AN OVERVIEW ON STRATEGICAL PROCESS OF DEVELOPMENT OF HIV AND THERAPEUTIC PROCESS IN INDIAN POPULATION

Abstract

Globally, approximately 75 million individuals have been affected with HIV, since some instances were initially discovered in California, USA, in 1981. The first few HIV cases in India were found in sex workers in Chennai in 1986. 25 to 30% of HIV infections are transmitted during the late stages of pregnancy or antenatally, whereas Labour and delivery are the times when 70 to 75 percent of HIV transmission occurs. India has one of the top HIV surveillance systems in terms of size, durability, and performance. Heterosexual relationships were responsible for 87% of new HIV infections in India. Manipur, Mizoram, Nagaland, Andhra Pradesh, and Karnataka are the five states in India with the highest HIV prevalence rates, but several other states in the northern and north-eastern regions of the country have also recorded increased HIV prevalence rates. North-eastern states or UTs such as Nagaland, Mizoram and Manipur have comparatively higher adult HIV prevalence 1.44%, 1.15% and 2.37% respectively; moreover, other states like Meghalaya, Karnataka, Telangana and Andhra Pradesh have higher prevalence (0.53%, 0.45%, 0.48% and 0.66%) more than 0.40% as reported. Among the total number of infected individuals 44.3% were female and 3.5% were children. There are now 26 ARV drugs available, divided into 5 primary classes. NACO presently advises a straightforward ART regimen in India that consists of a single tablet with a fixed-dose combination of tenofovir, lamivudine, and dolutegravir. We have provided how the reviewed models are mathematically formulated for differential games, control problems, and dynamic systems.

Keywords: HIV, Indian scenario, mathematical models, disease development, HIV treatment.

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I. INTRODUCTION

HIV prevalence has increased in developing countries since 1980, and this has had a significant impact on a variety of economic, demographic, and social factors [(Whiteside, 2001), (Mothi et al., 2016)]. Adults who engage in unsafe sexual activity are most likely to contract HIV. A significant number of vertical transmissions have been documented from pregnant women to their new-borns throughout pregnancy in utero, during late pregnancy, or afterwards through breastfeeding [(Suryavanshi et al., 2018), (Tank & Damania, 2006)]. In India, this phenomenon is aptly known as parent-to-child transmission (PTCT), taking into account the parental involvement of the male partner who transmits the virus to his spouse. New-born babies are only infected due to transmission from the mother in this situation (Suryavanshi et al., 2018). In contrast, 25 to 30% of HIV infections are transmitted during the late stages of pregnancy or antenatally, whereas Labour and delivery are the times when 70 to 75 percent of HIV transmission occurs [(Irene & Arun, 2010), (Bhatta et al., 2020)]. Globally, India has one of the top HIV surveillance systems in terms of size, durability, and performance (Garcia et al., 2010). Even before the first case of HIV infection was discovered in the country, the ICMR (Indian Council of Medical Research) began HIV surveillance in India in 1985 to hunt for HIV infection all throughout the country. In 1995, 52 sentinel sites were used for HIV sentinel surveillance (HSS) [(Lal, S., 2003), (Sangal et al., 2018)]. In the HSS from 2015, 89% of the 640 districts included having at least one sentinel point. The third-largest HIV epidemic infection rate in the world is found in India. The prevalence of HIV in India in 2015 was approximately 0.26 %. Overall, the HIV epidemic in India is waning. Between 2007 and 2015, AIDS-related fatalities decreased by 54%, and new HIV infections fell by 32% (86,000 in 2015). Heterosexual relationships were responsible for 87% of new HIV infections in India in 2015 (Sangal et al., 2018). Karnataka, Andhra Pradesh, Nagaland, Mizoram, and Manipur are the five states in India with the highest HIV prevalence rates, but several other states in the north and north-eastern regions of India have also recorded increased HIV prevalence rate (Singh, et al., 2019). This diversity in HIV epidemiology calls for various creative strategic approaches that can be implemented in various Indian states and union territories. HIV testing and counselling services were introduced in India in 1997, and since then they have expanded to a variety of medical facilities. According to WHO/UNAIDS 2017, at the end of 2016, 30% of Indians who were HIV-positive had not received an HIV test and were still unsure of their status (Sangal et al., 2018). India is dedicated to implementing the global 90-90-90 initiatives, which will assist in identifying 90% of those affected, getting 90% of them on medication, and ensuring 90% of them have their infection under control (Singh, et al., 2019). HIV vulnerability is significantly influenced by gender. The term "gender" refers to the socially created influences, norms, attitudes, roles, values, and behaviours that a given society deems proper for women, Trans women, Trans men, and men [(Anthony et al., 2016), (Pomerantz, R. J., 2002)]. Between 2010 and 2019, it is estimated that there were 37% fewer new HIV infections each year, and there were 66% fewer AIDS-related deaths each year. In India in 2019, there were 59,000 AIDS-related deaths and an additional 69200 new HIV infections. In India, some key affected communities such as transgender (TG), people who inject drugs (PWID), men who have sex with men (MSM), and female sex workers (FSW) are 3.14%, 6.26%, 2.6%, and 1.56%, respectively are responsible for epidemic of HIV (Rewari et al., 2021).

