr>
<tr>
<td>( c_{X4} )</td>
<td>Adaptive immune response against X4 variant</td>
<td>Cells mm(^{-3})</td>
</tr>
</tbody>
</table>
Table 2 Parameters used in the model (1a)–(1d)\textsuperscript{29,36,52}

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_{R5}$</td>
<td>Growth rate of R5 viral variant</td>
<td>$\sim 0.5$ virons/µL day</td>
</tr>
<tr>
<td>$r_{X4}$</td>
<td>Growth rate of X4 viral variant</td>
<td>$\sim 1$ virons/µL day</td>
</tr>
<tr>
<td>$d_{R5}$</td>
<td>Death rate of R5 specific immune response</td>
<td>$\sim 3$ cells/µL day</td>
</tr>
<tr>
<td>$d_{X4}$</td>
<td>Death rate of X4 specific immune response</td>
<td>$\sim 1$ cells/µL day</td>
</tr>
<tr>
<td>$s_{R5}$</td>
<td>Antigenic stimulation of immune response against R5 viral variant</td>
<td>$\sim 1$ cells/µL day</td>
</tr>
<tr>
<td>$s_{X4}$</td>
<td>Antigenic stimulation of immune response against X4 viral variant</td>
<td>$\sim 1$ cells/µL day</td>
</tr>
<tr>
<td>$a_{R5}$</td>
<td>Immune response reduction rate caused by R5 viral variant</td>
<td>$\sim 0.5$ cells/µL day</td>
</tr>
<tr>
<td>$a_{X4}$</td>
<td>Immune response reduction rate caused by X4 viral variant</td>
<td>$\sim 0.1$ cells/µL day</td>
</tr>
<tr>
<td>$p_{R5}$</td>
<td>Immune response activation rate against R5 viral variant</td>
<td>$\sim 0.25$ cells/µL day</td>
</tr>
<tr>
<td>$p_{X4}$</td>
<td>Immune response activation rate against X4 viral variant</td>
<td>$\sim 0.25$ cells/µL day</td>
</tr>
<tr>
<td>$k_{R5}$</td>
<td>Carrying capacity of R5 viral variant</td>
<td>$\sim 1000$ virons/µL day</td>
</tr>
<tr>
<td>$k_{X4}$</td>
<td>Carrying capacity of X4 viral variant</td>
<td>$\sim 1000$ virons/µL day</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\dot{v}_{R5} &= r_{R5}v_{R5} \left(1 - \frac{v_{R5}}{k_{R5}}\right) - p_{R5}v_{R5}c_{R5} \quad \text{(1a)} \\
\dot{v}_{X4} &= r_{X4}v_{X4} \left(1 - \frac{v_{X4}}{k_{X4}}\right) - p_{X4}v_{X4}c_{X4} \quad \text{(1b)} \\
\dot{c}_{R5} &= s_{R5}v_{R5}c_{R5} - d_{R5}c_{R5} - a_{R5}c_{R5}v_{X4} \quad \text{(1c)} \\
\dot{c}_{X4} &= s_{X4}v_{X4}c_{X4} - d_{X4}c_{X4} - a_{X4}c_{X4}v_{R5} \quad \text{(1d)}
\end{align*}
\]

In (1a)–(1d), $v_{R5}$ and $v_{X4}$ are the viral loads and $c_{R5}$ and $c_{X4}$ the adaptive immune responses against viruses of the R5 and X4 variants, respectively. In Wodarz (2006), the immune responses were taken as memory CTL cell levels. We note, however, that similar equations, albeit with slightly different dependences for immune response stimulation, have been used to model antigenic variation specifically in HIV (Nowak and May 2000). The analysis in Nowak and May (2000), however, left the exact nature of the immune response open, and we will adopt a similar description, suggesting that $c_{R5}$ and $c_{X4}$ may approximate either levels of CTL cell-mediated viral clearance, or levels of antibody neutralization invoked by proliferation of B-cells.

Note that the model makes a number of assumptions that are worth mentioning explicitly (Wodarz 2006).

(i) In the absence of an immune response, viral growth is exponential, with a rate constant $r_i$ which may be different for the different variants, $i = R5, X4$. Viral
growth of a variant, however, is slowed by specific immune responses against it at a rate proportional to both its viral load, and the level of the immune system activation that it evokes, \( p_i v_i(t) c_i(t) \).

(ii) In the absence of antigenic stimulation, immune responses have a death rate of \( d_i \). Antigenic stimulation though causes proliferation of a variant specific immune response at a rate proportional to both the existing level of the immune response (positive feedback) and the concentration of antigen present in the system, \( s_i v_i(t) c_i(t) \).

