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The Establishment of the Model of HIV Transmission Between Individuals

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Abstract

By reading related literature, we summarize the HIV transmission pathways and establish a mathematical model to calculate transmission rate. The model distinguishes different intercourse methods and transmission direction, simulates four different conditions such as infection between the heterosexual through vaginal sex and infection between the homosextual through anal sex. According to the study, HIV can enter the body directly through abrasion, by Langerhans cell uptake or by M cell transcytosis. The parameters include viral load in different body fluids, HIV viability in different environments, Langerhans cell, $CD4^+$ cell and M cell density in different mucus. Taking the HIV carrier in asymptomatic stage as the subject, we consider the viral load change with time to obtain a dynamic transmission rate. Besides, we put in the data of ART treated patient to simulate transmission course and compare the results of both conditions. With the background of medical knowledge, this model demonstrates the change of HIV transmission rate so that it can be used in other models and makes the consequence closer to the reality.

Keywords

HIV, CD4 Cell, Mathematical Model, Numerical Simulation

1. Medical Theoretical Background

1.1. Basic Knowledge on HIV

Human Immunodeficiency Virus (HIV), targeting at human T lymphocytes, is a kind of virus causes immune system deficiency which is mainly known as Acquired Immune Deficiency Syndrome (AIDS). It widely distributes in patients' body fluid such as blood, semen and virginal secretion.

1.2. Infection Mechanism of HIV

After HIV virus invades into the host, any cells with CD4 surface molecule, including $CD4^+$ T cells, mononuclear macrophages and dendritic cells can be its target. Gp120, the envelope glycoprotein of HIV, binds with surface receptor CD4 and co-receptor CXCR5 or CCR5 on target cell, transforming its conformation and exposing gp41 which directly inserts into target cell membrane. Indicated by hydrophobic interaction, viral envelope merges with cell membrane, which gives way to viral core to get inside the target cell.

1.3. Immunologic Mechanism of HIV

Similar to the immune reaction against other viral infection, nonspecific and specific immune reaction are activated in succession to fight against HIV. At the initial stage, Langerhans cells (LC), dendritic cells (DC), γδT cells and macrophages recognize the antigen. Later on, neutrophils, mononuclear macrophages, plasmacytoid dendritic cells and natural killer cells move to infection site and eradicate some of the virus through nonspecific immune reaction. Antigen presenting cells (APC) like LCs, DCs and macrophages ingest and possess antigens, then following lymph to the lymph nodes and presenting antigens to B cells and T cells, thus activating specific immune reaction. On the one hand

neutralizing antibodies secreted by B cells aim at HIV envelope proteins and core proteins to prevent HIV from merging with target cells. They also assist NK cells by ADCC to destroy the cells expressing HIV on surface. On the other hand $CD4^+$ Th cells promote neutralizing antibody secretion and produce lymphokines to facilitate CD8+ to directly destroy virus-infected cells. Meanwhile interferonγ (INFγ) secreted by $CD4^+$ T effector cells blocks viral reproduction. Neither nonspecific nor specific immune reaction, however, can eradicate virus once and for all. Since our study is based on a single intercourse, we only focus on the initial immune reaction related to how HIV gets into the body.

1.4. Transmission Methods of HIV

There are three ways of HIV transmission. First of all, HIV directly get into submucosa through minor mucous abrasion in reproductive tract and rectum and bind with $CD4^+$ cells in the interstitial fluid. Secondly, LC locates in stratified squamous epithelium whose protrusions are close to the surface so that it is easy for HIV to bind with LC and to be carried to lymph nodes. Thirdly, Microfold cells (M cell) serve as the medium of HIV transmission. M cell, a kind of specialized epithelial cell, mainly exists in MALT tissue. Situated in mucous layer, M cells can recognize antigens and transport them to $CD4^+$ cells through phagocytosis and excytosis. All the three transmission mechanisms work in both reproductive tract and rectum but the chances are different because of different physiological characteristics. [1]

1.5. Anatomy

Female Genital Tract

Here we mainly study cervix uteri and vagina. The upper end of cervix named internal orifice of cervix connects to corpus uteri while the lower end named external orifice of cervix protrudes into vagina and form a circular space which is uterus dome. The surface between internal and external orifice is type I epithelium and that inferior to external orifice, including vagina, is type II epithelium. The border of these two types of epithelium is called transformation zone. According to normal physiological structure, we assume that the surface area of vagina is 150 cm^2 and the part between internal and external orifice 20 cm^2.

