Introduction

1.1: History of HIV/AIDS

In the United States and Europe during the late 1970s to early 1980s, patients exhibiting a new immunologic dysfunction of unknown etiology attracted the attention of health care professionals [1]. Subsequently, the abnormal incidence of *Pneumocystis carinii* pneumonia (PCP) in five homosexual men from Los Angeles was reported to the Centers for Disease Control and Prevention (CDC) in 1981 [2, 3]. Later, numerous similar reports describing male homosexuals and intravenous drug users with damaged immune systems and T lymphocytes were sent to the CDC [4]. The new term “gay-related immunodeficiency” (GRID) came into existence because more than 90% of these cases occurred in homosexual or bisexual men. In the following year (1982), hundreds of similar cases had been reported not only in homosexual and bisexual men, but also in hemophiliacs, blood-transfusion recipients, intravenous drug users, heterosexual adults from the Caribbean and Central Africa, and infants born to mothers with the syndrome [5]. Furthermore, in 1983, scientists at the Pasteur Institute in France discovered a virus in the lymph nodes of an asymptomatic individual, and they presented their discovery, along with that of Gallo and colleagues, at the National Institutes of Health [6].

Subsequently, the isolation of retroviruses from acquired immune deficiency syndrome (AIDS) patients was reported by Gallo, which they named human T-cell lymphotropic virus-III (HTLV-III). The new retrovirus associated with AIDS was subsequently renamed human immunodeficiency virus-1 (HIV-1) because it exhibited typical morphologic and genetic characteristics of the *Lentivirus* genus among patients in the United States, Europe, and central Africa [7]. A less pathogenic human retrovirus (now called HIV-2) was recovered from individuals residing in several Western African countries in 1986 [8]. A similar retrovirus was isolated from both AIDS patients and
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healthy individuals from the various at-risk groups by Levy et al in 1994 [9], which they named the AIDS-associated retrovirus (ARV).

The first AIDS case in India was detected in 1986, and since then, HIV infections have been reported in all states and union territories. India responded promptly to the HIV/AIDS challenge at the initial stage by setting up an AIDS Task Force under the Indian Council of Medical Research. To strengthen the management capacity, a National AIDS Control Board (NACB) was started, and an autonomous National AIDS Control Organisation (NACO) was set up for project implementation [10].

1.2: Epidemiology and Mechanism of Action

HIV-1 infections remain most prevalent throughout the world, including in India, and HIV-1 comprises several viral sub-types with different geographic distributions [11-13]. However, HIV-2 infections are precisely confined to West Africa. It is presumed that the common chimpanzee (Pan troglodytes) is the natural reservoir for HIV-1, as well as the most likely source of the original human infection. The infectivity of HIV-1 is high, while that of HIV-2 are low.

HIV has an icosahedral structure that contains numerous external spikes formed by the two major envelope proteins, the external gp120 and the transmembrane gp41. The virus buds from the surface of infected cells, and it incorporates a variety of host proteins, including major histocompatibility complex (MHC) class I and II antigens into its lipid bilayer [14]. HIV is an RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme reverse transcriptase. The replication cycle of HIV begins with the high-affinity binding of the gp120 protein (Figure 1.1), via a portion of its V1 region near its amino terminus, to its receptor, CD4, as well as its co-receptors C-C chemokine receptor type 5 (CCR5) or C-X-C chemokine receptor type 4 (CXCR4), on the host cell surface [15, 16]. The CD4 molecule is a 55-kDa protein found predominantly on a subset of T lymphocytes that are responsible for helper functions in the immune system.
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Figure 1.1: Inner shape of HIV virus

1.3: Treatment Strategy

Antiretroviral (ARV) drugs, which were first developed in 1996, are medications that are used to treat retrovirus infections, primarily HIV infections. Different classes of ARVs act disrupt viral replication during different stages of the HIV life cycle. 52% of the estimated 785,000 (681,000–872,000) people living with HIV (PLHIV) who needed treatment received antiretroviral therapy (ART) in 2011 compared with only 17% in 2007 [11]. While more than 400 ART centers across the nation provide free HIV care, only half of the eligible patients are receiving ART. Theoretically, ARV drugs can act in any of the following ways during different stages of viral replication [17]:

i. Block binding of HIV to target cells (*fusion inhibitors*)

ii. Block viral RNA cleavage and inhibit reverse transcriptase (*reverse transcriptase inhibitors*)

iii. Block the enzyme integrase, which aids in the incorporation of the proviral DNA into the host cell chromosome (*integrase inhibitors*)

iv. Block the RNA to prevent viral protein production

v. Block the enzyme protease (*protease inhibitors*)

vi. Inhibit the budding of virus from host cells
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**Table 1.1: Classification of drugs used for HIV care (Source: NACO)**