(iii) Finally, heterologous antigenic stimuli reduce the specific immune responses to virus \( i \) at a rate \( a_i \).

In Wodarz (2006), the mechanism suggested for immune interference by a heterologous viral variant was the upper limit on the total size of the memory CTL cell pool. In Nowak and May (2000), however, a similar reduction term was attributed to the effects of HIV on CD4 T-lymphocytes, and thus on the degree of stimulus provided by helper T-cells. If we adopt the interpretation in Nowak and May (2000), our parameter \( s_i \) can be taken as the net growth rate, with \( s_i = s'_i - a_i \), where \( s'_i \) is the actual growth rate, and \( a_i \) is the reduction in immune response strength caused by loss of CD4 T-cell help as a result of viral variant \( i = R5, X4 \). It should be noted that in (1a)–(1d) we have assumed no cross-reactive immune response for the R5 and X4 viral variants. An additional term may be added to (1a) and (1b) to account for cross-reactivity, however, our analysis shows that these terms, provided they are small, do not alter the qualitative predictions of our model.

Since we are concerned with the long term behavior of the HIV viral load and the immune system response against it, we will focus our attention on the steady-states in (1a)–(1d). Here, we note that the long-term behavior corresponds to the asymptomatic period of HIV infection. A system with a single viral variant (i.e. \( v_j(t) = 0 \)) has the following stable fixed points:

\[
\begin{align*}
\text{For } s_i k_i & \le d_i \frac{d_i}{s_i}, & v_{i,s}^{1*} &= k_i, & c_{i,s}^{1*} &= 0, \\
\text{For } s_i k_i & > d_i \frac{d_i}{s_i}, & v_{i,s}^{2*} &= \frac{d_i}{s_i}, & c_{i,s}^{2*} &= \frac{r_i (k_i - d_i)}{p_i k_i s_i},
\end{align*}
\]

where the superscripts 1 and 2 are used to denote the two different solutions possible for the different regions of parameter space. A system with both the R5 and X4 viral variants has fixed points at

\[
\begin{align*}
\text{For } s_i k_i & < d_i + a_i k_j \text{ and } s_j k_j < d_j + a_j k_i, & v_{i,d}^{1*} &= k_i, & v_{j,d}^{1*} &= k_j, & c_{i,d}^{1*} &= 0, & c_{j,d}^{1*} &= 0, \\
\text{For } s_i k_i & < d_i + \frac{a_i d_j}{s_j} \text{ and } s_j k_j > d_j + a_j k_i, & v_{i,d}^{2*} &= k_i, & v_{j,d}^{2*} &= \frac{d_j + a_j k_i}{s_j}, & c_{i,d}^{2*} &= 0, & c_{j,d}^{2*} &= -\frac{r_j (-k_j s_j + d_j + a_j k_i)}{p_j k_j s_j},
\end{align*}
\]

Since we are concerned with the long term behavior of the HIV viral load and the immune system response against it, we will focus our attention on the steady-states in (1a)–(1d). Here, we note that the long-term behavior corresponds to the asymptomatic period of HIV infection. A system with a single viral variant (i.e. \( v_j(t) = 0 \)) has the following stable fixed points:
For \( s_ik_i > d_i + \frac{a_id_j}{s_j} \) and \( sjk_j > d_j + \frac{a_jd_i}{s_i} \)

\[
\begin{align*}
\nu^{3*}_{i,d} &= \frac{d_is_j + a_id_j}{(s_is_j - a_ia_j)} , \\
\nu^{3*}_{j,d} &= \frac{d_js_i + a_jd_i}{(s_js_i - a_ia_j)} , \\
\end{align*}
\]

\[
\begin{align*}
c^{3*}_{i,d} &= \frac{r_i(d_is_j + a_id_j + (a_ia_j - s_is_j)k_i)}{p_ik_i(a_ia_j - s_is_j)} , \\
c^{3*}_{j,d} &= \frac{r_j(d_js_i + a_jd_i + (a_ia_j - s_js_j)k_j)}{p_jk_j(a_ia_j - s_js_j)}
\end{align*}
\]

where, once again, superscripts 1, 2 and 3 denote the three possible solutions in the different regions of parameter space. Clinical data reveal that during HIV infection, the concentration of the virus never gets high compared to the number of T-cells, thus from here on we adopt the assumption that the carrying capacity is large compared to the viral load \( s_ik_i \gg d_i + a_id_j/s_j \) and consider only steady states (2b) and (3c).