Male External Genitals

The surface of penis is stratified squamous epithelium with thick stratum corneum so that virus can be obstructed efficiently. Glans penis, however, is covered by prepuce whose inner surface is type II epithelium. In this case, LCs are close to the surface, which is one of the ways how HIV infects the male and how circumcision reduces HIV infection rate. [2] Normal ejaculate volume is between 1.5-6 mL and we assume it 4 mL in our study.

Rectum

The surface of rectum is type I epithelium with a lot of goblet cells and MALT tissue. Capillary vessels are abundant in the submucosa which increase the infection rate.

2. Mathematical Modeling

2.1. Hypothesis

Our study is based on a single intercourse and we establish the model in accordance with the working mechanisms of each factor.

The assumption is that in a single intercourse, one participant is infected with HIV who can be at acute stage, potent stage or AIDS, and the other participant is healthy with no abrasion in reproductive tract or rectum. There are four kinds of infection transmission: the male towards the female through vaginal intercourse, the female towards the male through vaginal intercourse, the top towards the bottom through anal intercourse and the bottom towards the top through anal intercourse. We also assume that the subject is infected as soon as there is one HIV virus get into $CD4^+$ T cell. Infected LC is also a sign of infection since HIV can be carried to lymph node without reproduction or reduction. If HIV virus fails to invade into $CD4^+$ T cells or LCs, it loses its infectivity in vaginal fluid, semen and blood.

2.2. Parameter Analysis

Viral Load

When HIV virus gets into the body, it reproduces rapidly and activates immune reaction of the body at the acute stage. After virus amount decreases because of immune reaction, it remains at a pretty low level which is the potent stage and waits till immune system is destroyed, coming into AIDS. [3]

In the model, serum viral load is related to what stage the subject is enduring. The viral load is 7 $\log_{10}$ RNA copies/mL in the acute stage and decreases more than 2 $\log_{10}$ RNA copies/mL in the potent stage where HIV reproduction and body immunity strike a balance. After that, the balance point increase at the rate of 0.0094 $\log_{10}$ copies/mL per month and goes into AIDS. Though the viral load in semen is not exactly the same as that in serum, they are relative to each other (p =0.07-0.60). [4] The viral load of vaginal fluid is also relative to that of serum (p =0.64). Here we assume that the viral load of vaginal fluid, semen and serum are all at the same level. Additionally, the viral load of rectal secretion is slightly higher, which is 4.96 log10 copies/mL. [5]

HIV Vitality

According to a study, pH can influence HIV vitality quite obviously, which reach its highest point when pH is 7.0-7.1. The average pH of vaginal fluid among the infected is 4.1 and that among healthy people is 3.8. The average pH of semen is also about 7.3 and drops to 6.5 when mixed with vaginal fluid, which enhances the binding ability of HIV. [6]

$CD4^+$ Cell

Immunohistochemical staining shows that $CD4^+$ cell count is about 40/mm^2 in the lamina propria of vagina and about 120/mm^2 in external cervix. T cell count in prepuce is 133±51/mm^2. [7]

Langerhans Cell

Indirect immunoperoxidase technique is always used to do morphemic analysis of vagina, cervix and prepuce. LC density

is 12.9±1.8/mm^2 in vaginal epithelium, 13.4±2.3/mm^2 in cervical epithelium and 12.0±1.2/mm^2 in internal prepuce surface. [8]

M Cell

Gut-associated lymphoid tissue (GALT), a type of MALT tissue, is an important barrier in rectum and M cell is the portal for pathogen to get into body. In rectum, lymphoid follicle density is about 25.4±4.9/cm^2 and its diameter is around 0.5-2mm. [9] GALT area is relative to lymphoid follicle and M cells take up about 10% of GALT tissue. [10] We assume that the area of lymphoid follicle is 1mm^2 which accounts for 0.25 of total rectal area, therefore, M cells take up 0.025 of total rectal area.

