

Statistical Model for HIV Replication In The $[(CD)]_{4^+}$ T cell

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Abstract: For the last four decades the major challenge of the medical department is to cure the HIV infection as there is no proper medicine to cure HIV infection. However, practicing of the Anti-Retrieval Therapy (ART) is only the medicine to improve the human immune system. In this regard, the finding of HIV replication in a $[(CD)]_{4^+}$ T cells is very much useful for providing treatment for the HIV infected persons. In this connection, this paper illustrates a statistical model which explains as how does HIV replicate in a $[(CD)]_{4^+}$ T cell.

Keywords: Host $[(CD)]_{4^+}$ T cell, Model of 5 stages of host cell and HIV Replication.

INTRODUCTION

HIV is the incurable viral infection and it is biggest challenge to doctor's to suggest a proper medicine and treatment to the HIV infected persons. The illness alters the immune system, making people much more vulnerable to infections and diseases. This susceptibility worsens as the syndrome progresses.

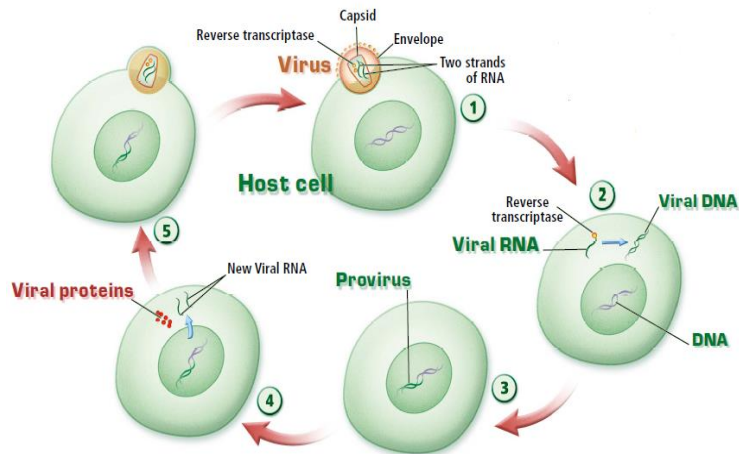
The HIV affected cell has the process as follows

Membranes of the virus and the host cell membrane, fuses then viral RNA in the mechanizing reverse transcriptase to enter the host's cytoplasm. Reverse transcriptase allows viral RNA to be copied DNA. Viral DNA is incorporated into the host chromosome as provirus.

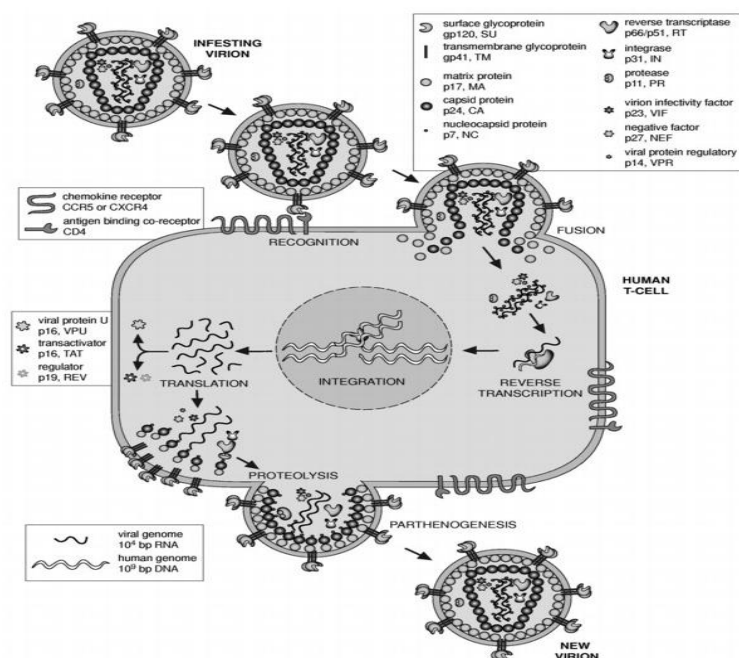
Transcription and translation of viral proteins: viral RNA becomes incorporated as to viral particles and is transcribed as well. Viral particles bud out of the host cell, acquiring an envelope in the process.