Since we are ultimately interested in the transition from the R5 viral strain to the X4 viral strain, we use parameters from (1) to further define \( t_m \), the time at which the X4 viral variant appears. To incorporate mutation, and the appearance of the X4 viral variant into the model, we assume that there is a constant per replication probability, \( m_{R5} \), that an R5 virus will acquire the mutation(s) necessary to convert it into an X4 virus. From (1) and (2b), we find the replication rate for the R5 variant, \( \omega_{R5} \), as the viral influx term evaluated at the single infection steady state viral load \( v^*_{R5,s} \)

\[
\omega_{R5}(t) = v^*_{R5,s}(t) \left( r_{R5} - \frac{v^*_{R5,s}(t)}{k_{R5}} \right)
\]

The mutation rate, \( \gamma_{R5} \), then becomes

\[
\gamma_{R5} = m_{R5}v^*_{R5,s} \left( r_{R5} - \frac{v^*_{R5,s}}{k_{R5}} \right) \approx m_{R5}v^*_{R5,s}r_{R5}
\]

where the approximation follows from our assumption that the R5 carrying capacity is large compared to the R5 viral load \( k_{R5} \gg v^*_{R5,s} \). Because APOBEC3G drives mutation from G-to-A, which is in the R5 to X4 direction, we assume that \( m_{R5} \gg m_{X4} \), and take the limit \( m_{X4} \sim 0 \) ignoring any backward mutation from an X4 virus into an R5 virus.

While there is significant controversy surrounding the exact timing of the R5 to X4 coreceptor switch and how it relates to the mutation rate of HIV in general (Pastore et al. 2004), we approximate the average coreceptor switch time from (5) by defining a probability density function, \( f_{R5 \rightarrow X4} \), for mutation from variant R5 to variant X4 at time \( t \)

\[
f_{R5 \rightarrow X4}(t) = \gamma_{R5} e^{-\gamma_{R5}t}
\]
Assuming that the end of the game is the death of the host at time $t = t_f$, the average coreceptor switch time becomes

$$t_m = \int_0^{t_f} f_{R5\to X4}(t) \, dt + \int_{t_f}^{\infty} f_{R5\to X4}(t) \, dt = \frac{1 - e^{-m_{R5}v^*_R5,s_{R5}}} {m_{R5}v^*_R5,s_{R5}}$$  \hfill (7)

If we assume a linear dependence of $m_{R5}$ on excess APOBEC3G levels, we then have

$$t_m = \frac{1 - e^{-\xi(u_A - u_v)v^*_R5,s_{R5}}} {\xi(u_A - u_v)v^*_R5,s_{R5}}$$  \hfill (8)

with

$$m_{R5} = \xi(u_A - u_v)$$  \hfill (9)

where $u_A$ is the APOBEC3G concentration, $u_v$ the Vif concentration and $u_A > u_v$.

As a final consideration, we incorporate the effect of mutation into the replication rate of the virus by assuming a linear dependence of $r_{R5}$ and $r_{X4}$ on $m_{R5}$ such that

$$r_{R5} = r^0_{R5} - \mu_{R5}m_{R5} = r^0_{R5} - \mu_{R5}\xi(u_A - u_v)$$  \hfill (10a)

$$r_{X4} = r^0_{X4} - \mu_{X4}m_{R5} = r^0_{X4} - \mu_{X4}\xi(u_A - u_v)$$  \hfill (10b)

where $r^0_{R5}$ and $r^0_{X4}$ are the replication rates of the R5 and X4 viruses respectively in the absence of APOBEC3G induced mutation, while $\mu_{R5}$ and $\mu_{X4}$ are constants which determine the strength APOBEC3G induced reduction in viral replication rate.

### 3 Game Theoretic Formulation

While our game theoretic formulation focuses on APOBEC3G and Vif levels, we are interested in elucidating a possible relationship between those levels and the observed low transmission of the X4 viral variant. To highlight this relationship, we treat transmission on a higher level, showing how the presence or absence of X4 transmission set up strikingly different games requiring strikingly different strategies in terms of APOBEC3G and Vif production. In formulating our game theoretic model out of the basic dynamics described above, we again assume that there is zero probability of random backward mutation from X4 to R5, meaning that the X4 viral variant becomes an absorbing state. In other words, any infection with an initial inoculum of X4 will be transmitted as X4 to all subsequent hosts. This is not the case, however, when the initial inoculum contains R5 (or R5 and X4) viruses. Indeed, when R5 viruses are present, the infection has a finite probability of transmitting to a new host as either R5 or X4 (or both). Over time then, we expect that transmission of X4 will lead to a slow drain of R5 viruses into the X4 state. We therefore assume that HIV-1 can develop in two directions based on whether or not X4 viruses are transmitted. First, the virus can suppress transmission of the X4 variant entirely. Under this scenario, the R5 virus population will be maintained, despite the fact that X4 viral variants will arise during the course of infection. For future reference, we term this the ‘R5’
The R5 to X4 Coreceptor Switch: A Dead-End Path, or a Strategic Game. Second, the virus can allow transmission of the X4 variant. Under this option, the R5 virus will eventually disappear from the population, leaving only X4. As a result, choosing to transmit X4 is essentially choosing infection by X4 without the possibility of mutation to an alternate variant with a different coreceptor usage. For future reference, we term this the ‘X4’ game. In reality, backward mutation from X4 to R5 likely occurs to some small extent, however given the expected slow rate of A to G substitution, the faster rate of G to A substitution, and the reported low fitness of viral variants intermediate between the R5 and X4 states (Pastore et al. 2004), we do not expect backward mutation to be significant.