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II. ORIGIN OF THE INFECTION

Globally, approximately 75 million individuals have been affected with HIV, since some instances were initially discovered in California, USA, in 1981 (Rewari et al., 2021). Worldwide, a 38 million individuals are thought to be HIV positive as of today, and nearly death cases of 37 million individuals from HIV as reported (Rewari et al., 2021). In Comparison to 4.1% in African sub-Saharan area, the total adult frequency in the South-East Asia (SEA) part is 0.3%. However, the SEA Region a 3.8 million individuals are estimated to live with PLHIV, or 10% of the total worldwide (Pradesh, A., 2022). The first few HIV cases in India were found in prostitute in Chennai in 1986. India has the second-highest HIV prevalence worldwide despite its low incidence, with an expected 23.19 million PLHIV in 2020. HIV/AIDS is still a problem for India's public health. India is dedicated towards achieving the "End of AIDS" as a public health issue by 2030 as part of its commitment to the United Nation's Statement on Sustainable Development Goals (SDGs). As a result, India has established particular 2020 Fast-Track Targets for preventing new HIV infections, scaling up testing and treatment, ending mother-to-child HIV transmission (EMTCT), and ending HIV/AIDS-related discrimination and stigma, as adopted around the world, to serve as an anchor for the global AIDS response and guide strategies towards the "ENDGAME" by 2030.

III. DEVELOPMENTAL STRATEGIES OF HIV

HIV infection triggers cellular and humoral responses as well as innate and adaptive immunity. However, cellular latency, genetic diversity, and integration of the viral genome contributes to persistence of HIV as a chronic infection, which allows for immunological escape. Initially controlling viremia is greatly aided by CD8+ lymphocytes, but subsequently the immune system runs out of steam and breaks down. (Streeck, H., et al., 2008). T cells become dysfunctional with repeated antigenic stimulation, but the absence of CD4+ T helper cells is a sign of HIV infection (North, R. J., & Jung, Y. J., 2004). HIV is a retrovirus, and after incubation in host cells, its ssRNA transforms into dsDNA, which is known as the provirus. Additionally, this provirus fuses with human DNA, controls the machinery of the host cell, and begins generating countless numbers of fresh virion particles. It is extremely difficult to identify a suitable treatment because the entire life cycle HIV occurs inside the host cell. As a result of AIDS, the body's immune system becomes weakened and more open to opportunistic infections. People with HIV may experience vomiting, mouth sores, flu-like symptoms, nausea, difficulty swallowing, weight loss etc. in the early stages of the disease (Carr, A., 2003).

IV. INDIAN SCENARIO OF HIV INFECTIONS

The anticipated HIV prevalence among adults (15–49 years) nationwide in 2020 was 0.22% (0.17%–0.29%); among males, it was 0.23% (0.18%–0.31%), and among females, it was 0.20% (0.15%–0.26%). From a projected peak level of 0.54% in 2000–2001 HIV prevalence among adults down to 0.22% in 2020. North-eastern states or UTs such as Nagaland, Mizoram and Manipur have comparatively higher adult HIV prevalence 1.44%, 1.15% and 2.37% respectively; moreover, other states like Meghalaya, Karnataka, Telangana and Andhra Pradesh have higher prevalence (0.53%, 0.45%, 0.48% and 0.66%) more than 0.40% as reported on 2020. In addition to these States, Chhattisgarh and Haryana had estimated adult HIV prevalence in between 0.20-0.21%, whereas Tamil Nadu, Goa,

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Puducherry, Punjab, Maharashtra and Delhi had estimates that were higher than the national prevalence (0.22%). In India total number individuals living with HIV was 23.19 lakh as estimated in 2020. Among the total number of infected individuals 44.3% were female and 3.5% were children. The highest number (3.90 Lakh) of people with PLHIV was in Maharashtra and the minimum number (0.25 Lakh) of people with PLHIV was in Kerala (Pradesh, A., 2022).