Human immune deficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV). Following initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the infection progresses, it interferes more and more with the immune system, making the person much more susceptible to common infections like tuberculosis, as well as opportunistic infections and tumors that do not usually affect people who have working immune systems. The late symptoms of the infection are referred to as AIDS. This stage is often complicated by an infection of the lung known as pneumocystis pneumonia, severe weight loss, a type of cancer known as Kaposi's sarcoma, or other AIDS-defining conditions.

Effectively, the virus has now hijacked the host cell's own replication system. As a result, when the cellular DNA is transcribed, so is the viral DNA to form an RNA transcript. Further processing of this RNA into messenger RNA (mRNA) and genomic viral RNA occurs. The viral mRNA is then translated into viral proteins, which along with the genomic RNA, are assembled into new virus particles. This last stage requires the viral enzyme, protease [1]. Finally, the new viral particles are released from the infected cell and go on to infect other cells in the body.



Picture-I: Biological structure of hiv reverse transcription in a host cell



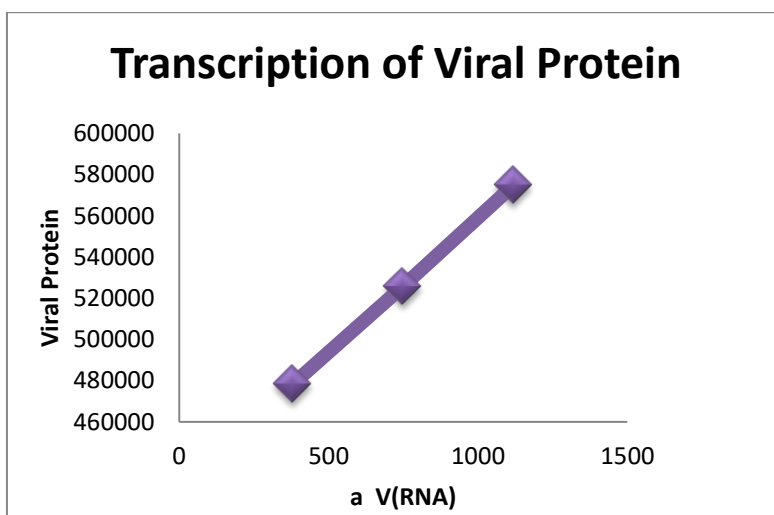
Picture-II: Biological structure of hiv replication

At this stage, levels of HIV are so high that the virus is able to infect and destroy CD4+T lymphocytes at a faster rate than the body is able to produce new immune cells (including CD4+T-lymphocytes). This leaves the body unable to mount an effective immune response against these pathogens. Eventually, clinical symptoms of HIV appear, such as neurological deterioration (erg. AIDS dementia complex), as well as other opportunistic infections (erg. Pneumocystis carinii pneumonia) and cancers (e.g. Kaposi's sarcoma), indicating that the infection is in its advanced stages [2]. This entire course of events varies considerably amongst individuals but is, on average, approximately 12 years. Viruses are totally dependent on living cells to survive as they utilize the host cell's own replication processes; HIV is a member of a class known as Retroviruses. These viruses store their genetic information as ribonucleic acid (RNA), unlike most viruses which store their genetic information as deoxyribonucleic acid (DNA). Before viral replication can take place, the RNA must be converted to DNA by reverse transcription, HIV comprises an outer envelope consisting of a lipid bilayer with spikes of glycoprotein's (gp), gp41 and gp120. These glycoprotein are linked in such a way that gp 120 protrudes from the surface of the virus. Inside this envelope is a nucleocapsid (p17), which surrounds a central core of protein, p24. Within this core, are two copies of single-stranded RNA (the virus genome). Proteins, p7 and p9, are bound to the RNA and are believed to be involved in regulation of gene expression. Multiple molecules of the enzyme, reverse transcriptase (R T), are also found in the core. This enzyme is responsible for converting the viral RNA into proviral DNA.

