The role of mutation accumulation in HIV progression

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The onset of AIDS is characterized by the collapse of the immune system after a prolonged asymptomatic period. The mechanistic basis of this disease progression has remained obscure, hindering the development of effective therapies. Here I present a mechanism that underlies the deterioration of the immune system during HIV infection. The elevated turnover of lymphocytes throughout the asymptomatic period is postulated to result in the accumulation of deleterious mutations, which impairs immunological function, replicative ability and viability of lymphocytes. This mutational meltdown is proposed to occur throughout the hierarchy of lymphocyte progenitors, resulting in the deterioration of lymphocyte regeneration and an ensuing rise in viral loads. A mathematical model is used to illustrate this mechanism of progressive immunological deterioration. Mutation accumulation may explain not only the decline in CD4\(^+\) T cells, but also the functional deterioration of CD4\(^+\) T cells, CD8\(^+\) T cells and B cells, and the exhaustion of lymphocyte regeneration.

Keywords: AIDS/HIV; lymphocytes; model; mutation; progression

1. INTRODUCTION

The progression of HIV infection to AIDS is marked by a widespread and extensive destruction of the immune system (Fauci 1993; Pantaleo et al. 1993). Characterization of the patterns of HIV progression has advanced considerably over the last decade, but its mechanistic basis remains unresolved. An asymptomatic period masks the chronic drain of lymphocytes that generates enormous turnover in lymphocyte populations (Ho et al. 1995; Wei et al. 1995; Ramratnam et al. 1999). This drain of CD4\(^+\) arises from virus-mediated destruction, in addition to the perpetual immune activation-mediated apoptosis through both non-specific stimulation by cytokines and antigen-specific stimulation that also elevate turnover of CD8\(^+\) (Fauci 1993; Mohri et al. 1998, 2001; Hazenberg et al. 2000) and B cell populations (Fauci 1993; Mohri et al. 1998, 2001; De Boer et al. 2003). Coupled to this drain of lymphocytes, their precursors undergo elevated turnover as they are stimulated through homeostatic feedback mechanisms to maintain lymphocyte counts. As disease progression advances, these lymphocyte (Clerici et al. 1989; Fauci 1993; Miedema et al. 1994) and progenitor populations deteriorate (Moses et al. 1998), triggering collapse of the immune system. Here a singular mechanism of HIV progression that unifies these empirical observations to explain exhaustion of the immunological regenerative capacity is formulated.

Previous models of HIV progression have focused on accounting for the decline of CD4\(^+\) counts on a more proximate level. Although these proximate hypotheses emphasize different aspects of progression, generally they are not fundamentally contradictory. The major previous hypotheses fall into three categories, each of which can be supplied with an ultimate mechanistic basis by mutation accumulation processes. Proponents of the ‘antigenic diversity threshold theory’ suggest that beyond a threshold of antigenic diversity the immune response loses control over the viral population, triggering a surge in viral load (Nowak et al. 1991). Others have postulated that depletion of CD4\(^+\) arises primarily from accelerated destruction (Ho et al. 1995; Mohri et al. 2001; Ribeiro et al. 2002), either directly from viral infection or indirectly because activated lymphocytes have a shorter half-life. Another argument emphasizes the proximate importance of the exhaustion of T cell regeneration (Hellerstein et al. 1999), but the ultimate etiology of this progenitor dysfunction remains unexplained. HIV infection not only results in the decline of CD4\(^+\), as described by these previous hypotheses, but additionally results in the immunological dysfunction of CD8\(^+\) and B cells (Clerici et al. 1989; Fauci 1993; Miedema et al. 1994), even though they are not infected by HIV. Thus, a complete mechanism for the progression of HIV infection to the onset of AIDS should account for the observed deterioration of all lymphocyte classes, in addition to exhaustion of lymphocyte regeneration.