V. TREATMENT PROCESS

HIV infection cannot be cured by antiretroviral medications because the virus hides in the "immunological sanctuaries" of our body, which makes it challenging to remove. Early in acute HIV infection, a pool of chronically infected CD4+ cells are formed, and it endures in the organs, tissues, and fluids even after receiving effective treatment (Pomerantz, R. J., 2002). The objectives of Anti-Retroviral Therapy (ART) are to reduce the replication of virus, restore immunological function, and ultimately extend life while enhancing quality of life. By suppressing viral growth, ART also stops the spread of HIV. In 1985, the first medicine to be proven to be successful in opposition to HIV was zidovudine, however the virus swiftly developed resistance to this treatment. The outcomes of a combination of three drugs using new, extremely strong drugs called protease inhibitors marked a bench mark in the treatment choices in 1996. However, they were related to problems with several pills, high expenses, and toxicity. The development of non-nucleoside reverse transcriptase inhibitors, such as nevirapine and later efavirenz, made the use of two nucleoside reverse transcriptase inhibitors and other drugs more efficiently. and led to their rapid adoption as standard of care. Drugs used to treat HIV are categorised according to how they affect the replication process. There are now 26 ARV drugs available, divided into 5 primary classes (Sharma, S., 2023). Triple-drug therapy is currently the recommended treatment option for HIV-1 infection. which consists of two NRTI (nucleoside reverse transcriptase inhibitors) or NtRTI (nucleotide reverse transcriptase inhibitors) backbones combined with a NNRTI (non-nucleoside reverse transcriptase inhibitor). The Indian guidelines and WHO recommended starting ART in the individuals with less than 200 CD4 levels or those in clinical stages 3 or 4 during the early stages of ART scale up in 2004. Over time, information from randomized clinical trials including SMART, HPTN 052, CIPHRA HT 001 and the more recently TEMPRANO and START trials has led to revisions in the recommendations for when to start taking antiretroviral therapy, in 2002 from CD4+ count below 200 cells/μl, and in 2010 it was 350 to 2013 it was 500, and now the recent advice in 2016 of starting ART in every patient regardless of CD4 count. In 2016, WHO advised using a first-line regimen based on a fixed dosage combination (FDC) of efavirenz, lamivudine, and tenofovir for adults and adolescents, while abacavir was to be used in place of tenofovir for children under 10 and ritonavir/lopinavir was to be begun for children under 3 instead of efavirenz (Maartens et al., 2014), furthermore, in 2017, NACO adopted this. In July 2019, WHO policy has been updated from recommends an integrase inhibitor, Dolutegravir (DTG) in conjunction with a NRTI backbone as the best first-line regimen for persons living with HIV commencing ART. For infants and kids for whom no certified DTG dosage is available, an alternate first-line regimen based on Raltegravir (RAL) may be advised (Mirzayev et al., 2021). NACO presently advises a straightforward ART regimen in India that consists of a single tablet with a fixed-dose combination of tenofovir, lamivudine, and dolutegravir (Sharma, S., 2023). Since dolutegravir is regarded as safe to administer during pregnancy, efavirenz is now only offered to women who refuses to take dolutegravir (Ford et al., 2014), for all new patients

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who are starting ART, NACO has now decided to substitute dolutegravir (DTG) instead of efavirenz. Presently, over 553 ART centres and 1261 linked ART centres are serving 1.38 million patients getting ART, of whom 65,000 patients are getting second-line ART and 2,800 individuals are getting third-line ART of the free ART programme in India, which was launched in 2004. Rifampicin and efavirenz can be provided together because rifampicin reduces the AUC (area under the curve) for efavirenz (López-Cortés et al., 2002) by 22-26%, whereas nevirapine can induce a reduction of up to 31%. (Ribera et al., 2001). Due to a drug-drug interaction with Rifampicin when a DTG-based ART regimen is utilised, the dose of DTG must be increased to 50mg twice daily. Rifabutin causes a reduction in Protease Inhibitor (PI) AUC of 15% to 45%, whilst Rifampicin causes a drop of 35% to 92%. [(Burman, W. J., & Jones, B. E., 2001)]. When utilising a Protease Inhibitor-based ART concurrently, rifabutin is favoured over rifampicin. HIV patients frequently have uncontrollable diarrhoea, which can cause malabsorption of ATT and ARV medications and eventually result in the development of treatment resistance. The potential for drug toxicity to cause a patient to stop receiving ART must be taken into consideration.