3.1 Host’s Strategy

As suggested in the Introduction, we formulate our game theoretic model under the assumption that host produced APOBEC3G aids the transitional pathway from R5 to X4. Because APOBEC3G regulates G-to-A hypermutation and because APOBEC3G can stimulate the R5 to X4 transitional pathway, APOBEC3G introduces a very interesting trade-off in terms of battling HIV-1. On the one hand, up-regulating APOBEC3G increases the rate of deleterious mutations in the HIV-1 genome (Pastore et al. 2004). In addition, APOBEC3G appears to have another as yet uncharacterized antiviral defense mechanism. As a result, high levels of APOBEC3G are expected to lower the overall fitness of HIV-1 and aid the host in clearance of the virus. On the other hand, since higher quantities of APOBEC3G increase the rate of G-to-A hypermutation, they also have the potential to increase the rate of progression from infection with R5 to coinfection with R5 and X4. In contrast to APOBEC3G’s antiviral activity, its tendency to stimulate R5 to X4 mutation is harmful to the host, as the presence of X4 is correlated with higher overall viral loads, and a more rapid progression toward AIDS (Richman and Bozzette 1994; Connor et al. 1997). The host then is trapped in a situation where the optimal level of APOBEC3G production is not necessarily the biologically constrained maximum that can be produced in the absence of HIV-1, but rather a lower level that represents a balance between maximizing antiviral activity and minimizing the rate of emergence of X4 viral variants. Given these arguments, our game theoretic control parameter for the immune system is the APOBEC3G level expressed by the host.

We assume that the host’s goal is to clear as many viruses as possible, thus we describe the host payoff function with (11)

\[
F_H = \begin{cases} 
-(v_{R5,s}^{*} + \beta c_{R5,s}^{*})t_m \\
-(v_{R5,d}^{*} + v_{X4,d}^{*} + \beta c_{R5,j}^{*} + \beta c_{X4,j}^{*})(t_f - t_m) \\
-\kappa_{AP}u_A^2 + \kappa_{1mh,R5m}m + \kappa_{2mh,R5m}m^2, & \text{R5 game} \\
-(v_{X4,s}^{*} + \beta c_{X4,s}^{*})t_f - \kappa_{AP}u_A^2 + \kappa_{1mh,X4m}m + \kappa_{2mh,X4m}m^2, & \text{X4 game}
\end{cases}
\]  

(11)

In (11), there is a negative cost associated with increased viral load and a negative cost associated with an increased adaptive immune response toward each viral variant (first two terms in the R5 game and first term in X4 game). Second, we include a quadratic term which reflects the cost of APOBEC3G production (third and second
Table 3  Parameters used in the host payoff function (11)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>1</td>
<td>Cost of an increased adaptive immune response</td>
</tr>
<tr>
<td>$\kappa_{AP}$</td>
<td>$8 \times 10^{11}$</td>
<td>Cost of APOBEC3G production</td>
</tr>
<tr>
<td>$\kappa_{1mh,i} \ (i=R5,X4)$</td>
<td>$2 \times 10^8$</td>
<td>The first order gain of host mutation for the two virus strains</td>
</tr>
<tr>
<td>$\kappa_{2mh,i} \ (i=R5,X4)$</td>
<td>$5 \times 10^{10}$</td>
<td>The second order gain of host mutation for the two virus strains</td>
</tr>
</tbody>
</table>