2.3. Modeling

Based on what we mention above, we establish a model as followed:

$$y = \frac{v(t)}{n} * l * h * m * (po * cd4t + lc + mcell)$$

v(t): viral load, l: amount of semen, h: HIV virus vitality, n: number of cell in semen per mL, m: number of cell on mucous surface per cm^2, lc: LC percentage in an area unit, cd4t: CD4 T cell percentage in an area unit, po: chance of abrasion, mcell: M cell percentage in an area unit.

Virginal Intercourse

If HIV is passed on from the male to the female, on the one hand the rub between vagina and penis causes abrasion of vaginal mucus membrane, which lead to direct contact of virus and local CD4$^+$ T cells, on the other hand semen in vaginal dome completely contact with external vagina so that HIV in semen can be captured by LC in external vagina. Additionally, some of HIV particles lose vitality because of acidic environment.

According to the model:

$$y = \frac{v(t)}{n} * l * h * m * (po * cd4t + lc + mcell)$$

Substitute numerical values:

$$v(t) = 10^{2+0.0094t} \text{ copies/mL}$$

$$l = 4 \text{ mL}$$

$$h = 1$$

$$n = 10^9 \text{ /mL}$$

$$m = 10^6 \text{ cm}^2$$

$$lc = 13/10000$$

$$cd4t = 40/10000$$

$$po = 0.01$$

$$mcell = 0$$

Then we get HIV transmission trend as shown in Figure 1.

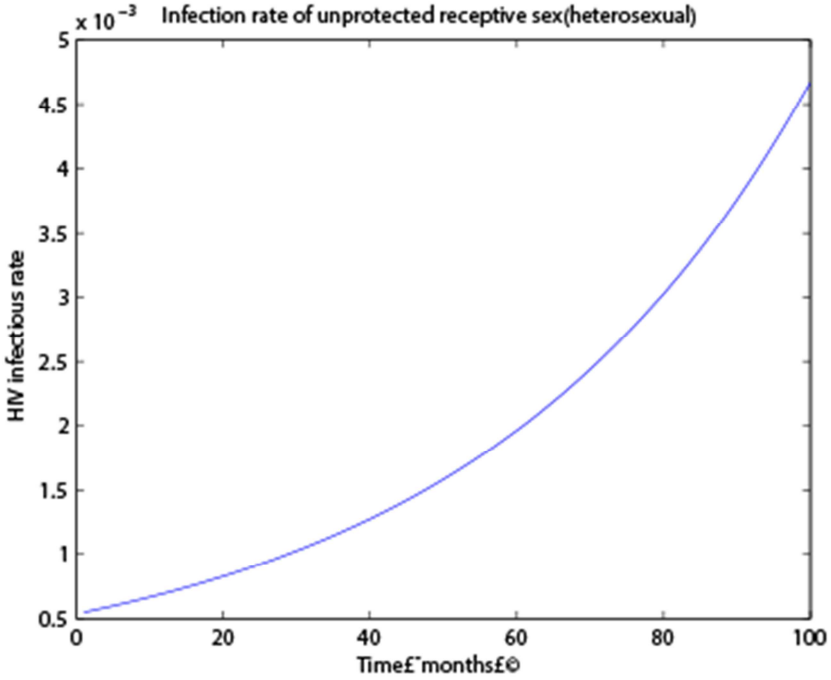

Figure 1. *Male towards female through vaginal intercourse.*

On the situation where the female passes HIV to the male, virus in vaginal fluid can be directly captured by LCs on surface of prepuce and by CD4$^+$ cells if there is abrasion on prepuce.

According to the model:

$$y = \frac{v(t)}{n} * l * h * m * (po * cd4t + lc + mcell)$$

Substitute numerical values:

$$v(t) = 10^{2+0.0094t} \text{ copies/mL}$$

$$l = 4 \text{ mL}$$

$$h = 0.3$$

$$n = 10^9 \text{ /mL}$$

$$m = 10^6 \text{ cm}^2$$

$$lc = 13/10000$$

$$cd4t = \frac{133}{10000} * 0.32$$

$$po = 0.01$$

$$mcell = 0$$

Then we get HIV transmission trend as shown in Figure 2.

