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MATHEMATICAL MODELS OF CORECEPTOR USAGE AND A DENDRITIC CELL-BASED VACCINE DURING HIV-1 SUBTYPE C INFECTION

MANGA, U. S

Department of Mathematics, Shobhit University, Meerut, Uttar Pradesh, India

ABSTRACT

Due to costs, most vaccine development is carried out Europe(subtype B) rather than Africa and Asian (subtype C) countries. However since the mechanisms of disease progression in HIV-1 subtype B may be different from those in HIV-1 subtype C, it is interesting to investigate if and how a dendritic cells based vaccine can be used on individuals in Africa and Asia. To investigate this, mathematical models and sensitivity analysis techniques are used to understand the mechanisms of disease progression in two HIV-1 subtypes. These models are then extended to explore the ways in which the vaccine could be used to treat these different HIV-1 subtypes. It is found that the level of immune activation plays a large role in determining the mechanism of disease progression and can itself be a means to the development of AIDS. It is also shown that the dendritic cells based vaccine could reduce the viral load but not eliminate the virus resulting in a viral rebound. To maintain a low viral load, vaccination would have to be repeated. Unfortunately, repeated vaccination may lead to the overproduction of proinflamatory cytokines resulting in severe side effects however this could be avoided by using a carefully planned treatment schedule. We conclude that the dendrite cells based vaccine can be used in individuals in either subtype B or subtype C region as long as the correct treatment schedule is followed.

KEYWORDS: HIV/AIDS, Coreceptor Usage, Dendritic Cells and Vaccine

1.1 INTRODUCTION

The HIV epidemic causes problems in both industrialized and developing countries. The World Health Organization estimates that as of 2012, 37.2 million adults and 2.2 million children were living with HIV worldwide (Avert, 2013). Sub-Saharan Africa is currently the worst affected region as it is home to 60% of the world's HIV infected population. Most individuals in this region are infected by HIV-1 subtype C, making it the most prevalent subtype in the world. This subtype is not only associated with Sub-Sahara but also in India, high incidence is also associated with accelerated disease progression hence the high mortality rate in this region (Monosi, et al, 2013). Although there are other HIV-1 subtypes, subtype B and subtype C are the most widespread subtypes. Apart for its predominance in southern and eastern Africa, HIV-1 subtype C is also predominant in India and Nepal while subtype B is common in Europe, the Americas, Japan and Australia. One of the major differences between these HIV-1 subtypes is their choice of coreceptor usage during the course of disease progression. Co receptors usage has been associated with different disease progression dynamics (Monosi, et al, 2013). To reduce mortality and morbidity due to AIDS, a number of drugs and interventions have been developed and are still being developed. Although this is encouraging news, most research on drug development has been conned to industrialized nations while very little is being done in the developing nations which are home to 95 % of the world's HIV infected population (Avert, 2013). Even more disturbing is the fact that, since different world regions harbor different HIV-1 subtypes, there is a danger that the drugs developed for one region may not produce

the same effect in another region. There is therefore a need to understand the dynamics of the different viral strains to make suggestions on how drugs developed in industrialized nations may be used to produce the same effect in individuals in developing nations.

Mathematical models provide an alternative way to study the effects of different drugs, a procedure which is otherwise risky or unethical when carried out on patients. Although model animals such as monkeys are at times used, the ethical justification of this practice is controversial (Douek, et al, 2013). Apart from providing an alternate route that does not violate any rights, mathematical models also provide clinicians with almost instant results on studies that would have required several months or even years when conducted in animals or human beings. Such models have helped clinicians in making the complex choices involved in treating HIV-infected patients. The broader goal of this paper is to make use of mathematical models to explore how vaccines developed for individuals infected by HIV-1 subtype B may be used by HIV-1 subtype C infected individuals. To achieve these goal two mathematical models were developed. The first model was used to:

- To identify the factors that influences the choice of coreceptor usage during HIV-1 infection.
- To explain the difference in coreceptor switching frequency in HIV-1 sub-type B and HIV-1 subtype C. On the other hand, the second model was used to:
- To determine the long term outcomes of the clinical trial by (Lu, et al, 2004).
- To understand the possible effects of a dentritic cell based vaccine therapy on coreceptor switching.

Results from the two models with the help of another model that combines the two were used to infer how the dendritic cells based vaccine may be used in sub-Saharan Africa and India using structured treatment interruptions without causing adverse side effects. HIV is a retrovirus which means that its genome is RNA and is translated into DNA during its life cycle. This translation and completion of the viral life cycle requires a host cell. HIV attaches itself to a target host cell using a CD4 receptor and a coreceptor. Although there are other co receptors, the CCR5 and CXCR4 co receptors appear to be the most important for successful viral entry (Lusso, 2010).