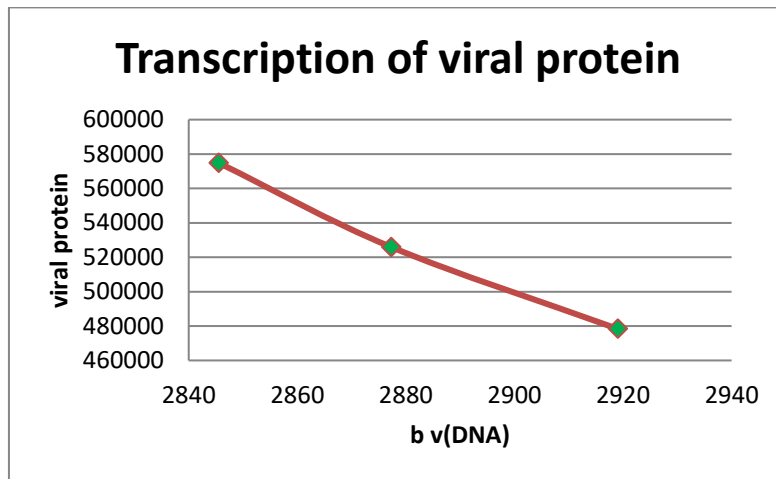
This paper present the statistical modeling of 5 stages of host cells function as binding, reverse transcriptase, integration, viral transcription viral assembly and maturation of $CD4^+$ T host cell.

REVIEW

R. Lakshmajayam and G. Meenakshi [3] paper includes HIV replication model for the succeeding period, which is numerically illustrated by David *et al.* [4]. David S Goodsell [4] Illustrations of the HIV Life Cycle. The illustrations include proteins, nucleic acids and membranes; small molecules and water are omitted for clarity. R. Lakshmajayam and G. Meenakshi [5] paper describes the model for HIV replication in the infected $CD4^+$ T -cells, under the assumption of law of mass action by using truncated logistic distribution and numerically illustrated the replication of viral load for the future period. R. Lakshmajayam and G. Meenakshi [6] the model can be used for future studies of HIV intracellular replication. It will also promote better understanding of the HIV/AIDS transmission dynamics, the study will also add to the existing body of knowledge on mathematical application in the field of epidemiology. Michael I Bukrinsky [7] article provides a brief overview of the HIV life cycle and focuses on receptors that determine viral binding and entry into the target cells. Joshua T. Schiffer *et al.* [9] had developed a Mathematical Model Predicts that Increased HSV-2 Shedding in HIV-1 Infected Persons Is Due to Poor Immunologic Control in Ganglia and Genital Mucosa. Meghna Verma *et al.* [8] had developed a model to determine when HPV infection continues to persist in the short run in a co-infected patient undergoing antiretroviral therapy. Lastly, the model predicts that, under efficacious antiretroviral treatment, human papilloma virus HPV infections will decrease in the long run due to the restoration of $CD4^+$ T cell numbers and protective immune responses. Anass Bouchnita *et al.* [8] has developed model of Acute HIV Infection and Distinct activation thresholds were used in the model to relate different modes of cellular responses to the hierarchy of the relative levels of the cytokines and they specified a reference set of model parameter values for the fundamental processes in lymph nodes that ensures a reasonable agreement with viral load and $CD4^+$ T cell dynamics in blood. They have also explained virus infection; immune response; acute phase; HIV spread; multi-scale model; single-cell regulation; reaction-diffusion and spatial dynamics. Anupriya Aggarwal *et al.* [10] provided evidence in resting $CD4^+$ T cells that dynamin directly regulates the HIV fusion reaction at the plasma membrane. They confirmed this latter observation using 2 divergent dynamin modulating compounds, one that enhances dynamin conformations associated with dynamin ring formation (ryngo-1-23) and the other that preferentially targets dynamin conformations that appear in helices (dyngo-4a). Ahmad R. Sedaghat [11] used a mathematical model to investigate the effects of various drug classes on the dynamics of HIV-1 decay and show that the stage at which a drug acts affects the dynamics of viral decay and they find that the drug class acting latest in the viral life cycle dictates the dynamics of HIV-1 decay and they proposed that clinically observed viral decay rates for HAART regimens should be evaluated in the context of the drug classes that are represented. Effectively, the virus has now hijacked the host cell's own replication system. As a result, when the cellular DNA is transcribed, so is the viral DNA to form an RNA transcript. Further processing of this RNA into messenger RNA (mRNA) and genomic viral RNA occurs. The viral mRNA is then translated into viral proteins, which along with the genomic RNA, are assembled into new virus particles. This last stage requires the viral enzyme, protease [12]. Finally, the new viral particles are released from the infected cell and go on to infect other cells in the body.