Table 4  Variables used in the host payoff function (11)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c^*_i,s \ (i=R5,X4)$</td>
<td>The steady state immune response levels towards viral variant when $i$ is singly present in the host</td>
</tr>
<tr>
<td>$c^*_i,d \ (i=R5,X4)$</td>
<td>The steady state immune response levels towards viral variant when $i$ is jointly present in the host</td>
</tr>
<tr>
<td>$t_f$</td>
<td>The time of host death</td>
</tr>
<tr>
<td>$m$</td>
<td>The rate at which R5 mutates to X4</td>
</tr>
<tr>
<td>$l_m$</td>
<td>Switching time when the X4 variant appears</td>
</tr>
<tr>
<td>$u_A$</td>
<td>APOBEC3G produced by host</td>
</tr>
</tbody>
</table>

terms in R5 and X4 games, respectively). Finally, we assume that the host payoff has a term reflecting additional effects that result from increased mutation (fourth and fifth terms in R5 game and third and fourth terms in X4 game). The term describing the additional effects is formed assuming that these effects can be expanded in powers of the mutation rate from R5 to X4. We suggest that mutation, beyond triggering emergence of X4, is largely beneficial to the host thus we take the additional mutational terms as positive gains, rather than as negative costs. Some of the effects contributing to the overall benefit that the host accrues from increased APOBEC3G induced mutation are a slower rate of viral replication, a longer time required for the virus to establish steady state viral loads, an increased probability that HIV-1 will be cleared rather than spreading, and a reduction in the levels of additional adaptive and innate immunity required to battle the virus. The parameters used in the host payoff function are shown in Table 3 and variables are shown in Table 4.

3.2 Virus’s Strategy

In formulating the viral strategy, the obvious choice for the viral control is the level of Vif produced, and thus the degree to which APOBEC3G induced hypermutation is suppressed. As with host selection of APOBEC3G levels, viral selection of Vif levels depends on a trade-off between the negative effects of an overall increased mutation rate (and any additional antiviral activity exhibited by APOBEC3G), and the positive effects of a specifically enhanced rate of transition to X4 coreceptor usage. Qualitatively, then the viral Vif levels should depend both on the APOBEC3G levels produced by the host and on the particular benefits accrued by having the possibility of mutation from one coreceptor usage to another.
We take the virus’ goal as its ability to replicate through future generations, thus the virus payoff function can be formed as in (12). We then assume that HIV transmission from the initial host to a new host can occur at any time from the beginning of the infection, \( t = 0 \), up until the time of the host death at \( t = t_f \). For any specific point in time, \( t \), we assume that transmission of variant \( i \) is proportional to the variant’s steady state viral load at that time. By defining transmission in terms of steady state population levels, we neglect the effects of transient dynamics both during establishment of the initial infection, and if it occurs, during invasion of the R5 population by the X4 variant.

\[
F_v = \begin{cases} 
  v_{R5,s}^* t_m + v_{R5,d}^* (t_f - t_m) - \kappa_{vif} u_v^2, & \text{R5 game} \\
  v_{X4,s}^* t_f - \kappa_{vif} u_v^2 - \kappa_{1mv,R5} m - \kappa_{2mv,R5} m^2, & \text{X4 game}
\end{cases}
\]

In (12), there is a positive benefit associated with viral load (the first and second terms in the R5 game and the first term in the X4 game), a negative cost associated with Vif production (the third term in the R5 game and the second term in the X4 game), and as in the case of the host payoff function, two terms associated with additional costs of increased mutation (the fourth and fifth terms in the R5 game and the third and fourth terms in the X4 game). Justification for the payoff function above is as follows: First, since we have assumed that persistence of R5 in the viral population requires complete suppression of X4 transmission, there is no payoff associated with X4 viral levels in the R5 game. In contrast, when X4 viral variants have the ability to transmit to a new host, we assume that they are the only viral variant present at equilibrium, thus the payoff for a strategy which assumes infectious X4 is proportional to the X4 viral load, \( v_{X4,s}^* \) in a host singly infected with an X4 strain.

We assume a quadratic function for the cost of Vif production on the general grounds that Vif production is expected to become increasingly difficult at increasing higher Vif levels. Finally, the additional cost of mutation is represented by both a linear and a second order term, and as before, we use this functional form assuming that mutation costs can be expanded in powers of the mutation rate from R5 to X4. The costs to the virus represented by this term are the earlier appearance of X4 and the related faster progression of the host to AIDS and death (limiting spread of the virus to new hosts) as well as a lower overall replication rate of the virus which, while it does not change the steady state viral loads, does increase the length of time required to reach those steady state levels. Given that there are a range of effects contributing to mutational costs, we allow for the possibility that \( \kappa_{1mv,R5} \) and \( \kappa_{2mv,R5} \) differ depending on the overall viral strategy assumed, thus \( \kappa_{1mv,R5} \) and \( \kappa_{2mv,R5} \) may differ from