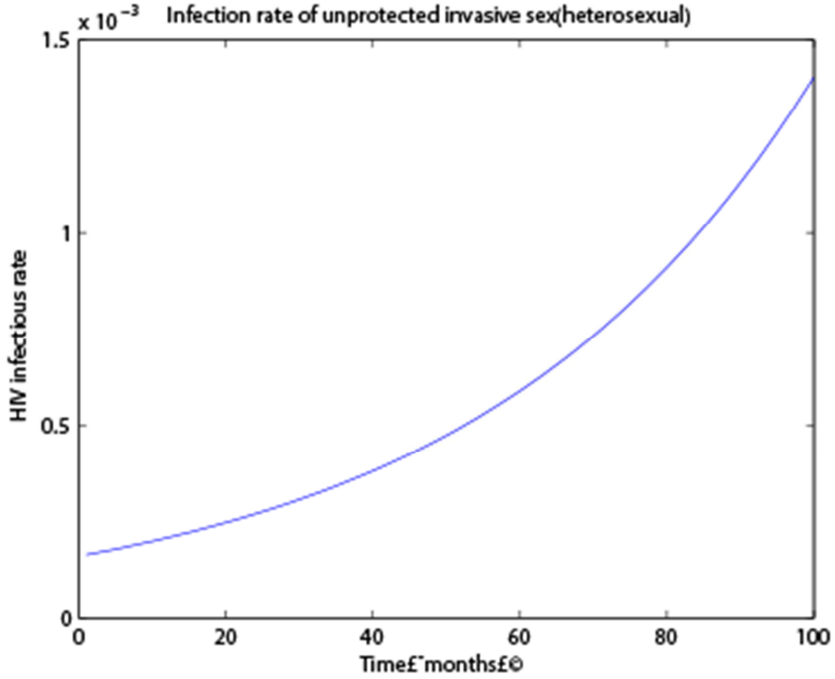

Figure 2. *Female towards male through vaginal intercourse.*

Anal intercourse

Anal intercourse is widely used in men to men relationship. If HIV is transmitted from the bottom to the top, there must be rectal abrasion and blood carrying HIV virus contact with prepuce.

According to the model:

$$y = \frac{v(t)}{n} * l * h * m * (po * cd4t + lc + mcell)$$

Substitute numerical values:

$$v(t) = 10^{2+0.0094t} \text{ copies/mL}$$

$$l = 4 \text{ mL}$$

$$h = 1$$

$$n = 10^9 \text{ /mL}$$

$$m = 10^6 \text{ cm}^2$$

$$lc = 13/10000$$

$$cd4t = \frac{133}{10000} * 0.32$$

$$po = 0.01$$

$$mcell = 0$$

Then we get HIV transmission trend as shown in Figure 3.

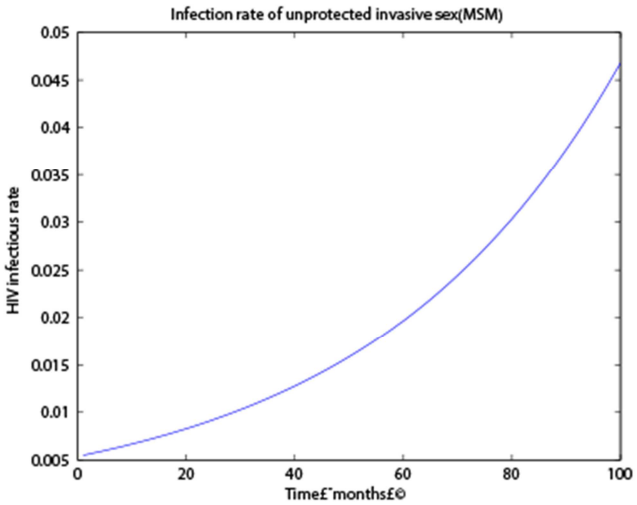

Figure 3. *Bottom towards top through anal intercourse.*

If HIV is transmitted from the top to the bottom, semen becomes the media. Besides T cells in the submucosal layer, HIV also invades M cells in the MALT tissue.