Figure 1.1 shows diagrammatic representation of the interaction between the virus, target cell receptors and co receptors. Using these, the virus then gains entry into the target cell where it takes over control of the replication machinery to complete its own life cycle. Target cells of HIV include macrophages, dendritic cells and CD4+ T lymphocytes. Most of these CD4+ target cells play a role in the establishment of immune responses against infections. A healthy human adult has about 1000 CD4+T cells per microlitre of blood, but in an infected patient, the CD4 count can drop to lower levels as the immune system also collapses. Currently, if a patient has a CD4 count of below 200 CD4 cells per microlitre, he or she is said to have AIDS.

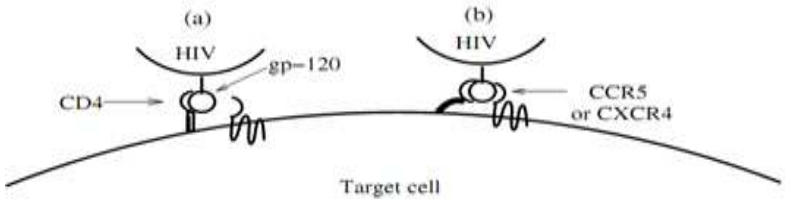

Figure 1.1: A Diagrammatic Representation of the Interaction between Viral Protein, Target Cell Receptor and Co Receptor

- Represents binding of gp-120 to the CD4 receptor while
- Represents the subsequent binding of gp-120 to a coreceptor which can either be CCR5 or CXCR4 depending on the type of target cell.

Although there is a wide range of immune responses, research in HIV infection has focused largely on the role of T helper cells and CD8 cells. CD8 responses are divided into two.

- Lytic response which is carried out by cytotoxic T lymphocytes (CTLs) which make use of proteins in their cytoplasm such as peforin and granzymes for cell lysis. This is also known as the direct killing response.
- Non-lytic responses are soluble substances or chemokines secreted by CD8 cells. These work by either inhibiting HIV replication or inhibiting viral entry into target cells. The relation between CD8+ cells, CD4+ cells and HIV has been used to describe the course of disease progression during HIV infection (Pastores, et al, 2004). The dynamics of CD4+ and CD8+ cells can be used to characterize the different stages of disease progression in HIV infection. Disease progression is divided into three phases summarized in figure (1.2).

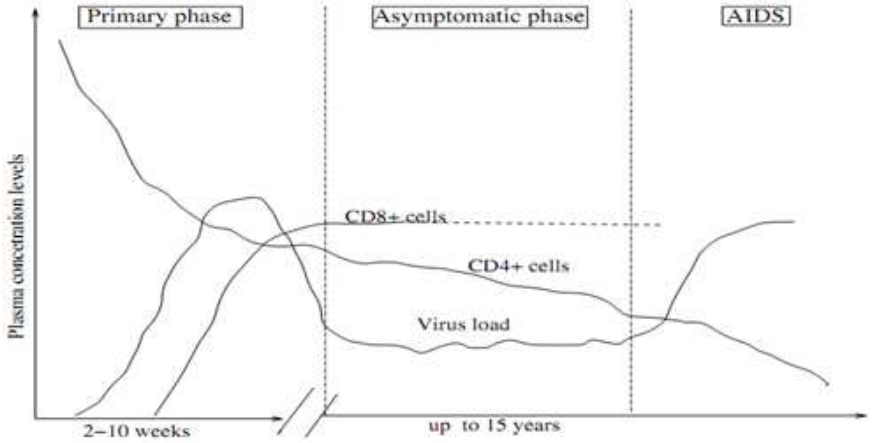

Figure 1.2: A Qualitative Diagram to Show the Time Course of HIV Infection in a Typical Infected Adult Infection (Pastores, et al, 2004)

Primary Phase: During the first few weeks after infection with HIV, patients experience a period of increasing viral load and a decline in CD4+ T cells numbers. Flu like symptoms has been associated with this phase. The end of this period coincides with the CD8+ immune response against HIV (Perelson, et al, 1996).

Asymptomatic Phase: Although there are no visible symptoms present, the replication kinetics of the virus are extremely fast (Perelson and Nelson, 1999). However, there is little change in the viral load. The CD8 responses are thought to control the virus to low levels but the CD4+ T cell numbers continue to decline. The length of this phase may range from a few months to 15 or more years. (Perelson, et al, 1996).