Picture– I: Biological structure of hive reverses transcription in a host cell



Picture- II: Biological structure of hiv replication

HIV cell actually attacks directly into T-helper cells and it comes upto the cell surface it use receptor that on T-helper cells an exclusive the T- helper cells which are $[[CD]]_4^{+}$ T receptor. $[[CD]]_4^{+}$ T molecules which are really defines on T-helper cells that the surface receptor that bunds the envelope protein it that causes the confirmation of chain and allow the second receptor to grump over the envelope this is the chemokine receptor (CCR5) what happens now is the stock of the envelope protein pushes from the virus into the host cell and stitch to draw the two cell membrane and the viral membrane together and also its happening is fusion of those two membrane and the viral inject material is injected essentially into the cell and the envelope proteins are left at the cell surface. The virus capsid are separated then the reverse transcriptase takes the viral RNA using host nuclei ties converts that viral RNA into a single stand DNA while it does makes some random error which is reverse transcriptase it was really very poor proof reading activity that single stand DNA now is again reverse transcriptase into double stand DNA at the point another enzyme that is coming with virus in the beginning called integrase essentially gramp hold that double stand DNA and carries through nucleus hole into the nucleus of the cell. Within the nucleus of the cell it finds the host chromosome in it. Basically the integrase enzyme makes a nick in a host DNA, and then RNA polymerase comes alone and makes mRNA. Those mRNA grows different types of proteins end up association with ribosome on the surface of rough endoplasmic reticulum and through the endoplasmic reticulum the produced proteins are taken to the cell surface where at the cell surface it becomes embedded in the cell membrane at that point is connecting with envelope protein on the surface at the same time there are other mRNA being produced and it makes multi protein chain with help of Ribosome. These multi proteins are taken to the cell surface where at the cell surface it becomes embedded in the cell membrane. Then these are buds on cell surface but it is not mature because the poly protein chain needs still separated into component parts that's done by embedded protease. The protease breaks up those poly protein chains it automatically at last finally structure makes up in the cell as HIV structure.

For a budding yeast cell of $40 \mu m^3$ (haploid, BNID 100430, 100427) the two estimates give a range of 90-140 million proteins per cell. Extrapolating these protein densities to mammalian cells a value of about 1010 proteins per cell is predicted for characteristic cell lines that have average volumes of 2000-4000 μm^3 .

The Statistical modeling of HIV replication in the host $[[CD]]_4^{+}$ T cell Binding

Viral envelope protein attracted to the $[[CD]]_4^{+}$ T surface receptor. This action is carried out by the Newton's third law. ie) HIV envelope protein pressure quantity is inversely proportion to the $[[CD]]_4^{+}$ T surface receptor namely chemokine coreceptor (CCR5). There is equal and opposite forces.

$v(p) \propto 1/([CD]_4^{+} T (CCR_5))$, Where $v(p)$ is viral envelope protein force and CCR5 is chemokine coreceptor force. At that stage, the two membranes are fuses. When force of viral envelope protein is greater than the receptor force.
 ie) $v(p) > 1/([CD]_4^{+} T (CCR_5))$

Their exist the Newton second law, ie) Magnitude of the net force of viral protein is inversely proportional to the mass of the coreceptor. There binding is take place.