The mutation accumulation mechanism advanced here is based on the observed rapid turnover of T and B cells, and ultimately of their progenitors, generated during HIV infection (Ho et al. 1995; Wei et al. 1995; Ramratnam et al. 1999). Clonal cell lines, including those of lymphocytes and their progenitors, are prone to the accumulation of deleterious mutations with each cell division (Muller 1964). Thus, this turnover leads to the accumulation of detrimental mutations that cause the deterioration of the immune function, replicative ability and viability of the lymphocytes. As immune function erodes, control over the viral population is lost, concomitant with increasing infection and plummeting CD4\(^+\) counts. Lymphocyte destruction and impaired production have tended to be viewed as separate mechanisms, but mutation accumulation unifies these processes in a causal and effect relationship.

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2. MODEL STRUCTURE

A mathematical model is developed to illustrate the mutation accumulation mechanism. The processes of CD4⁺ infection, immune proliferation of CD4⁺, CD8⁺ and B cells, homeostatic regeneration of these lymphocytes from their progenitors, and viral replication are modelled. I also incorporate mutation accumulation in lymphocyte effector and progenitor populations that results in reduced viability and immunological function. The total population sizes of uninfected CD4⁺ (T), infected CD4⁺ (I), CD8⁺ (C), B cells (B) and progenitors (P) are modelled, as well as the viral load (V). Subscript W refers to wild-type lymphocytes/progenitors, while M refers to deleteriously mutated lymphocytes/progenitors. The equations for the dynamics of CD8⁺ and B cells are of the same form as those for the uninfected CD4⁺ below (T_W and T_M), except the infection term is removed for CD8⁺ and B cells. Initial counts (τ) are given by τ_T = 1100 μl⁻¹, τ_C = 550 μl⁻¹ and τ_B = 400 μl⁻¹. It is assumed that concentrations are averaged across all anatomical sites. Within-host modelling of spatially explicit viral dynamics may provide more accurate predictions of progression dynamics, but is not essential for the mechanism presented here.

\[ T_W = P_W h T_W - d_T T_W - (\beta + \eta_T) V T_W + \gamma V T_W - m_T \gamma V T_W, \]

\[ T_M = m_T \gamma V T_W + P_M h T_W - (d_T + s) T_M, \]

\[ I = \beta V T_W - \delta I, \]

\[ V = p I - c V, \]

\[ P_W = -m_P \lambda_T h P_W, \]

\[ P_M = m_P \lambda_T h P_M - s P_W. \]

(a) Mutation accumulation

Lymphocyte populations are assumed to accumulate mutations with each round of replication. Immunological activation stimulates clonal proliferation, in which activated lymphocytes undergo three replications d⁻¹ (γ; Goldsby et al. 2000). The rate at which deleterious mutations are accumulated per replication was calculated as follows. There are 3×10⁹ bp in the human genome, although only about 5% is coding (Consortium 2001). The mutation rate per site per replication of lymphocytes has been estimated at 10⁻¹² (Wabl et al. 1987). Three-fifths of mutations are non-synonymous, while an estimated 38% of non-synonymous mutations that occur in the human genome (above and beyond repair of DNA damage) are significantly detrimental to function, viability or replication (Eyre-Walker & Keightley 1999). These factors give the probability that a deleterious mutation occurs per replication (m_T) as 3.4×10⁻⁵ for activated lymphocytes. Stem cell mutation rates are greatly reduced relative to effector cells (Cairns 2002; Marsham et al. 2002). Human stem cells are able to divide an estimated 5000 times (Marsham et al. 2002), two orders of magnitude greater than Hayflick’s limit of 50 replications (Hayflick & Moorhead 1961). Accordingly, the baseline mutation rate of progenitors per round of replication (m_P) is assumed to be two orders of magnitude lower than that of the effector lymphocytes. Sensitivity analysis for this parameter is presented in figure 2.

Mutation accumulation is expected to have fitness repercussions for both the function and viability of lymphocytes. It is assumed that mutated lymphocytes cannot be activated, are dysfunctional immunologically and thus do not contribute to control over the viral population. Inactivated CD4⁺ are also markedly less susceptible to HIV infection (Sugaya et al. 2004) and to bystander effects (Alimonti et al. 2003). Furthermore, the mortality rate of mutated lineages is assumed to be elevated by s=5%. The initial number of common lymphoid precursors (τ_P) is assumed to be 10⁶, the estimated number of progenitors in a healthy adult (Shochat et al. 2002). It is assumed that the immune system does not harbour any mutations initially (table 1).