AIDS: This is the final stage of the disease. CD4+ T cells fall below 200 microlitres and as an overall weakness in the immune system allows opportunistic infections to frequently occur. (Perelson, et al, 1996). Diseases from these infections eventually lead to death.

HIV can exhibit distinct cellular tropisms that have important implications for the viral pathogenesis and disease progression (Perelson, et al, 1996). During the asymptomatic stages of HIV-1 infection, the virus may evolve to show

increased tropism for T cells. This phenotypic switch from CCR5 to CXCR4 coreceptor usage has been shown to coincide with the first immunological and clinical signs of chronic disease progression (Regoes and Bonhoeer, 2012). HIV-1 has been found to predominantly use the CCR5 coreceptor during the primary stage of infection and the asymptomatic phase (Regoes and Bonhoeer, 2012). The viral strain that uses the CCR5 coreceptor is known as the R5 strain. It is characterized by a slow replication rate (Regoes and Bonhoeer, 2012), relative acytopathicity and is of the non-synctium inducing (NSI) phenotype.

2.0 METHOD

A phenotypic switch, although more common in HIV-1 subtype B than in subtype C individuals, has only been observed in about 50% of HIV-1 subtype B infected patients during the late stages of infection typically after 8 to 10 years of infection (Regoes and Bonhoeer, 2005). The phenotypic switch is rarely associated with a complete loss of CCR5 usage (Regoes and Bonhoeer, 2012). (Regoes and Bonhoeer, 2005), suggesting that the use of CXCR4 by HIV-1 is not an absolute requirement for development of AIDS (Lusso, 2010). In HIV-1 subtype C, previous studies in India, Ethiopia, Malawi and South Africa (Monosi, et al, 2003) showed that there was an almost exclusive use of the CCR5 coreceptor throughout the course of infection. However, recent findings in India, suggests that the frequency of an R5 to X4 switch may be higher than previously suggested. These studies (Monosi, et al, 2003) argued that results from previous studies (Perelson, et al, 1996), may be because the cohorts of patients in the study were in the early stages of HIV-1 infection when the X4 strain is unlikely to emerge. This area investigates whether the difference in choice of coreceptor usage in subtype B and subtype C has a virological, immunological or an environmental basis. Environmental factors refer to host factors affecting the switch time other than the immune response, for example, target cell availability.

A mathematical model is developed based on previous models (Regoes and Bonhoeer, 2012). However the model in this paper describes the dynamics of two different target cells that are infected by two viral strains, X4 and R5, with the R5 strain evolving towards the X4 strain as a result of selection pressure.

3.0 MODEL DEVELOPMENT

These models describes the dynamics of two viral strains, the CCR5 using strain (R5) and the CXCR4 using strain (X4), each infecting a different and specific target cell. It is assumed that the two target cell populations are macrophages (M) and CD4+ T cells (T). The macrophages carry the CCR5 coreceptor while the CD4+ T cells carry the CXCR4 coreceptor. Unlike macrophages, CD4+ T cells require activation for infection by the virus; hence the CD4+ T cells population is divided into resting CD4+ T cells (S) and the uninfected but activated CD4+ T cells (T). Upon activation the CD4+ T cells can then be infected by the X4 viral strain while the macrophages get infected by the R5 strain. Although the R5 strain can also infect CD4+ T cells, in these models we do not take this into account. After a successful infection, presentation of antigens by infected cells results in stimulation of a CD8 immune response. The CD8 memory cells (W), which develop in response to the antigen presentation with the help of CD4+ T cells, lack the effectors function.

However, the CD8 memory cells differentiate into CD8 effectors cells (C) which then carry out the immune response against the infection. The CD8 effectors cells respond by either lysing infected CD4+T cells or producing chemokines that inhibit the infection of macrophages. This is based on studies that have shown that macrophages are more resistant to TCL lysis compared to CD4+ T cells. The above processes are described by nine nonlinear ordinary differential equations given by (3.1)-(3.9). Table (3.1) gives a summary of the variables described in the model:

$$\dot{S} = \lambda - d_S S - gS(T^* + M^*) \tag{3.1}$$

$$\dot{T} = gS(T^* + M^*) - d_T T - \beta T X_4 \tag{3.2}$$

$$\dot{T}^* = \beta T X_4 - d_{T^*} T^* - pT^* C \tag{3.3}$$

$$\dot{M} = \mu - d_m M - \frac{\beta M R_5}{kC + 1} \tag{3.4}$$

$$\dot{M}^* = \frac{\beta M R_5}{kC + 1} - d_{m^*} M^* \tag{3.5}$$

$$\dot{R}_5 = k_{R_5}(1 - e_v) M^* - d_v R_5 \tag{3.6}$$

$$\dot{X}_4 = k_{X_4} T^* + k_{R_5} e_v M^* - d_v R_5 \tag{3.7}$$

$$\dot{W} = r(T^* + M^*)WT - fW(T^* + M) - d_w W \tag{3.8}$$

$$\dot{C} = fW(T^* + M^*) - d_c C \tag{3.9}$$

Equations (3.1) and (3.2) describe the dynamics of uninfected resting and activated CD4+ T cells, respectively. There is a constant input (λ) of resting CD4+ T cells from a source such as the thymus, while the activated CD4+ T cells are derived from the resting cells in response to antigen. Loss of these cells may be a result of natural death (dt). In addition to natural death, Equations (3.4) and (3.5) describe the dynamics of the macrophage population which do not require activation [21].

Table 3.1: A Summary of Variables Used in the Model (Equations 3.1-3.9)

Variable	Description	Initial Value	Units
S	Resting uninfected $CD4^+$ T cells	1000	cells mm^{-3}
T	Active uninfected $CD4^+$ T cells	500	cells mm^{-3}
T^*	Infected $CD4^+$ cells	0	cells mm^{-3}
M	Uninfected macrophage	1000	cells mm^{-3}
M^*	Infected macrophages	0	cells mm^{-3}
R_5	R5 viral strain	0.001	virions mm^{-3}
X_4	X4 viral strain	0	virions mm^{-3}
W	CD8 memory cells (precursors)	100	cells mm^{-3}
C	CD8 effectors cells	0	cells mm^{-3}

Also from a source such as the bone marrow, it is assumed that the loss of macrophages is also a result of natural death (dt). Of interest in this section are the dynamics of coreceptor usage during the course of HIV-1 infection hence the inclusion of equations (3.6) and (3.7) that describe the dynamics of the R5 and X4 viral strains.

The R5 strain infects macrophage cells and not CD4+ T cells, while the X4 strain infects the CD4+ T cells. The viral strain with dual tropism (the R5X4 strain) is included in the X4 strain population as it preferentially makes use of the CXCR4 coreceptor. The Inuk of free R5 virus is from infected macrophage cells at a rate kR5 (equation 3.6) and free X4 virus is derived from infected CD4+ T cells at a rate kX4 (equation 3.7).

To account for the difference in replication rate and cytopathicit between theR5 and X4 strains (Regoes and Bonhoeer, 2012)., Loss from both viral 3populations is due to viral decay at a rate dv. During viral replication within the macrophage cell, the R5 strain is allowed to evolve to the X4 strain through mutations. This process is described in equation (3.6) in which a fraction (e_v) of the new virus produced by an infected macrophage are X4 strain.

Lastly, equations (3.8) and (3.9) describe the development and differentiation of the CD8 immune response. The CD8 memory cells (W) proliferate from an initial pool of memory cells. However infected cells interact with CD4 T helper cells resulting in the development of CD8 memory cells. The CD8 memory cells then differentiate into CD8 effectors, as a result of the presence of antigens but this process does not require CD4 helper cells. The CD8 effectors have the capacity to lyse infected CD4+ T cells and inhibit infection of macrophages. The model is used to investigate the factors that influence the choice of coreceptor usage during HIV-1 infection.

A description and plausible values of parameters in equations (3.1) to (3.9) are given in Table 3.2, while a schematic representation of the model is given in Figure. (3.1).