Reverse Transcription

V (DNA) = f(RNA)+ Genetic material of $[[CD]]_{-4}^{+}$ T cell.

Where f(RNA) – function of viral RNA, f(RNA)= (two strands RNA of genes) × enzymes. f(RNA) → Viral capsid (viral RNA + important enzymes). Viral enzyme called as reverse transcription. Viral enzyme produce the new DNA called as proviral DNA, v (DNA) → viral DNA is function of f (RGE+ $[[CCR]]_{-5}$ + Error)

V (DNA) = (2RNA) × (viral genes) × enzymes viral + T cells protein + Biological factors are Consider as error components

$$=2(\alpha R) \times [\beta(G)] \times [\gamma(E)] + T_{p+e} \quad , e \sim N(0, \sigma^2) \quad , \sigma^2 > 0$$

Where v(DNA) – viral DNA ,G – viral genes (KDa) , E – viral enzymes (KDa),R – viral RNA (number), α -proportion of viral genes(ml), β -proportion of viral enzymes(ml) γ -proportion of viral RNA (ml), Tp – host T cells protein ,e – random biological error.

V (RNA) = $2(\alpha R) \times [\beta(G)] \times [\gamma(E)] + \delta(CCR_{-5})$ +functionof random process = proviral DNA.

Integration

Proviral DNA is carried to the $[[CD]]_{-4}^{+}$ T cell nucleus and virus another enzyme called integrase used to hide the proviral DNA into cell DNA then cell try to makes new proteins. Then it make new virus. Cell DNA→f(nucleus)+f(enzyme integrase).

Cell DNA→f(nucleus)+f(enzyme integrase) ×protein DNA and proviral DNA =A(magnitude of Nucleus)×B(magnitude of proviral DNA)

cell DNA=(A nucleus×B proviral nucleus)+(Enzyme integrase ×proviral DNA)

cell DNA →New protein →New HIV. Where A – proportion of nucleus and B – proportion of Enzyme

Transcription

Once HIV’s genetic material (called as strands of viral DNA) enters the nucleus, the special enzymes create complementary strands of genetic material (called as messenger RNA or mRNA), and it makes the new HIV. New viral protein = f(mRNA)

f (strands of viral DNA)×(cell nucleus viral genetic material)= new viral protein v(DNA)×cN=mRNA. Where v-proportion of DNA and c-proportion of nucleus.

MRNA = f(E) = K1 Surface glycoprotein (gp120, SU) + K2 Transmembrane glycoprotein (gp41, TM) + K3 Matrix protein (p12, MA) + K4 Capsid protein (p24, CA) + K5 nucleo capsid protein (p7,NC) + K6 Reverse transcriptase (p66/p51,RT).

Where K1- proportion of Surface glycoprotein (gp120, SU), K2- proportion of Transmembrane glycoprotein (gp41, TM), K3- proportion of Matrix protein (p12, MA), K4- proportion of Capsid protein (p24, CA), K5- proportion of nucleo capsid protein (p7, NC), K6- proportion of Reverse transcriptase (p66/p51, RT).Where mRNA = f (enzymes). Viral genome (104 by RNA) → human genome (109 bp DNA).

Enzyme = f (reverse transcription,P66/P51,RT),integrase(P31,IN),protease(P11,PR), Virion infectivity factor (P23, VIF),(viral protein regulary)(P14,VPR).

Since, New viral protein = function of enzyme with part of viral RNA and specific part of cell DNA. Viral protein = (a V (RNA) + b V (DNA)) × E, Where a- proportion of viral RNA and b- proportion of $[[CD]]_{-4}^{+}$ T cell DNA.