<table>
<thead>
<tr>
<th><strong>Classes of drugs available</strong></th>
<th><strong>Nucleoside reverse transcriptase inhibitors (NRTIs)</strong></th>
<th><strong>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</strong></th>
<th><strong>Protease inhibitors (PIs)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT/ZDV)*</td>
<td>Nevirapine* (NVP)</td>
<td>Saquinavir* (SQV)</td>
<td></td>
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<tr>
<td>Stavudine (d4T)*</td>
<td>Efavirenz* (EFV)</td>
<td>Ritonavir* (RTV)</td>
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<tr>
<td>Lamivudine (3TC)*</td>
<td>Delavirdine (DLV)</td>
<td>Nelfinavir* (NFV)</td>
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<tr>
<td>Didanosine (ddl)*</td>
<td>Fusion inhibitors (FI)</td>
<td>Amprenavir (APV)</td>
<td></td>
</tr>
<tr>
<td>Zalcitabine (ddC)*</td>
<td>Enfuvritide (T-20)</td>
<td>Indinavir* (INV)</td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)*</td>
<td>Integrase Inhibitors</td>
<td>Lopinavir/Ritonavir (LPV)*</td>
<td></td>
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<tr>
<td>Emtricitabine (FTC) (NtRTI)</td>
<td>Raltegravir</td>
<td>Fosamprenavir (FPV)</td>
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</tr>
<tr>
<td>Tenofovir (TDF)*</td>
<td>CCR5 Entry Inhibitor</td>
<td>Atazanavir (ATV)*</td>
<td></td>
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<tr>
<td><em>Available in India</em></td>
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Increasing access to the antiretroviral treatment has also indicated that an increasing number of people living with HIV in India are developing drug resistance. When a first-line HIV treatment fails, the treatment regimen needs to be changed to second-line ARVs. As with many other resource limited countries, second-line treatments in India are far more expensive than first-line treatments. In 2008, the NACO began to roll out government-funded second-line antiretroviral treatments in two centers in Mumbai and Chennai. However, the coverage remains limited to 5,000 HIV/AIDS patients [11]. Interestingly, India is a major manufacturer of first-line generic ARV drugs. However, the cost of second-line treatments is approximately 10 times higher than that of first-line treatments.

#### 1.3.1: Goals of Antiretroviral Therapy

Currently ARV drugs cannot eradicate HIV from patients. This is because a pool of latently infected CD4 cells is established during the earliest stages of an acute HIV infection, and it persists within the organs/cells and fluids (e.g., liver and lymphoid tissue) even with prolonged suppression of plasma viremia to <50 copies/ml by ART.
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[18]. As per the national guidelines for ART, the primary goals of ARV drugs are presented in table 1.2 [17]:

Table 1.2: The goals of antiretroviral therapy according to the NACO guidelines

<table>
<thead>
<tr>
<th>Goals of ARV therapy</th>
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<tr>
<td><strong>Clinical goals:</strong> Prolongation of life and improvement in quality of life</td>
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<tr>
<td><strong>Virological goals:</strong> Greatest possible reduction in viral load for as long as possible</td>
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<tr>
<td><strong>Immunological goals:</strong> Immune reconstitution that is both quantitative and qualitative</td>
</tr>
<tr>
<td><strong>Therapeutic goals:</strong> Rational sequencing of drugs in a fashion that achieves clinical, virological, and immunological goals while maintaining treatment options, limiting drug toxicity, and facilitating adherence</td>
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<tr>
<td><strong>Reduction of HIV transmission in individuals:</strong> Reduction of HIV transmission by suppressing viral load</td>
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To achieve viral suppression, the use of ARV regimens requires at least two, or preferably three, active drugs from two or more drug classes. Baseline resistance testing and patient characteristics guide the specific treatment regimen design [19]. The increasing number of drugs and drug classes makes viral suppression below detection limits an appropriate goal in all patients, even in those with primary or acquired drug resistance. Viral load reduction to below assay detection limits in an ART-naïve patient usually occurs within the first 12–24 weeks of therapy [20]. The factors related to virologic success include:

- High potency of the ARV regimen
- Excellent adherence to the treatment regimen [21]
- Low baseline viremia [22]
- Higher baseline CD4 count (>200 cells/ml) [23]
- Rapid reduction in viremia in response to treatment [24, 25]

1.3.2: Antiretroviral Therapy Regimens

Currently, the national program provides the following drugs/combinations for first-line regimens [17]:

i. Zidovudine (300 mg) + Lamivudine (150 mg)


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ii. Tenofovir (300mg) + Lamivudine (150 mg)
iii. Zidovudine (300 mg) + Lamivudine (150 mg) + Nevirapine (200 mg)
iv. Efavirenz (600 mg)
v. Nevirapine (200 mg)

Commonly fixed-dose combinations (FDCs) are preferred because they are easy to use, have distribution advantages (procurement and stock management), improve adherence to treatment, and, thus, reduce the chances of developing drug resistance. The current national experience shows that bid (twice per day) regimens of FDCs are well tolerated and complied with.

1.4: Other Effects of Antiretroviral Therapy

ARV drug treatment guidelines have changed over time. Before 1987, no ARV drugs were available, and the treatment consisted of treating complications from the immunodeficiency. After the discovery of ARV medications, most clinicians agreed to treat HIV-positive patients with low CD4 counts, but no consensus was formed regarding whether to treat patients with high CD4 counts. These ARV drugs stop viral replication and delay the development of AIDS. However, they also have side effects that can be severe. These include decreased levels of red or white blood cells, inflammation of the pancreas, liver toxicity, rash, gastrointestinal problems, elevated cholesterol level, diabetes, abnormal body-fat distribution, and painful nerve damage. HIV-positive pregnant women require HIV care immediately because ART reduces the risk of transmitting the virus to the fetus. However, these drugs could be harmful to the baby. Therefore, seeing a physician to discuss anti-HIV medications is crucial because the primary purpose of ART is to reduce HIV-associated morbidity and mortality.

This is best accomplished by using ART to maximally inhibit HIV replication, as measured by consistent plasma HIV RNA (viral load) values below the level of detection of commercially available assays. Additional benefits of ART, which are supported by accumulating evidence, are a reduction in HIV-associated inflammation and its
associated complications, as well as a reduction in HIV transmission. Guidelines for the initiation of ART in adults and adolescents are different in developed and resource poor countries like India. A "hit hard, hit early" was also promoted with multiple ARV drugs early in the course of the infection. Later reviews noted that this approach has significantly increased the risks of side effects, as well as the development of multidrug resistance, and this approach has largely been abandoned.

1.5: Global Burden

HIV/AIDS-related illness remains a global public health concern, and it remains one of the important causes of morbidity and mortality worldwide since the first case was reported in the early 1980s. Since the start of the epidemic, around 78 million (71–87 million) people have become infected with HIV, and 39 million (35–43 million) people have died of AIDS-related illnesses. Approximately 35 million people (33.2–37.2 million) were living with HIV worldwide in 2013, a 17% increase from 2001 [26, 27]. This reflects the continued large number of new HIV infections and a significant expansion of access to ART, which has helped reduce AIDS-related deaths, especially in more recent years. AIDS-related deaths have been fallen by 35% since the peak in 2005, and the number of people dying of AIDS-related causes fell to 1.5 million (1.4–1.7 million) in 2013, down from a peak of 2.4 million (2.2–2.6 million) in 2004.

Tuberculosis remains the leading cause of death among PLHIV, with an estimated 360,000 (311,000–410,000) deaths in 2013 [26]. As of June 2014, 13.6 million PLHIV had access to ART and 38% [36–40%] of all adults living with HIV are receiving treatment. According to new calculations by the Joint United Nations Programme on HIV/AIDS (UNAIDS), a total of 2.5 million deaths have been averted in low- and middle-income countries since 1995 due to the introduction of ART [18].
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1.6: HIV/AIDS in India