In order to provide an overview of how the reviewed models are mathematically formulated for differential games, control problems, and dynamic systems. To facilitate better comparisons between the models, the notation has been uniformly made. At time ‘t’ the following functions represented are I(t): infected T lymphocytes of immune response cells, V(t): infected T lymphocytes of viruses, $T^i(t)$: infected T lymphocytes, T(t): the number of healthy T lymphocytes.

Dynamic Systems: The basic model that defines how HIV and T cells interact is represented by the system of deterministic differential equations as follows. $N_{rti}(t) \epsilon$ (0, 1) is the exogenous functions which is the representative of intensity of treatment of reverse transcriptase inhibitors at time ‘t’ during therapy.

$$T(t) = \alpha - (1-\eta_{rti}(t))\,\beta T(t)V(t) - \mu_T T(t) + rT(t)\left(1 - \frac{T(t)}{Tmax}\right) \ldots \quad (1)$$

$$T^i(t) = (1-\eta_{rti}(t))\,\beta T(t)V(t) - \mu_T{}^i T^i(t) \ldots \quad (2)$$

$$V(t) = N\mu_T{}^i T^i(t) - \mu_V V(t) \ldots \quad (3)$$

The equations (1) and (2) representing the effect of inhibitors on infected and uninfected T-cells Perfect inhibition occurred when $\beta = 0$ or $\eta_{rti}(t) = 1$; and $(1-\eta_{rti}(t))\,\beta T(t)V(t)$ represent the action of the inhibitors. $\mu_T{}^i$ and μ_T the frequency of infected and uninfected CD4+ T cell mortality. $\left(1 - \frac{T(t)}{Tmax}\right)$ in equation (1) indicates the cloning-induced T-cell production in the presence of an antigen yet considering the maximum possible lymphocyte population. $N\mu_T{}^i$ in equation (3) representing the quantity of free viruses generated by infected T cells to measure the viral proliferation; whereas, μ_V indicates the mortality rate of virions.

1. **Optimal Control Strategy:** The goal of the optimum control strategy is used to calculate the ideal drug dosage aimed to increase the number of T cells and subsequently immunological effectors while minimising drug toxicity. Drug therapy intensity

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determines the control functions, whereas the numbers of various T lymphocyte subtypes and viruses determine the state functions.

$$\max J(u(t)) = \int_0^{tf} (T(t) + I(t) - \frac{Bu\,2(t)}{2}) dt$$

Subject to

$$T(t) = \alpha - (1- u(t))\, \beta T(t) T^i(t) - \mu_T T(t), \ldots \quad (4)$$

$$T^i(t) = (1- u(t))\, \beta T(t) T^i(t) - \mu_T{}^i T(t) - \rho T^i(t)\, I(t), \ldots \quad (5)$$

$$I(t) = \gamma\, T(t)\, T^i(t)\, I(t) - \mu_T I(t), \ldots \quad (6)$$

$$T(0) = T_0,\ T^i(0) = T^i_0,\ I(0) = I_0,\ u(t) \epsilon\ (0,1).$$

Equations [4] and [5] are similar to Equations (1) and (2) with $T^i(t)$ substituting V(t). Equation (6) illustrates the evolution of the immune response, which is dependent on both the quantity of healthy T-cells (which remember cell mediated immunity based on the quantity of viruses in circulation) and the quantity of infected T-cells (which can manufacture new virions). The first two terms in the objective functional, respectively, stand for the advantages of T cells and immune response cells. The quadratic function $u^2(t)$, which measures the severity of the side effects of the drugs, is used to calculate the third term, which is the systemic cost of the drug treatments.