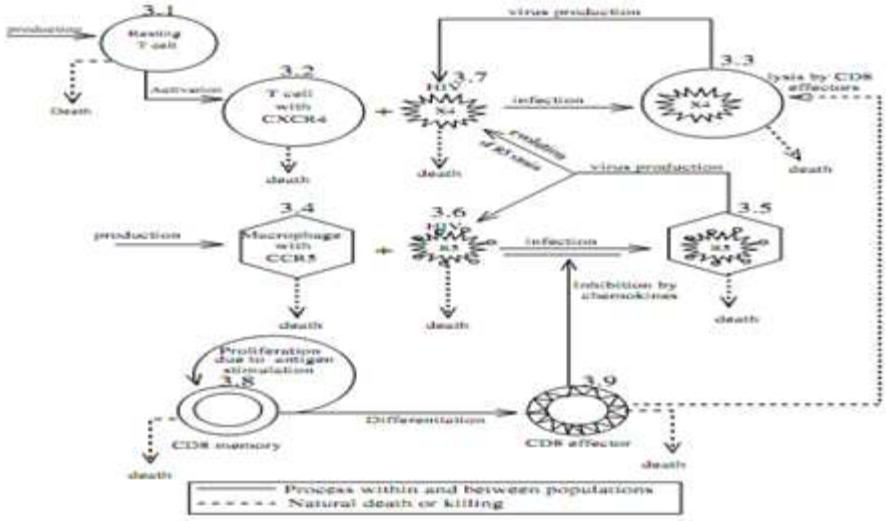

Figure 3.1: A Diagrammatic Representation of the Model. The Numbers 3.1 to 3.9 Correspond to the Equations Numbers in the Model

Table 3.2: A Summary of Parameters Used in the Model (Equations 3.1-3.9)

Parameter	Description	Value	Units
λ	Production rate of resting $CD4^+$ T cells	1.5	$day^{-1}\ mm^{-3}$
μ	Production rate of macrophages	5	$day^{-1}\ mm^{-3}$
G	Activation rate of $CD4^+$ T cells	0.01	$day^{-1}\ mm^{-3}$
β	Infection rate for the R5 and X4 viral strain	$2.4*10^{-4}$	$day^{-1}\ mm^{-3}$
k_{R_5}	Viral production rate by infected macrophages	62.5	day^{-1}
k_{X_4}	Viral production rate by infected CD4 cells	90	day^{-1}
e_v	Evaluation rate of the R5 strain to the X4 strain	5.28*10-^{5}	scaller
P	Rate at which CD8 effectors cells (CTL_S) lyse $CD4^+$ T cells	0.78	day^{-1}
K	Efficiency of inhibition of macrophage infection by CD8 effectors chemokines	20	$cell^{-1}\ mm^3$
F	Rate of differentiation of CD8 memory cells into CD8 effectors	0.5	$day^{-1}\ mm^3$
R	CD8 immune responsiveness	0.005	$day^{-1}(m^3)^2$
d_s	Death rate of resting $CD4^+$ T cells	0.001	day^{-1}

Table 3.2: Contd.,

d_T	Death rate of resting of activated but uninfected $CD4^+$	0.24	day^{-1}
d_{T*}	Death rate of infected $CD4^+$ T cells including virus induced death	0.01	day^{-1}
d_m	Death rate of infected macrophage	0.005	day^{-1}
d_{m*}	Death rate of infected macrophage including virus induced death	0.03	day^{-1}
d_v	Decay rate of free viral particles	2.4	day^{-1}
d_c	Decay rate of CD8 effectors	0.3	day^{-1}
d_w	Decay rate of CD8 memory cells	0.01	day^{-1}

4.0 RESULTS AND DISCUSSIONS

Using the initial values given in table (3.1), the model discussed in this paper gives four different outcomes dependent on the values of the infection.