(b) Regeneration of effector cells

CD4⁺, CD8⁺ and B cells die at rates d_T=0.9%, d_C=1.1% and d_B=1.6% d⁻¹, respectively, in healthy macaques (De Boer et al. 2003). In the absence of infection, the lymphocyte replenishment rate per progenitor (τ_P, k and λ_B) was assumed to be exactly sufficient to maintain lymphocyte levels and is consistent with empirical measurements (De Boer & Noest 1998). Loss of T cells occurs by both direct viral destruction and through indirect bystander mechanisms (Meyaard et al. 1992; Finkel et al. 1995). For example, many lymphocytes are killed by a Fas-mediated mechanism or as a result of HIV proteins released from infected cells that stimulates apoptosis in uninfected bystander cells (Alimonti et al. 2003). Indeed, most of the CD4⁺ death during HIV infection is thought to result from bystander death (e.g. Alimonti et al. 2003), which also occurs in CD8⁺ (Stevenson 2003; Ahr et al. 2004) and B cells (De Milito 2004), although may be higher in CD4⁺ cells. Thus, it was assumed that bystander deaths, denoted τ_P, η_C and η_B, are approximately equivalent to apoptosis arising from immune-activation and infection.

New uninfected CD4⁺ without mutations (T_W) and with mutations (T_M) are regenerated by progenitors at a rate \( P_W h T_W \) and \( P_M h T_M \), respectively. The proliferative capacity of progenitors is given by \( h = \frac{\tau_P}{\gamma}(1 - (1 - P(\gamma P))^2), \) which increases regeneration when T cell counts fall below those of a healthy adult (Almeida et al. 2001), but declines as progenitors are lost. The nonlinearity of this function captures an increasingly rapid deterioration of regeneration as the number of progenitors decline. A linear function of progenitor abundance for lymphocyte regeneration generates a more linear decline of CD4⁺ counts. An equivalent process of homeostatic regulation occurs in CD8⁺ and B cells. In addition to the homeostatic regeneration of lymphocytes, viral-stimulated proliferation is also assumed to occur as \( \gamma V T_W \) with activated lymphocytes undergoing 3 replications d⁻¹ (γ; Goldsby et al. 2000).

(c) Progenitor replication

When progenitors replicate they produce a new lymphocyte and a new progenitor cell, thereby maintaining progenitor abundance. Under normal circumstances, hematopoietic progenitors do not die. However, progenitors are assumed to accumulate mutations at a rate proportional to their turnover, which is determined by overall demand for lymphocyte regeneration \( \lambda_Z = (\lambda_T + \lambda_C + \lambda_B) \kappa \). The scaling factor \( \kappa = 5\times10^6 \) converts...
Table 1. Model parameters and independent variables.