2. **Game Theory:** Using differential games to address the HIV issue, where one participant is the HIV virus while another is the immune system (host) assisted by drug therapy, is an intriguing strategy. The goal of the HIV player is to increase the proportion of viruses that are drug-sensitive, drug-resistant, and T cells that are both latently and actively infected, while reducing the costs associated with mutation. The host, on the contrary, desires to increase the number of T cells and reduce drugs toxicity. The drug amounts for treatment and the viral mutation rates are examples of potential strategies. In terms of advantages, the immune system/therapy tries to increase the proportion of non-infected macrophages while reducing drugs toxicity.

$$J_H(u_1, u_2) = \int_{t0}^{tf} [T^2(t) - (A_1 u^2_{RT}(t) + A_2\, u^2_{PI}(t))]\, dt$$

where $u_{RT}(t)$ is the dosage of RT, $u_{PI}(t)$ the dosage of PI, and the two constants A_1, $A_2 > 0$ represent the desired "weight" on the cost of the drugs.

The virus strains into sensitive $V_s(t)$ and mutated viruses $V_r(t)$ the HIV virus aims at maximizing the number of drug sensitive viruses, the number of drug resistant viruses, while minimizing its mutation costs,

$$J_v(u) = \int_{t0}^{tf} [V^2{}_s(t) + V_r{}^2(t) - A_3 u^2(t)]\, dt$$

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where u (t) is the mutation rate of HIV from a drug-sensitive strain to a drug-resistant strain.

The game dynamics and constraints are

$$T(t) = \alpha - \mu_T T(t) - \beta\,(1 - u_{RT}(t))\,V_s(t)T(t) - \delta T(t)V_r(t), \ldots \quad (7)$$

$$T_s(t) = \beta\,(1 - u_{RT}(t))\,V_s(t)T(t) - \mu_{Ts}T_s(t), \ldots \quad (8)$$

$$T_r(t) = \delta V_r(t)T(t) - \mu_{Tr}T_r(t), \ldots \quad (9)$$

$$V_s(t) = P_1(1- u_{PI}(t))\,(1- u_v(t))\,T_s(t) - \mu_{Vs}\,V_s(t), \ldots \quad (10)$$

$$V_r(t) = P_2T_r(t) + P_1u_v(t)\,T_s(t) - \mu_{Vr}\,V_r(t), \ldots \quad (11)$$

$$T(0) = T_0,\ T_s(0) = T_{s0},\ T_r(0) = T_{r0},\ V_s(0) = V_{s0},\ V_r(0) = V_{r0},\ u_{RT}(t),\ u_{PI}(t),\ u(t) \in (0,1).$$

Equation (10) explains how the proportion of susceptible viruses Vs (t) which have not been affected by the treatment and have not evolved into resistant viruses Ts (t) is given. According to equation (11), the proportion of sensitive viruses that infected Ts (t) and transformed into resistant viruses, Tr (t), is used to calculate the quantity of resistant viruses Vr (t).

VI. CONCLUSION

According to the results of the study, there is a significant gap between understanding about HIV/AIDS and the appropriate ways to avoid it. The study shows that even though women make up a significant portion of the HIV/AIDS epidemic, many of them are unaware of the ways in which the disease spreads. However, the widespread knowledge of HIV/AIDS means that women are just hearing about the disease; this is insufficient to prevent serious HIV/AIDS-related diseases. Even if society as a whole is fully informed and aware of this sickness, it can provide the best moral support to patients and their families. As understanding of HIV/AIDS and the correct methods of transmission in rural regions was quite poor, it is necessary to raise awareness of these issues. Strong community-based campaigns are required to emphasise HIV/AIDS awareness and thorough understanding of HIV/AIDS prevention techniques. To stop the spread of HIV/AIDS, education is the only available strategy. Additionally, NFHS and other studies show that there is a low level of public awareness of AIDS, therefore efforts to prevent it are focused solely on raising awareness. This is a crucial area that requires development, and both government and non-governmental organisations (NGOs) should work to promote awareness in both urban and rural areas. However, rural areas and regions with greater HIV/AIDS prevalence should receive more attention because they are more likely to have a higher rate of transmission. However, more research was required before these correlations could be established. Although India is a long way from completely eliminating MTCT of HIV, the Indian AIDS control programme has achieved success in lowering HIV transmission from infected pregnant women to their new-born offspring. The foundation of contemporary therapy is antimicrobials. Although a single medication is usually sufficient, there are some clinical situations where a combination is required. Fixed Dose Combinations [FDC] are widely used

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because they have higher compliance rates and other benefits. FDC combinations that make sense are effective, but those that don't make sense are risky. These should only be recommended when their dosage is sensible and suitable.

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