Translation

MRNA →Nucleus gives the viral protein by means of carrying mRNA instruction. New viral protein = f(nucleus cell) + f(mRNA). MRNA strands is processed through chromosomes with integrase enzyme that gives the string of proteins.String of protein → f(mRNA strand) + chromosomes + f(integrase enzyme).String protein broken out single protein.

$$(aN) \times (mRNA) + \text{chromosome} \times \text{enzyme} = (aN) \times b(mRNA) + (cC \times dE) \\ = \sum_{i=1}^n n_{\text{protein}}$$

Where a is proportion of nucleus, N – nucleus of $[(CD)]_4^{+}$ T cell (KDa), b- proportion of mRNA (messenger RNA) (ml), c- proportion of chromosome (ml), C- chromosome (KDa), d- proportion of enzyme (ml), E- enzyme (KDa), $\sum_{i=1}^n n_{\text{protein}}$ - string of protein

Viral Assembly and Maturation

The string of protein is cut up by a viral enzyme called protease into small proteins. These proteins serve a variety of functions some become structural elements of new HIV, while others become enzymes such as reverse transcriptase. The string of protein

$(\sum_{i=1}^n n_{p_i})$ (viral enzymes), Where p_i - is protein, $(\sum_{i=1}^n n_{p_i}) E = \text{viral particles} + \text{Enzymes}$, $\sum_{i=1}^n n_{[v(p_i)]} \rightarrow \text{new (HIV) with viral proteins} = \text{HIV}[(p)_i]$ from the host cell ($[(CD)]_4^{+}$ T cell)

CALCULATION

Table – I:

CCR5	1/CCR5	V(P)
1.2	0.83	1
1.26	0.79	1.1
1.3	0.76	1.2
1.36	0.73	1.3
1.4	0.71	1.4

Where Protein density 1.2 – 1.4 per ml. Table-I illustrate that viral envelope protein is greater than the coreceptor force (CCR5).

Table-II: $v(DNA) = 2(\alpha R) \times [\beta(G)] \times [\gamma(E)] + T_p + e$

α	R	$2(\alpha R)$	β	G	$\beta(G)$	γ	E	$\gamma(E)$	T_p	e	v(DNA)
0.1	10	2KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	94KDa	5	1022.52
0.1	10	2KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	66.2KDa	5	994.72
0.1	10	2KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	45.0KDa	5	973.52
0.1	10	2KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	33KDa	5	961.52
0.1	10	2KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	26KDa	5	954.52

Where $2(\alpha R) \times [\beta(G)] \times [\gamma(E)] = 923.52KDa$ and KDa – kiloDalton, Where RNA ranges from 10-30pg per cell, viral gene – $\{4.5kb + 2.0kb\} = 6.5kb \times 37KDa = 240.5KDa$, $1kb = 37KDa$

Table-II illustrate that based on fixing viral RNA (ie,R= 10) viral DNA is decreasing with fixed error as 5 and with proportions of $\alpha = 0.1, \beta = 0.2$ and $\gamma = 0.3$.

Table-III

α	R	$2(\alpha R)$	β	G	$\beta(G)$	γ	E	$\gamma(E)$	T_p	e	v(DNA)
0.1	20	4KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	94KDa	5	1946.04
0.1	20	4KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	66.2KDa	5	1918.24
0.1	20	4KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	45.0KDa	5	1897.04
0.1	20	4KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	33KDa	5	1885.04
0.1	20	4KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	26KDa	5	1878.04

Where $2(\alpha R) \times [\beta(G)] \times [\gamma(E)] = 1847.04KDa$. Table-III illustrate that based on fixing viral RNA (ie,R= 20) viral DNA is decreasing with fixed error as 5 and with proportions of $\alpha = 0.1, \beta = 0.2$ and $\gamma = 0.3$.