At the beginning of 1986, around 20,000 AIDS cases were reported worldwide, while India had no reported cases of HIV/AIDS [28, 29]. The first case of HIV was diagnosed among sex workers in Chennai, Tamil Nadu [30]. This may have resulted from contact with foreign visitors, who played a vital role in initial infections among sex workers. In 1987, a National AIDS Control Programme (NACP) was launched to co-ordinate national responses. The activity of the NACP covered surveillance, blood screening, and health education [31]. By the end of 1987, out of 52,907 tested samples, around 135 people were found to be HIV-positive and 14 had AIDS [32]. At the beginning of the 1990s, infection rates continued to increase and in 1992 the government set up the NACO to supervise the formulation of policies, prevention, and control programs relating to HIV and AIDS [33]. In the same year, the government launched Strategic Plans and the first NACP for HIV prevention and control. This plan established the administrative and technical basis for program management, and it also set up State AIDS Control Societies (SACSs) in 25 states and seven union territories. Through this strategy, a number of important improvements in HIV prevention, such as improving blood safety, were attained. Initially, it was estimated that around 5 million people were living with HIV in India - more than in any other country, but subsequently, by including the results of a national family health survey conducted from 2005–2006 (NFHS-III) led to a major revision of the prevalence estimate in 2007 [32].

The NACO conducts annual HIV Sentinel Surveillance (HSS) in designated sites throughout the country to monitor HIV trends in various at-risk populations. As the data from the HSS are not representative of the general population, certain assumptions were used to generate estimates of the prevalence, incidence, and mortality in the general population. Over the years, these assumptions have been gradually improved with the help of other available data sources and by customizing the models using more inputs based on Indian data. The HIV estimates also highlighted the programs and interventions
that have yielded impacts, and they indicated where further focus was required. It is also suggested that state level responses need to be increasingly tailored according to each state’s epidemiological and social-developmental factors to end the epidemic [11]. The twelfth round of the HSS was conducted from 2010–2011 with the introduction of key strategies for improving the quality and comprehensiveness of the data. The number of sentinel sites increased from 1,223 in 2008 and 2009 to 1,359 in 2010 and 2011, with a major increase in the number of sites for high-risk groups (HRGs) and the bridge population. A random sample of 400 people was assigned to the low-risk general population (e.g.; ANC) and 250 people were assigned to the high-risk population (e.g.; MSM, FSW, IDU, etc.) and the bridge population (e.g.; truckers).

1.7: National HIV Estimates

The national adult HIV prevalence is the estimated percentage of population that is HIV-positive within a particular time period. It is calculated by aggregating the number of PLHIV in all states, dividing by the total adult population, followed by multiplying by 100 to obtain the percentage. The adult HIV prevalence in India was estimated to have peaked in 2002 at a level of 0.41% (95% CI: 0.35–0.47%), which was followed by a progressive decline in the estimated prevalence in subsequent years. The national adult HIV prevalence in 2011 was estimated to be 0.27% (95% CI: 0.22–0.33%) (Figure 1.2). States with adult HIV prevalences higher than the national average of 0.27% include Andhra Pradesh, Mizoram, Nagaland, Karnataka, Goa, Maharashtra, Odisha, Gujarat, Tamil Nadu, and Chandigarh.
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The Third National Family Health Survey (NFHS-III) in 100,000 tested adults reported a higher prevalence in urban areas (0.35%) than in rural areas (0.25%), and a considerably higher prevalence in men than women [34, 35].

The estimated number of PLHIV (adults and children) in India in 2011 was 2,088,000 (1,720,000–2,530,000), compared with an estimated 2,252,000 (1,918,000–2,534,000) PLHIV in 2007. A comparison between the 2007 and 2011 estimates shows an approximately 8% decline in the total number of PLHIV in the past five years (Figure 1.3). The number of adults (15+ years) living with HIV in India is declining. The estimate for this indicator in 2011 was 1,943,000 (1,592,000–2,372,000) compared with 2,109,000 (1,792,000–2,363,000) in 2007. Out of the total adult PLHIV population, females accounted for approximately 39% of infections, whereas males accounted for approximately 61% of infections in 2011. The estimated number of people living with HIV in 2011 was highest in Andhra Pradesh, approximately 420,000, followed by Maharashtra at 315,000. The other states with more than 100,000 estimated HIV
infections in 2011 were Karnataka, Tamil Nadu, West Bengal, Gujarat, Bihar, Uttarakhand, and Odisha.