According to the model:

$$y = \frac{v(t)}{n} * l * h * m * (po * cd4t + lc + mcell)$$

Substitute numerical values:

$$v(t) = 10^{2+0.0094t} \text{ copies/mL}$$

$$l = 4 \text{ mL}$$

$$h = 1$$

$$n = 10^9 \text{ /mL}$$

$$m = 10^6 \text{ cm}^2$$

$$lc = 0$$

$$cd4t = \frac{133}{10000} * 0.32$$

$$po = 0.1$$

$$mcell = 0.025$$

Then we get HIV transmission trend as shown in Figure 4.

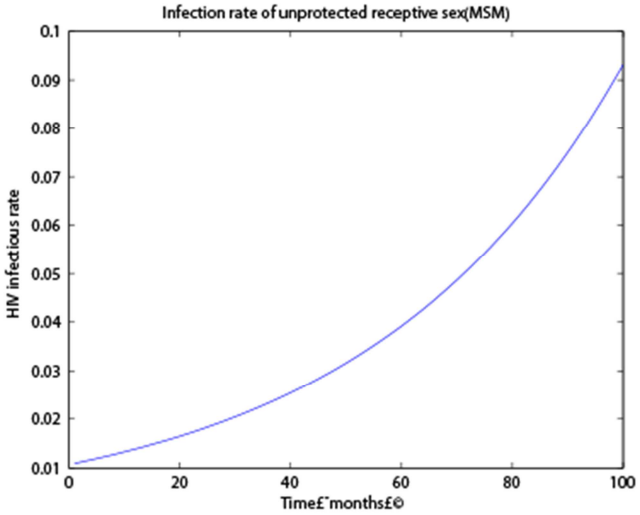

Figure 4. *Top towards bottom through anal intercourse.*

3. Numerical Simulation

Antiretroviral therapy (ART) is recognized as an effective treatment to HIV infection, which keeps HIV viral load at a low level and thus reduce its infection rate. As is shown in a study, after appliance of ART drugs, HIV RNA load in rectum fluid is $3.6\log_{10}$ copies/mL, in semen $2.6\log_{10}$ copies/mL, in serum $2.4\log_{10}$ copies/mL.

According to the model:

$$y = \frac{v(t)}{n} * l * h * m * (po * cd4t + lc + mcell)$$

We assume that under the control of ART, HIV viral load is stable so we can get average infection rate. The infection rate of male towards female is 0.000161, female towards male 0.000536, top towards bottom 0.00537, bottom towards top 0.1069.

4. Discussion

The infection rate derived from this model is basically the same as the trend in reality and the difference between different situations is quite reasonable. We get Figure 5 if we compare the four situations together.

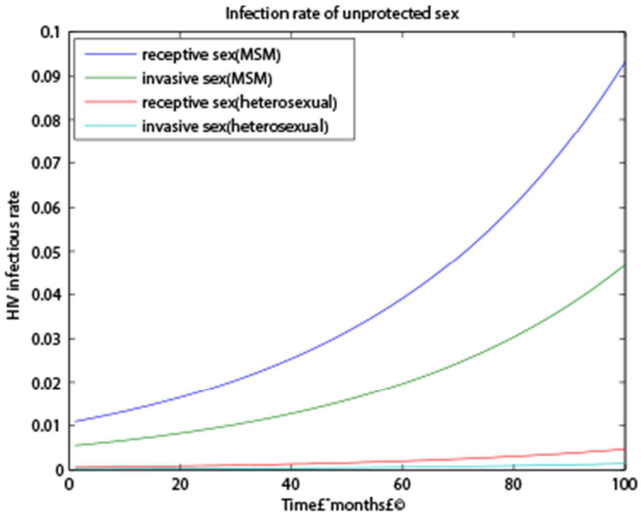

Figure 5. *Infection rate of four situations.*

It is obvious that the infection rate of anal intercourse is much higher than vaginal intercourse because the single columnar epithelium on rectal mucous layer is susceptible to abrasion, which is why men who have sex with men are of high risk to HIV.