Table-IV

α	R	$2(\alpha R)$	β	G	$\beta(G)$	γ	E	$\gamma(E)$	T_p	e	v(DNA)
0.1	30	6KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	94KDa	5	2869.56
0.1	30	6KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	66.2KDa	5	2841.76
0.1	30	6KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	45.0KDa	5	2820.56
0.1	30	6KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	33KDa	5	2808.56
0.1	30	6KDa	0.2	240.5KDa	48.1KDa	0.3	32KDa	9.6KDa	26KDa	5	2801.56

$2(\alpha R) \times \beta(G) \times \gamma(E) = 2770.56 \text{KDa}$. Table-IV illustrate that based on fixing viral RNA (ie, R= 30) viral DNA is decreasing with fixed error as 5 and with proportions of $\alpha = 0.1, \beta=0.2$ and $\gamma=0.3$.

$$V(\text{RNA}) = 2(\alpha R) \times \beta(G) \times \gamma(E) + \delta(\text{CCR}_5) + \text{function of random process}$$

ie) $V(\text{RNA}) = 2(\alpha R) \times \beta(G) \times \gamma(E) + \delta(\text{CCR}_5) + e$

$$2(\alpha R) \times \beta(G) \times \gamma(E) - \delta(\text{CCR}_5) - e = V(\text{RNA})$$

Table-V

$2(\alpha R) \times \beta(G) \times \gamma(E)$	$\delta(\text{CCR}_5)$	e	$V(\text{RNA})$
923.52KDa	21	5	949.52KDa
1847.04KDa	21	5	1873.04KDa
2770.56KDa	21	5	2796.56KDa

Table-V illustrate that based on RNA (ie, ranges from 10- 30 pg) viral RNA is increasing with fixed error as 5 and with proportions of $\alpha = 0.1, \beta=0.2$ and $\gamma=0.3$.

$$\text{MRNA} = K1_1 + K2_2 + K3_3 + K4_4 + K5_5 + K6_6$$

$$= (120 + 41 + 12 + 24 + 7 + 66) \text{KDa} = 270 \text{KDa}$$

$$\text{Enzyme} = (66 + 31 + 11 + 23 + 14) \text{KDa} = 145 \text{KDa}$$

$$\text{Viral Protein} = \{a\text{RNA} + b\text{DNA}\} \times E$$

Table-VI

a	V(RNA)	aV(RNA)	b	V(DNA)	bV(DNA)	$\{aV(\text{RNA}) + bV(\text{DNA})\} \times E$
0.4	949.52	379.808	0.5	5838.12	2919.06	478,335.86KDa
0.4	1873.04	749.216	0.5	5754.72	2877.36	525853.52KDa
0.4	2796.56	1118.624	0.5	5691.12	2845.56	574806.68KDa

Table-VI illustrate that viral protein is increasing based on the proportion of viral RNA increasing and proportion of viral DNA is decreasing with proportions of $a = 0.4, b = 0.5$.

$$\sum_{i=1}^n \text{protein} = aN \times b(\text{mRNA}) + (cC \times dE)$$

$$= \{[0.6(4.95) \times 0.7(720)] + [0.8(51111) \times 0.9(145)]\} \text{KDa}$$

$$= (1496.88) + 5335988.4$$

$$= 5337485.28 \text{KDa}$$

$$\text{String of protein (ie) } (\sum_{i=1}^n P_i) / E = 36810.243310344 \text{KDa}$$

Graph-I: Viral Protein replication based on the proportion of Viral RNA
The graph I illustrate the increment of viral protein according to the quantity of viral RNA.

Graph-II: Viral Protein replication based on the proportion of Viral DNA
The graph II illustrate the gradually decrease of the viral protein according to the quantity of viral DNA.

CONCLUSION

This paper concentrated, for every period, how many $[[\text{CD}]]_4^+$ T cells infected, and the corresponding proportion of maturated HIV's broken out $[[\text{CD}]]_4^+$ T cell per period is modeled. Usually most of the literatures explained, HIV replication increased gradually at each period of time. Therefore this modeling of maturation of HIV is very much suitable for the HIV replication per $[[\text{CD}]]_4^+$ T cell. This model may be used to predict future period replication of HIV in the infected persons that will be given an idea of planning and the treatment to the infected patient.

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