<table>
<thead>
<tr>
<th>parameters</th>
<th>definition</th>
<th>values used</th>
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<tbody>
<tr>
<td>( \tau_T )</td>
<td>initial counts of CD4(^+) cells</td>
<td>1100 µl(^{-1})</td>
</tr>
<tr>
<td>( \tau_C )</td>
<td>initial counts of CD8(^+) cells</td>
<td>550 µl(^{-1})</td>
</tr>
<tr>
<td>( \tau_B )</td>
<td>initial counts of B cells</td>
<td>400 µl(^{-1})</td>
</tr>
<tr>
<td>( \delta_T )</td>
<td>death rate of uninfected CD4(^+)</td>
<td>10(^{-6}) (Shochat et al. 2002)</td>
</tr>
<tr>
<td>( \delta_C )</td>
<td>death rate of uninfected CD8(^+)</td>
<td>0.9% d(^{-1}) (De Boer et al. 2003)</td>
</tr>
<tr>
<td>( \delta_B )</td>
<td>death rate of uninfected B cells</td>
<td>1.1% d(^{-1}) (De Boer et al. 2003)</td>
</tr>
<tr>
<td>( \lambda_T )</td>
<td>growth term of CD4(^+) cells</td>
<td>(\frac{0.41}{\tau_T}) µl(^{-1}) daily</td>
</tr>
<tr>
<td>( \lambda_C )</td>
<td>growth term of CD8(^+) cells</td>
<td>(\frac{0.25}{\tau_C}) µl(^{-1}) daily</td>
</tr>
<tr>
<td>( \lambda_B )</td>
<td>growth term of B cells</td>
<td>(\frac{0.27}{\tau_B}) µl(^{-1}) daily</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>activated lymphocyte replication</td>
<td>3 d(^{-1}) (Goldsby et al. 2000)</td>
</tr>
<tr>
<td>( m_T )</td>
<td>deleterious mutation occurs per replication in lymphocytes</td>
<td>(3.4 \times 10^{-7}) (Wabl et al. 1987; Eyre-Walker &amp; Keightley 1999; Consortium 2001) varied (figure 2) in the order of (m_T \times 10^{-2}) (Marsham et al. 2002)</td>
</tr>
<tr>
<td>( m_p )</td>
<td>deleterious mutation occurs per replication in progenitors</td>
<td>(1.5) days (Ho et al. 1995; Wei et al. 1995; Klenerman et al. 1996; Perelson et al. 1996)</td>
</tr>
<tr>
<td>( 1/\delta )</td>
<td>longevity of infected CD4(^+)</td>
<td>(10^{10}) d(^{-1}) (Ho et al. 1995; Wei et al. 1995; Haase et al. 1996; Perelson et al. 1996)</td>
</tr>
<tr>
<td>( p )</td>
<td>rate of viral production</td>
<td>maximum of 1.6 h(^{-1}) (Perelson et al. 1996; Ramratnam et al. 1999)</td>
</tr>
<tr>
<td>( c )</td>
<td>rate of viral clearance</td>
<td>assumed to be of same order as immune-mediated apoptosis (3 d(^{-1}); Alimonti et al. 2003)</td>
</tr>
<tr>
<td>( \eta_T, \eta_C, \eta_B )</td>
<td>bystander deaths</td>
<td>5%</td>
</tr>
<tr>
<td>( s )</td>
<td>mortality increase of mutated cells</td>
<td></td>
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(d) **Viral replication and infection**

HIV infects CD4\(^+\) at a rate proportional to the product of their abundances, \(BV_TW\). Infected CD4\(^+\) die at a rate \(\delta\), where \(1/\delta\) is 1.5 days (Ho et al. 1995; Wei et al. 1995; Klenerman et al. 1996; Perelson et al. 1996). During the asymptomatic period, viral production is on the order of at least \(10^{10}\) daily (Ho et al. 1995; Wei et al. 1995; Perelson et al. 1996), equating to viral production \((p)\) of 500 virions d\(^{-1}\) by each infected CD4\(^+\) (assuming that 0.1% of CD4\(^+\) are infected; Schnittman et al. 1989), and is consistent with clinical measurements (Haase et al. 1996). Clinical evidence suggests that the degree of control over viral load is governed by the immunological response from CD8\(^+\) (Jin et al. 1999; Schmitz et al. 1999; Cao et al. 2003), CD4\(^+\) (Rosenberg et al. 2000; Harari et al. 2004) and B cells (Emini et al. 1992; Mascola 2003; Trkola et al. 2004). It is assumed that virus is cleared at a rate of \(c = \mu(1 - (1 - TCB/\tau_TT_C T_B)^3)\). CD4\(^+\), CD8\(^+\) and B cells all play interdependent roles in the immune response against HIV (Cohen & Fauci 2001), hence \(TCB/\tau_T T_C T_B\) captures multiplicative interactions among lymphocyte classes. Initially \(TCB/\tau_T T_C T_B = 1\), but the above viral clearance function reflects an increasingly rapid deterioration of immunological clearance as the lymphocyte abundance declines. In line with empirical data, \(\mu = 1.6\) h\(^{-1}\) (Perelson et al. 1996; Ramratnam et al. 1999). The system is initiated with a single infected CD4\(^+\).