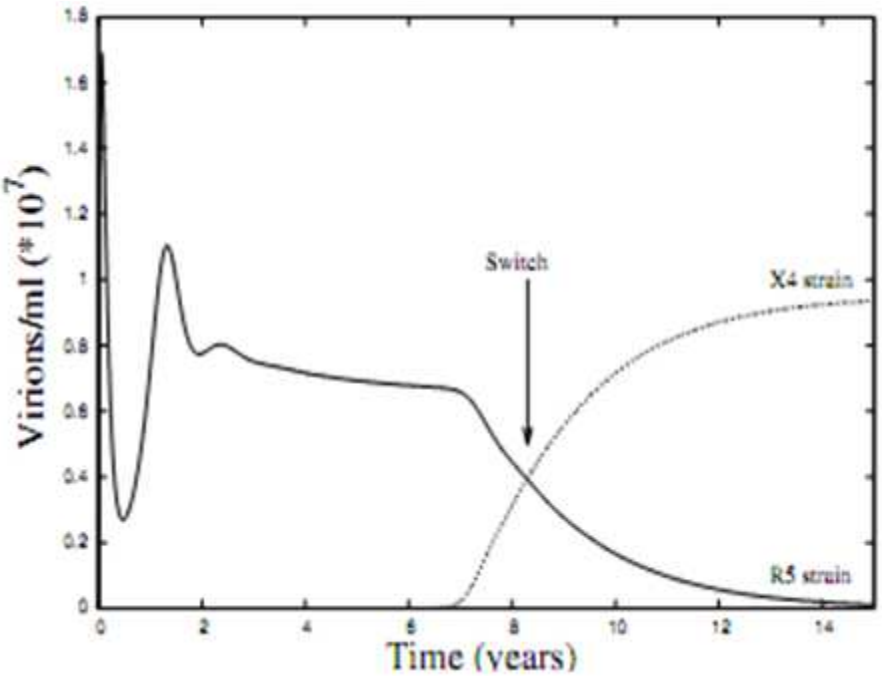

Figure 3.2: An Example of a Coreceptor Switch (Shown by Arrow) during a Model Simulation

The time corresponding to the switch position is the switch time". Parameter values as in table (3.2) with p= 0.5 and f= 0.1 and initial values given in table (3.1). rate summarized in Figure (3.3).

Disease progression for 5400 days was simulated and a phenotypic switch was define as the point where the X4 viral population first becomes larger than the R5 viral population (see Figure. 3.2).

The “switch time" was thus the time that lapses before this point is reached. It was found that when the infection rate is very low ($\beta < \beta_1$) the virus fails to establish an infection since the basic reproduction number, R_0, for the R5 strain is less than one.

The basic reproduction number is defined as the number of R5 viral particles that are produced as a result of a single R5 viral particle at the beginning of an infection. If however ($\beta < \beta_1$), the virus successfully establishes an infection and an immune response is also stimulated. Furthermore, the replacement number for the R5 strain, is always greater than one however as it decreases to approaches 1, the R5 viral population reaches an equilibrium ($R5$), about 3000 days post

infection, new a detectable equilibrium X0. As the two viral strains settle at the new equilibria, 1 and - 1. However due to the high cytopathicity of the X4 strain and increased infection rate, the phenotypic switch results in depletion of CD4+ T cells.

A low value of CD4+ T cells and high viral load then leads to CD8 cell exhaustion. CD8 cells that are produced may also be overwhelmed by the fast viral replications kinetics resulting in their exhaustion. In the absence of an immune response, the growth of the X4 population is then limited by the availability of CD4+ Tcells. CD8 exhaustion may also result in a negative CD8 population hence simulations of the model were done for $\beta_1 < \beta < \beta_4$ to ensure that the outcome of the model has a non-trivial and biologically plausible meaning.

5.0 CONCLUSIONS

Since individuals in subtype C regions are associated with a higher cytokine expression levels, vaccination may be detrimental to the individual if its results in overproduction of cytokines such as INF$-\gamma$. This can however be avoided through a number of ways.

- A lower dosage of the vaccine cans be given to such individuals to reduce the possibility of overproduction of cytokines. However a lower dose implies less efficiency in viral load reduction.
- An anti-parasitic drug could be given before administering the vaccine to reduce the immune activation. Alternatively, vaccination together with immumomodulatory drugs such as linomide may be helpful. Linomide has the ability to block proinamatory cytokines, prevent apoptosis of CD8 and CD4 cells, as well as increasing the production of nitric oxide which has antiviral and antimicrobial properties. This however would imply additional costs for treatment.
- To avoid reducing the dose of the vaccine or using additional drugs, a structured treatment schedule can be used to maintain a low viral load while at the same time preventing the overproduction of cytokines by minimizing CD8 memory production. This could be done with a strategy On the other hand, in 50% of HIV-1 subtype B infected individuals, and complications associated with increased cytokine levels may not be a huge concern. For these individuals, the major concern lies in the high probability of coreceptor switching which is an indicator of accelerated disease progression associated with accelerated CD4+ T cell depletion. In this case the initiation time of vaccination would be an important factor. Therefore, if a coreceptor switch has occurred the immune response is likely to be weaker hence the 32-STI would be a better strategy to use as it will efficiently reboots the immune response while suppressing the virus. Unfortunately this classification of the stage of disease progression cannot be used before the switch has occurred since only 50% of the HIV-1 subtype B infected individuals will exhibit a coreceptor switch. For those HIV-1 subtype B infected individuals that will not experience a switch, the mechanism of progression to AIDS would thus be similar to HIV-1 subtype C infected individuals. In this case the stage of disease progression would have to be determined by the strength of the immune response, viral load and level of CD4+ T cells as is the case with HIV-1 subtype C infected individuals. It can thus be concluded that a dendritic cell based vaccine developed in HIV-1 subtype B region can thus be used on both.

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