| Table 5 Parameters used in the virus payoff function (12) |
|----------------|----------------|----------------|
| Parameter       | Value          | Description    |
| \( \kappa_{vif} \) | \( 10^{10} \)  | Cost of Vif production |
| \( \kappa_{1mv,i} (i=R5,X4) \) | 0              | The first order cost of mutation |
| \( \kappa_{2mv,i} (i=R5,X4) \) | \( 7 \times 10^{10} \) | The second order cost of mutation |
Table 6  Variables used in the virus payoff function (12)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$v^*_i,s$ ($i=R5,X4$)</td>
<td>The steady state $i$ viral loads when $i$ is singly present in the host</td>
</tr>
<tr>
<td>$v^*_i,d$ ($i=R5,X4$)</td>
<td>The steady state $i$ viral load when $i$ is jointly present in the host</td>
</tr>
<tr>
<td>$u_v$</td>
<td>Vif level produced by virus</td>
</tr>
<tr>
<td>$t_f$</td>
<td>The time of host death</td>
</tr>
<tr>
<td>$m$</td>
<td>The rate at which R5 mutates to X4</td>
</tr>
<tr>
<td>$t_m$</td>
<td>Switching time when the X4 variant appears</td>
</tr>
<tr>
<td>$u_A$</td>
<td>APOBEC3G produced by host</td>
</tr>
</tbody>
</table>

$k_{lmv,X4}$ and $k_{2mv,X4}$. We expect, however, that $k_{vif}$ will be similar regardless of the viral transmission strategy involved. The parameters used in the virus payoff function are shown in Table 5 and variables are shown in Table 6.

4 Game Theoretical Analysis

The goal of our game theoretical analysis is to show how experimentally observed APOBEC3G and Vif production are qualitatively in keeping with predictions from games which restrict X4 transmission, and that overall, games with limited X4 transmission can outperform games with full X4 transmission, from the point of view of viral fitness.

4.1 Nash Equilibrium

We begin by searching for the Nash equilibrium to the APOBEC3G and Vif game defined in (11) and (12). This corresponds to finding $u_A$ and $u_v$ such that

$$\frac{\partial F_v(u_A, u_v)}{\partial u_v} = 0 \quad (13a)$$

$$\frac{\partial F_h(u_A, u_v)}{\partial u_A} = 0 \quad (13b)$$

subject to the constraints

$$\frac{\partial^2 F_v(u_A, u_v)}{\partial u_v^2} < 0 \quad (14a)$$

$$\frac{\partial^2 F_h(u_A, u_v)}{\partial u_A^2} < 0 \quad (14b)$$

$$u_A - u_v \geq 0 \quad (14c)$$

$$u_A \geq 0 \quad (14d)$$
In (13) and (14), we have shown the explicit dependence of the payoff functions, $F_v$ and $F_h$ on host APOBEC3G production, $u_A$, and viral Vif production, $u_v$. Constraints (14a) and (14b) assure that the solutions to (13) are maxima, constraint (14c) reflects the fact that biologically relevant mutation rates are always positive, and constraints (14d) and (14e) similarly reflect the fact that biologically relevant APOBEC3G and Vif levels are always greater than or equal to zero.

Given the nature of the equations involved, it is difficult to obtain closed form solutions for $u_A$ and $u_v$ from (13a) and (13b), thus we resort to numerical methods, presenting a sample Nash equilibrium analysis for a biologically reasonable set of model parameters (see Table 1) and weighting parameters. Specifically, we use the model parameters $r_{R5} = 0.5$, $r_{X4} = 1.0$, $d_{R5} = d_{X4} = 3$, $s_{R5} = s_{X4} = 1$, $a_{R5} = 0.5$, $a_{X4} = 0.1$, $p_{R5} = p_{X4} = 0.25$, $k_{R5} = k_{X4} = 1000$, $\mu = 1000$, and the weighting parameters $\beta = 1$, $\xi = 1$, $\kappa_{vif} = 1E10$, $\kappa_{AP} = 8E11$, $\kappa_{1mv,X4} = \kappa_{1mv,R5} = 0$, $\kappa_{2mv,X4} = \kappa_{2mv,R5} = 7E10$, $\kappa_{1mh,X4} = \kappa_{1mh,R5} = 2E8$, $\kappa_{2mv,X4} = \kappa_{2mv,R5} = 5E10$. Figure 1 shows graphs for the viral and host best response functions defined by (13). Given a set of system parameters, the viral best response is a function which describes the optimal level of Vif production for any level of APOBEC3G production, $u_v^*(u_A)$, where we have used (*) to denote optimality. Likewise, given a set of system parameters, the host best response is a function which describes the optimal level of APOBEC3G production for any level of Vif production, $u_A^*(u_v)$. The point(s) at which viral and host best response functions intersect are Nash equilibria, since they represent pairs of APOBEC3G and Vif values for which unilateral deviation on the part of the virus fails to increase the viral payoff and unilateral deviation on the part of the host fails to increase host payoff. In what follows, we will use $(u_v^N, u_A^N)$ to symbolize points which are Nash equilibria for the game described in (1) and (2).