3. RESULTS

Model results predicted that in the absence of replication-induced mutation, the levels of lymphocytes, progenitors and viral load remain constant after the initial establishment of HIV infection. Thus, progression did not occur in the absence of replication-induced mutation. In contrast, when replication-induced mutation and HIV infection were both incorporated into the model, the profile generated was typical of HIV progression (Sabin et al. 2000; figure 1a,b). Under the baseline set of parameters values presented in the model description, CD4\(^+\) counts fell to 200 µl\(^{-1}\) after 10 years, with a much slighter decline in CD8\(^+\) and B cell counts (figure 1b). Concomitant with the general decline in lymphocytes, immunological control over the viral population became progressively weaker, resulting in mounting viral loads (figure 1a,b).

There is considerable heterogeneity in the rate of progression to AIDS, with some individuals progressing to AIDS in under 5 years and others maintaining relatively stable CD4\(^+\) counts for over 15 years. In the model presented here, the rapidity of progression depends on the parameters employed. While virtually any of the parameters could vary among individuals and HIV populations, the greatest uncertainty of empirical estimates surrounds the mutation rate of the progenitors. Thus, sensitivity analysis with regard to this parameter is presented (figure 2). The progression rate was indeed found to be sensitive to the mutation rate of progenitors (figure 4), highlighting the importance of progenitor mutation accumulation to HIV progression.

Mutations were found to accumulate in all classes of lymphocytes and their progenitors (figures 3 and 4). Reducing the rate of progenitor mutation by 5% elevated CD4\(^+\) counts by 63% after 10 years and delayed progression by 6 months. Furthermore, CD4\(^+\) depletion and disease progression did not occur in the absence of progenitor mutation, despite mutation in the effector population.
A degree of progenitor mutation accumulation could be expected as a result of chronic immune stimulation from sources other than HIV, and as part of the normal aging process. The rate of progenitor deterioration associated with aging in the absence of HIV infection will also depend on the progenitor mutation rate. For the baseline parameter set, replication-induced mutation without HIV infection lead to a fall in CD4\(^+\) counts by 8% over 10 years (cf 450% if HIV infected).

Understanding the factors that govern the onset of AIDS is fundamental to the design of effective therapies. Viral load can be reduced by lowering the rate of viral production (p) or by decreasing viral transmission (β) within the host. Thus, p and β are prime targets for HIV therapy. Viral production can be reduced by antiviral therapy, while within-host transmissibility can be lowered by interfering with the CCR5 chemokine receptor, which is exploited by HIV to gain entry into CD4\(^+\) T cells (Dragic et al. 1996). Indeed, therapy that reduces viral production by 5% was predicted to elevate the CD4\(^+\) counts to 515 µl\(^{-1}\) after 10 years. Similarly, a 5% reduction in the baseline parameter value for β resulted in elevation of CD4\(^+\) counts to 515 µl\(^{-1}\) also after 10 years, delaying disease progression by 30 months.

4. DISCUSSION

The mutation accumulation mechanism of HIV progression is based on the perpetual loss of lymphocytes during HIV infection coupled with their homeostatic replenishment by progenitors through a proliferative hierarchy. Within this proliferative hierarchy, elevated demand is placed on the turnover of progenitors to regenerate lymphocytes, resulting in accelerated mutation accumulation. It is proposed that mutation accumulation generates a self-fuelling process: as progenitors deteriorate and effector cells fail to be replaced, immunological

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Figure 1. (a) Data from Pantaleo et al. (1993) and Sabin et al. (2000). There is considerable variability in profiles of HIV progression among individuals. Nonetheless, the general pattern is a decline in CD4\(^+\) counts (crosses and diamonds; Pantaleo et al. 1993; Sabin et al. 2000), while viral loads (triangles) increase (Sabin et al. 2000). These empirical profiles are averaged across multiple patients. (b) Infection trajectory predicted by model, with decline in CD4\(^+\) (black) and CD8\(^+\) (light grey) T cell counts, and increase in viral load (dark grey). Dynamics of B cell counts are qualitatively similar to the dynamics of CD8\(^+\) counts, with an initial increase followed by progressive decline that is more gradual than the decline in CD4\(^+\).