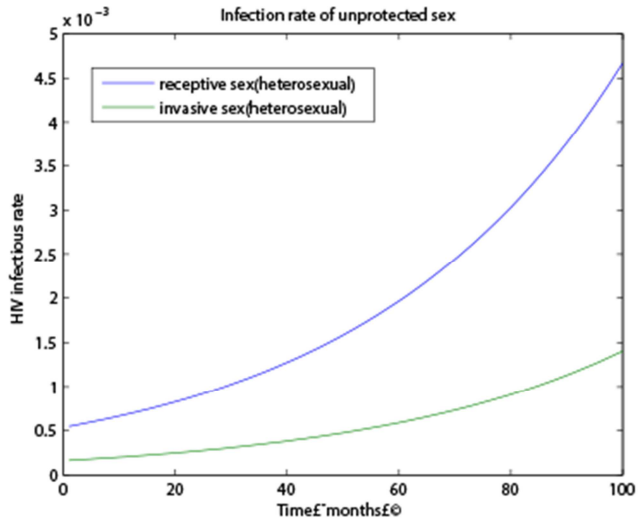

Figure 6. *Infection rate of vaginal intercourse.*

We can know from Figure 6 that the infection rate of male towards female is higher than that of female towards male. One possible reason is that HIV vitality largely decreases in vaginal fluid. Besides, circumcision is an effective way to reduce HIV infection rate.

The appliance of ART is also recommended because it reduces infection rate and controls the spread of HIV.

Last but not least, the model we establish in this study can provide sensible infection rate for other complicated transmission model like small-world model and scale-free model so as to construct a better HIV transmission model among people and predict epidemic trend with different interference.

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References

[1] Andrew E. Williams. Immunology Mucosal and Body Surface Defences 2012 [M]. 2012: 143. doi: 10.1002/9781119998648.

[2] Scott G. McCombe, Roger V. Short. Potential HIV-1 target cells in the human penis [J]. AIDS, 2006 Jul; 20 (11): 1491-1495.

[3] Lavreys L. Injectable Contraceptive Use and Genital Ulcer Disease during the Early Phase of HIV-1 Infection Increase Plasma Virus Load in Women [J]. J Infect Dis. 2004 Jan 15; 189 (2): 303-11. Epub 2004 Jan 9.

[4] Seth C. Kalichman. Human Immunodeficiency Virus Viral Load in Blood Plasma and Semen: Review and Implications of Empirical Findings [J]. Sexually Transmitted Diseases, 2008 Jan; 35 (1): 55–60 doi: 10.1097/OLQ.0b013e318141fe9b

[5] Richard A. Zuckerman, et al. Higher Concentration of HIV RNA in Rectal Mucosa Secretions than in Blood and Seminal Plasma, among Men Who Have Sex with Men, Independent of Antiretroviral Therapy [J]. J Infect Dis. 2004 Jul 1; 190 (1): 156-61. Epub 2004 Jun 9.

[6] Ana Ceballos, et al. Spermatozoa capture HIV-1 through heparan sulfate and efficiently transmit the virus to dendritic cells [J]. J. Exp. Med, 2009 Nov; 206 (12): 2717-2733. doi: 10.1084/jem.20091579. Epub 2009 Oct 26.

[7] Pudney J. Immunological Microenvironments in the Human Vagina and Cervix: Mediators of Cellular Immunity Are Concentrated in the Cervical Transformation Zone [J]. Biol Reprod. 2005 Dec; 73 (6): 1253-63. Epub 2005 Aug 10.

[8] L. A. Hussain, T. Lehner. Comparative investigation of Langerhans' cells and potential receptors for HIV in oral, genitourinary and rectal epithelia [J]. Immunology, 1995 Jul; 85 (3): 475-84.

[9] Langman JM, Rowland R. The number and distribution of lymphoid follicles in the human large intestine [J]. J Anat. 1986 Dec; 149: 189-94.

[10] NA Mabbott, et al. Microfold (M) cells: important immunosurveillance posts in the intestinal epithelium [J]. Mucosal Immunol, 2013, 6: 666–677. doi: 10.1038/mi.2013.30. Epub 2013 May 22.