The particular combination used in Fig. 1, gives $t_m = 3728$ days, which is in accordance with the experimental data of 8 to 10 years (Connor et al. 1993;
Bozette et al. 1993). In Fig. 1, the region of the $u_A / u_v$ plane with $u_A - u_v = m < 0$ is shown in grey, while the region with $u_A - u_v = m \geq 0$ is shown in white. We concern ourselves with game theoretic solutions for which $u_A - u_v = m \geq 0, u_A \geq 0$ and $u_v \geq 0$, since this is the biologically relevant region. Nash equilibria in the portion of the plane with $u_A - u_v = m \geq 0, u_A \geq 0$ and $u_v \geq 0$ are marked by open circles. Comparing the ‘R5’ and ‘X4’ games in Fig. 1, several general properties are apparent. First, it is clear that the optimal Vif level for the ‘R5’ game, $u^*_{v,R5}$, is significantly lower than the optimal Vif level for the ‘X4’ game, $u^*_{v,X4}$. Second, we see that the optimal APOBEC3G level for the ‘R5’ game, $u^*_{A,R5}$, is lower than the optimal APOBEC3G level for the ‘X4’ game, $u^*_{A,X4}$. In addition Vif production in the ‘R5’ game does not begin until APOBEC3G production has reached a critical level, which we term $u_{A_{onset}}$. In contrast, Vif production in the ‘X4’ game begins as soon as APOBEC3G production rises above zero. Furthermore, comparing the host best response curves, we see that APOBEC3G production falls of more sharply as a function of Vif levels in the ‘R5’ game than it does in the ‘X4’ game. Also, optimal APOBEC3G production in the absence of Vif, $u^*_A(0)$, is significantly lower for the ‘R5’ game than it is for the ‘X4’ game. Finally, we note that when the Nash equilibria $(u^N_{v,R5}, u^N_{A,R5})$ and $(u^N_{v,X4}, u^N_{A,X4})$ are substituted back into the R5 and X4 viral payoff functions, respectively; they yield payoffs of $F_{v,R5}(u^N_{v,R5}, u^N_{A,R5}) = 1.46E4$ and $F_{v,X4}(u^N_{v,X4}, u^N_{A,X4}) = 1.33E4$, thus for the set of parameters considered, the R5 game does, in fact, outperform the X4 game from the virus’ perspective. These observations from our sample simulation are analyzed and discussed below. A further analysis of the model in terms of more general parameters is outlined in the supplementary information.

5 Discussion

Several general conclusions can be drawn from the game theoretic analysis presented above. Most importantly, we have shown that the ‘R5’ transmission can, in fact, be an advantage to the virus despite the sacrifice in X4 transmission. Using game theory, we have highlighted the two main reasons for this ‘R5’ advantage. First, if X4 is capable of interfering with the immune system, the ‘R5’ game offers direct benefits to the virus in terms of an increased R5 viral load ($v^*_{R5,d} > v^*_{R5,s}$). This advantage is associated with $u^*_{v,R5} < u^*_{v,X4}$ and is expected only when the X4 virus interferes with the immune system thereby allowing a growth in the R5 viral population ($a_{X4} > 0$). Given that these advantages rely on $u^*_{v,R5} < u^*_{v,X4}$, they are expected to become more significant with increasing cost of Vif production, $\kappa_{vif}$.

The second advantage associated with the R5 game is independent of immune interference effects on the R5 virus population. Instead, it is a host controlled effect, making it easy to overlook without a game theoretic analysis. Namely, if the host plays according to the rules of the game as set up by the ‘R5’ game and, in particular, if the host takes into account the penalties associated with emergence of the ‘X4’ strain, then the host is forced to down-regulate APOBEC3G production in the presence of the R5 viral strain. In other words, the ‘R5’ game essentially turns one of the host’s primary retroviral defenses against itself. Several recent papers
have suggested the possibility that the clinically observed incomplete suppression of APOBEC3G by HIV Vif may indeed be evidence of HIV capitalizing on a host defense mechanism for generation of viral diversity, antigenic escape, and coreceptor switching (Berkhout and de Ronde 2004; Pastore et al. 2004; Pillai et al. 2008; Simon et al. 2005). To our knowledge, however, these studies have not considered the indirect consequences to the host when HIV-1 hijacks one of the immune systems most effective innate antiretroviral immune defenses for its own gain. In particular, our game theoretic analysis has shown that a viral strategy which relies on incomplete Vif suppression of hypermutation actually forces the host immune system to down-regulate APOBEC3G, which is favorable for the virus.