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control over the viral population is progressively lost, driving lymphocyte counts down further and elevating both the turnover and hence the mutation accumulation of progenitors. In addition, lymphocytes inherit mutations from their progenitor. Thus, mutation accumulation within progenitor populations leads to further mutation accumulation in effector cells, as well as the impairment of lymphocyte replenishment.

Empirical evidence suggests that a combination of peripheral T-cell expansion in lymphocyte tissues (Douek et al. 1998; Walker et al. 1998; Haynes et al. 1999) and the thymus (Douek et al. 1998) both contribute to CD4+ regeneration, as has been assumed here. There is some evidence to suggest that naive cells play a predominant role in regeneration (Walker et al. 1998; Haynes et al. 1999). In this case, the ‘progenitor’ population would correspond to naive cells, subject to equivalent processes of mutational accumulation with elevated turnover.

Mutation accumulation in all classes of lymphocytes should both reduce their viability and cause their immune function to deteriorate. These predictions are in accord with empirical observations of immunological dysfunction of lymphocytes that occurs during HIV progression (Clerici et al. 1989; Fauci 1993; Miedema et al. 1994). No previous model has addressed this hallmark of HIV progression.

Advanced HIV progression has been associated with an increased frequency of loss-of-function mutations and DNA damage in T cells (Paganin et al. 1997; Gil et al. 2003). The mutation accumulation process can also account for the empirical observations of selective depletion of T cells specific to HIV epitopes (Imberti et al. 1991) and depletion of antibody production against HIV epitopes (Clerici et al. 1989) that arises during progression. Lymphocyte lines with the highest affinity to HIV epitopes will be disproportionately stimulated, and thus will be particularly prone to mutation accumulation. Further experimental investigation into correlations between lymphocyte turnover, mutation and rate of disease progression will help to clarify the role of mutation accumulation in HIV disease progression. Clinical exploration of these processes is challenging, because mutations are expected to be distributed across multiple loci. Consequently, experimental studies will require the examination of multiple loci and extensive sample sizes.

The mutation rate per replication was assumed to be the same for CD4+, CD8+ and B cells. However, CD4+ are destroyed by both immune activation-mediated apoptosis and viral infection, while CD8+ and B cells are lost through the former process only. One consequence of the differential rates of destruction is the inversion of the ratio of CD4+ to CD8+ cells from the initial 2 : 1 to about 1 : 2 generated by the model for the baseline set of parameters and supported by clinical data (Murray et al. 1984).

The model predicted that disease progression is sensitive to progenitor mutation. If progenitors remain healthy, effector populations can compensate for the drain associated with HIV infection. The model presented here provides a mechanistic basis for the clinically identified deterioration of lymphocyte regeneration that is correlated with HIV progression. The elevated destruction and hence turnover is expected to have an increasingly pronounced effect on accelerating progression the higher up the lymphocyte progenitor hierarchy it occurs. Thus, HIV strains that preferentially infect thymocyte progenitors would be expected to accelerate disease progression. For example, CXCR4 strains target thymocyte progenitors (Hazenberg et al. 2003), and indeed the emergence of CXCR4 strains is correlated with accelerated progression (Hazenberg et al. 2003).

Mutation accumulation during HIV infection effectively accelerates the aging process of the immune system, with CD4+ being disproportionately affected. Indeed, inexorable destruction of lymph node germinal centres and thymocyte depletion is associated both with aging and with HIV disease progression (Douek et al. 1998). Furthermore, age exacerbates disease progression in HIV infection (Douek et al. 1998; Kaufmann et al. 2002). Similarly, concurrent infections could be expected to accelerate disease progression. Other persistent viruses, including hepatitis C virus (Idilman et al. 2004), hepatitis G virus (De Renzo et al. 2002), herpes virus-6 (Tailor et al. 2004), also cause lymphoproliferative disorders, to which mutation accumulation associated with immunological stimulation of lymphocyte turnover may likewise contribute. However, the deterioration of the immune system is not as extensive or as frequent in these other diseases compared to HIV. These correlations are consistent with the mutation accumulation hypothesis. Other persistent viruses either do not generate sufficiently elevated turn-over of lymphocytes, such as simian immunodeficiency virus (SIV) in their ‘natural’ sooty mangabey (Cercocebus atys) and red-capped mangabey (Cercocebus torquatus) hosts (Chakrabarti et al. 2000; Broussard et al. 2001), or the viruses enter into periods of prolonged latency, thereby mitigating mutation accumulation in the progenitors relative to HIV infection. In contrast, SIV does result in chronically elevated lymphocyte turnover in primate species that are not ‘natural hosts’, such as rhesus macaques (Macaca mulatta), in which CD4+ counts do progressively decline (Chakrabarti et al. 2000).