Figure 1.3: Estimated number of people living with HIV (All Ages) in India, 2007–2011, with 95% confidence intervals (Source: NACO)

The estimated number of new HIV infections has declined steadily by about 57% from 2000 to 2011 (Figure 1.4). During 2007, the first year of the NACP III, new HIV infections were estimated at 143,000 (104,000–203,000). The declining trend at the national level was sustained until 2010, when the estimate for this indicator was 130,000 (84,000–200,000). Between 2010 and 2011, the number of new HIV infections was estimated to have increased marginally. In 2011, it was estimated that 130,000 (82,000–218,000) adults and children were newly infected. Rapidly declining to stabilizing trends were found in the six high prevalence states of Andhra Pradesh, Karnataka, Maharashtra, Manipur, Nagaland, and Tamil Nadu from 2000 to 2010. However, an increasing number of new infections were observed in recent years in certain states in the northern part of...
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the country. Males accounted for approximately 61% of new annual HIV infections in 2011, while women accounted for an estimated 39% of new HIV infections.

Figure 1.4: Estimated number of new HIV infections (All Ages) in India, 2000–2011, with 95% confidence intervals (Source: NACO)

The total number of annual AIDS-related deaths in India has declined from 206,000 (167,000–245,000) in 2007 to 147,000 (113,000–178,000) in 2011. This represents a nearly 50,000 reduction in the number of AIDS-related deaths annually (Figure 1.5). Males accounted for nearly 65% of the estimated AIDS related deaths in 2007 and this proportion decreased gradually to 63% in 2011. In contrast, females accounted for an increasing proportion of the total estimated AIDS related deaths from 2004 to 2011. The increase was from approximately 34.5% in 2004 to 36% in 2007 and 37% in 2011. The proportion of adults accounting for the total number of AIDS-related deaths has decreased annually from approximately 94% in 2004 to approximately 93% in 2011. It is estimated that over 150,000 deaths (all ages) have been averted since the initiation and scale up of the ART services after 2004. In 2011, the states of Andhra Pradesh and
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Maharashtra accounted for the highest number of AIDS-related deaths, approximately 31,000 and 24,000, respectively, followed by Karnataka and West Bengal, with more than 10,000 annual AIDS-related deaths.

Figure 1.5: Estimated number of annual AIDS-related deaths (All Ages) in India and the number of people (All Ages) receiving ART from 2004–2011 (Source: NACO)

The national need for ART among adults has increased proportionally every year, along with the estimated number of HIV-positive adults in need of treatment. Of the estimated 568,000 (471,000–668,000) adult patients, approximately 17% were receiving treatment in 2007. The treatment coverage increased in 2011, as nearly 52% of the estimated 785,000 (681,000–872,000) PLHIV who needed treatment received ART. Following the revision of the ART guidelines for treatment initiation at CD4 counts ≤350 cells/ml from 2012 onwards, the projected need for treatment for adult PLHIV was estimated to be approximately 1,000,000 (881,000–1,145,000) in 2012. The state-wise proportional need
is highest in Andhra Pradesh and Maharashtra, where it was estimated that an average of 21% of PLHIV need ART, while the need in Karnataka was approximately 10%.

1.8: Need for Study

The success of the ART program depends upon proper monitoring for drug adherence, timely presentation and CD4 investigation, as well as motivation for pre-ART cases for on-time visits to the ART center for their further assessment to prevent the progression and transmission of HIV. It has been globally accepted that HIV-infected individuals have tendency to delay testing. Additional delays in reporting also leads to an increased risk of transmission and decreased survival, with a poor quality of life [17, 36, 37]. In fact, ART initiation during the asymptomatic phase could delay the progression to the clinically symptomatic phase [38]. A delay in first-time visits to ART centers, and subsequent CD4 assessments, could be due to the associated social stigma that leads to delays in HIV care.

Several scientific studies conducted worldwide have estimated the survival and hazards for HIV/AIDS patients; however, limited information is published at the state level in India. Similarly, different survival models have been used to predict survival, but there is a need to study their predictive performances with large, censored data sets. Keeping this in mind, studies of survival and hazard estimations, as well as the predictive performance of survival models for HIV/AIDS patients, are required to understand the pattern of survival and the factors related to mortality in the Indian population.
1.9: Objectives of the Study

The objectives of the present study are:

- To determine the survival probability after initiating ART among HIV/AIDS-infected patients.
- To estimate the relative survival and mean residual life of HIV/AIDS patients on ART.
- To study the changes in estimated hazard rates in different subgroups of HIV/AIDS patients.
- To quantify the predictive performance of survival models for censored data.
- To compare and validate the predictive performance of different survival models.