By using game theory to analyze the host response to viral Vif levels, we have rationalized poorly understood observations regarding APOBEC3G regulation. Several studies have shown that APOBEC3G mRNA expression levels are lower in HIV-infected subjects than they are in HIV-uninfected subjects (Cho et al. 2006). In Cho et al. (2006), the authors noted that this effect remains to be explained. Our analysis shows that the optimal strategy for the host does indeed involve down-regulating APOBEC3G levels from their biologically constrained maxima when in the presence of HIV-1. In addition, there is evidence that Vif can interfere with APOBEC3G mRNA translation (Van Rij et al. 2000), and while this mechanism has been attributed to a viral tactic for battling APOBEC3G defense, we suggest that it may actually reflect a host adaptation as well. Obviously, it is to the host’s advantage to encourage a lower level of APOBEC3G translation in the presence of Vif, thus it is not surprising that hosts might be selected such that APOBEC3G translation is impeded by high Vif levels. An interesting experimental comparison would be to determine APOBEC3G expression levels in patients infected with other viruses that are negatively impacted by APOBEC3G action. It appears that APOBEC3G levels are high in patients chronically infected with hepatitis C (Komohara et al. 2006), although similar results have been suggested for HIV long-term non-progressors (LTNP), thus at the moment it is difficult to determine whether differing APOBEC3G responses are dependent on the nature of the infecting virus, or the level of immune control and immune system function. Clearly, more experimental work is required in order to ascertain the degree to which the human immune system modulates APOBEC3G production in response to HIV-1.

While our model provides interesting insight into APOBEC3G expression levels, we want to highlight the more significant concept that we have presented, and that is that APOBEC3G regulated mutation has a definite direction due to preferential induction of G → A substitutions. As a result, a viral strategy which relies on incomplete APOBEC3G suppression can only be effective if A rich viruses tend to have less potential for transmission. Otherwise, an incomplete APOBEC3G suppression strategy will, over several generations, lead to viruses with an A-rich ceiling that are themselves more susceptible to APOBEC3G defense than their predecessors. By using game theory applied to the R5 and X4 viral strains, we have highlighted the advantages that are associated with incomplete Vif suppression of hypermutation (‘R5’ game). We suggest that when these advantages are significant, limited transmission of X4 variants should not be surprising, but, in fact, expected.

The question, then is whether or not the advantages associated with the ‘R5’ game are significant in HIV-1. Given the biological attributes of the X4 variant, including its
ability to directly infect and destroy precursor T-lymphocytes (Berkowitz et al. 1998; Panos and Nelson 2007), we suggest that there is ample evidence of X4’s ability to impede the efforts of the adaptive immune response, thus we expect $a_{X4} \gg 0$, automatically giving the ‘R5’ game an advantage over the ‘X4’ game, provided both strains replicate to similar viral loads in the absence of the other strain.

6 Conclusion

In this paper, we have shown how the observed Vif down-regulation and limited X4 transmission may be coupled if HIV-1 uses X4 emergence to increase R5 viral load or as a threat against APOBEC3G-mediated immune mechanisms. These considerations suggest that, contrary to a dead-end path, the X4 virus may, in fact, be part of an elaborate viral strategy to undermine one of the immune systems most potent antiretroviral defenses. In addition to rationalizing the relationship between Vif down-regulation and X4 transmission, we have found a potential explanation for the as yet unexplained lower levels of APOBEC3G transcription and translation in the presence of HIV-1/Vif that have been reported in the literature. In order to analyze the complex interactions, we have employed a game theoretic treatment of the host/virus system, since this allowed us to simultaneously consider the joint optimization problems faced by the two parties in the context of each other’s actions. In particular, we note how our predicted APOBEC3G and Vif strategies in the ‘R5’ and ‘X4’ games differ, and suggest that this clearly shows how a complete understanding of the interplay between HIV-1 and the host immune system can only be developed using a game theoretic or game theory related framework.

Finally, we note that the ‘R5’ game adopted by HIV-1 is particularly elegant, in that it is, essentially, a solution to the problems associated with an escalating arms race. If the virus cannot keep up with host APOBEC3G levels, as is likely, the virus will lose the war and be eliminated unless it can, through some alternative mechanism, force the host to limit APOBEC3G production. To circumvent its inherent disadvantage, it appears as if HIV-1 appends an additional cost to host defense, even at the expense of its own short-term fitness. Our game theoretic analysis clearly shows how this additional cost can alter the structure of the game, and how, in the long run, the loss of between-host X4 fitness can be outweighed by the substantial benefits associated with a collapse in the APOBEC3G/Vif arms race.

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References