It has been suggested that cell lines can only undergo a limited number of divisions before succumbing to replicative senescence as a result of telomere shortening, in the absence of telomerase (Hayflick & Moorhead 1961). However, empirical studies have found that CD4+ telomeres do not become shorter during HIV infection (Palmer et al. 1997; De Boer & Noest 1998). However, some empirical evidence has been contradictory (Bestulny et al. 2000), and other studies have found shortened telomeres in CD8+ cells (Effros et al. 1996). One explanation is that telomerase may be active in progenitor stem cells (Palmer et al. 1997; De Boer & Noest 1998), while another explanation focuses on the heightened death of CD4+ cells (Palmer et al. 1997; De Boer & Noest 1998; Ribeiro et al. 2002). As cells divide, they are targets for HIV and eliminated before their telomeres shorten (Palmer et al. 1997; De Boer & Noest 1998; Ribeiro et al. 2002), which is not the case for CD8+ cells. Thus this explanation could account for the differences in CD4+ and CD8+ cells (Ribeiro et al. 2002). Furthermore, if replicative senescence due to telomere shortening did play a significant role in HIV progression, the elevated telomere shortening in the CD8+ population would correlate with greater deterioration in the CD8+ population than in the CD4+ population, which is the reverse of the empirical observations. Therefore, exhaustion of
renewal capacity during HIV infection cannot be generated by telomere shortening. However, exhaustion of lymphocyte regeneration can be explained by mutation accumulation in progenitor populations.

Mutation accumulation in clonal cell lines is irreversible, consistent with the previously unexplained observations of persistent immunological dysfunction even after years of sustained viral suppression by antiviral therapy (Kauffman et al. 2002; Valdez et al. 2002). Nonetheless, some forms of treatment may slow the process of mutation accumulation during HIV infection. Model results predicted that suppression of viral production should reduce both immune stimulation and CD4\(^+\) infection, thereby slowing mutation accumulation and stalling disease progression. Indeed, antiviral therapy that suppresses viral production has been found to prolong the preservation of CD4\(^+\) counts (Mohri et al. 2001; Hazuda et al. 2004). Similarly, interfering with the CCR5 receptor is expected to reduce the rate of within-host CD4\(^+\) infection. Under such a regime of reduced within-host transmissibility, the model predicted decreased destruction, and hence turnover, of CD4\(^+\), in addition to reduced viral production and thus less immune stimulation. Indeed, therapy based on interference with the CCR5 receptor has been shown to hold promise in the treatment of HIV (Dragic et al. 2000; O’Brien & Moore 2000; Qin et al. 2003).

In summary, the enormously elevated turnover of lymphocytes during HIV infection has been well established (Fauci 1993; Ho et al. 1995; Wei et al. 1995; Mohri et al. 1998, 2001; Ramratnam et al. 1999; Hazenberg et al. 2000; De Boer et al. 2003). Consequently, mutation accumulation is expected during progression. If mutation accumulation does not occur, an unidentified mechanism must be operating to prevent it. In either case, mutation accumulation during HIV progression requires further research. Mutation accumulation can account for the fundamental patterns of disease progression in HIV infection, the effects that antiviral drugs have in reducing immune cell turnover and slowing progression, the deterioration of not only the CD4\(^+\) directly destroyed by HIV, but of CD8\(^-\) and B cells also, the dysfunction of lymphocyte regeneration, and corrosion of T and B cell diversity.

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As this paper exceeds the maximum length normally permitted, the authors have agreed to contribute to production costs.