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Full Length Research Paper

Estimation of HIV/AIDS Mortality in Hemophiliacs: A Decrement Table Approach

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The human immunodeficiency virus/ acquired immune deficiency syndrome (HIV/AIDS) epidemic represents the most serious public health problem in India. There is no denial of the enormity of the problem. The available surveillance data clearly indicates that HIV is prevalent in almost all parts of the country. Hence, knowledge of HIV incidence is important to formulate sensible strategies aimed at controlling the HIV/AIDS epidemic. The objective of this paper is to estimate the probability of dying in the stage of HIV (Grover and Das, 2005) in a year without passing to the state of AIDS (HIV mortality rate). Secondly, a double decrement life table approach (Biswas et al., 2006) has been followed for a cohort of hemophiliacs who were at risk of infection with the AIDS virus. This device consists essentially of two decrements: HIV positive hemophiliacs either depart from the AIDS-free group by eventually developing AIDS or by dying from other causes; those who eventually develop AIDS either remain alive with it until they die from it or die from other causes. The distribution of incubation period of AIDS is based on a two-stage parametric regression model (Brookmeyer and Goedert, 1989), proposed for the analysis of cohort of hemophiliacs.

Key words: HIV mortality rate, incubation period, two-stage parametric regression model, double decrement life table, sero-positivity.

INTRODUCTION

The human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS), is the leading infectious cause of adult deaths in the world. Given the scale of the epidemic, HIV/AIDS is now considered not only a health problem, but also a developmental and security threat. Even if a cure is found tomorrow, the toll of death and suffering by 2011 will far exceed any other recorded human catastrophe, any other previous epidemic, natural disaster, war, or incident of genocidal violence. The first case was reported among homosexual men in the USA in 1981 (Avert: http://www.avert.org). It has reached pandemic proportions, as no country in the world is free from HIV/AIDS. It ranks as one of the most destructive microbial scourges in human history and poses a formidable challenge to the biomedical research and public health communities of the world. AIDS and its related syndromes have changed virtually every aspect of medicine and society at large. AIDS is a condition in which the inbuilt immune mechanism of the human body breaks down completely. The process is gradual but ultimately suppresses the immunity of the individuals.

According to estimates from the UNAIDS (2009) Report on the global AIDS epidemic, around 31.3 million adults (aged 15 or above) and 2.1 million children (younger than 15) were living with HIV by the end of 2008. More than 25 million people have died of AIDS since 1981. At the end of 2008, women accounted for 50% (15.7 million) of all

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adults living with HIV worldwide. The epidemic had left behind 15 million AIDS orphans defined as those aged under 18 who have lost one or both parents to AIDS.

During 2008, some 2.7 million people became infected with HIV. Around half of the people who acquire HIV became infected before they turn 25 and typically die of the life-threatening illnesses called AIDS before their 35th birthday. Around 430,000 children aged 14 or younger became infected with HIV. Over 90% of newly infected children are babies born to women with HIV. The year also saw 2 million deaths from AIDS - a high global total, despite antiretroviral therapy, which reduced AIDS- related deaths among those who received it. Of the 2 million people who died of AIDS during 2008, more than one in seven was child. Every hour, around 31 children die as a result of AIDS. The number of deaths probably peaked around 2005, and has since declined only slightly (UNAIDS, 2009).

It is established (Dwyer, 1995) that HIV kills the most important or pivotal cells within the immune system, CD-4 lymphocytes, it compromises the immune system's ability to fight infection. The 1992 surveillance definition by Center for Disease Control (renamed as the Center for Disease Control and Prevention in 1993) for AIDS defined AIDS as including people with CD-4 counts of less than 200 cells per cubic millimetre (or a CD-4 person less than 14%) (Smith, 1996). No evidence exists to date to suggest that anybody infected with HIV has successfully eliminated the virus or produced an immunological response that would make one confident that AIDS will never develop, while 67% of patients infected with HIV will have developed AIDS within ten years of infection (Dwyer, 1995), those that stay well longer are currently being investigated to determine if they make a more effective immune response to HIV than those who are ill at the end of ten years of infection. This data suggest that not all HIV positive people are likely to develop AIDS. Preliminary evidence suggests that 5% of HIV positive individuals may never develop AIDS.

It follows that a sero-positive person is difficult to be identified (unless clinically declared as sero-positive) and thus most of the sero-positive individuals remain unidentified in the population. There are frequent deaths of sero-positive individuals reported as due to other visibly apparent causes. As HIV patients cannot be identified in general, therefore, the death of HIV is mistaken as being the death due to other diseases with related symptoms (like diarrhoea, tuberculosis, cardiac failure etc.). Hence, knowledge of HIV mortality rate can probably help in the adjustment of mortality rates due to other causes which are generally ascribed as apparently the causes for HIV mortality. Again, studies show that the hazard rate of an HIV individual at a given point of time remains the same irrespective of the fact that whether he is diagnosed as an AIDS patient or not. This is because of the complete lack of prognosis in the treatment of AIDS. Thus, neither the number of actual sero-positive persons nor their deaths over time are available for the estimation of HIV mortality rates. Hence, an approach of double decrement life table with two decremented forces of HIV, viz., mortality and conversion to AIDS, has been followed for estimating HIV mortality rates.

Hemophilia (heem-o-FILL-ee-ah) is a rare bleeding disorder in which blood does not clot normally. People having hemophilia, may bleed for a longer time than others after an injury. They also may bleed internally, especially in knees, ankles, and elbows. This bleeding can damage body organs or tissues and may be life threatening (http://www.nhlbi.nih.gov). The first cases of AIDS in persons with hemophilia were reported in 1981. In the early and mid-1980s, as many as two-thirds of all Americans with hemophilia became infected with HIV. The National Hemophilia Foundation reports that by June of 1992, 2,248 cases of AIDS had been confirmed among persons with hemophilia and an estimated 1,500 people with hemophilia had died from the disease. Ironically, use of the plasma concentrates that had ushered in hemophilia's "golden age" had become one of the most perilous risk factors for the disease (http://www.enotalone.com). Hemophilia-AIDS statistics from Germany reports that about 50% of the 6,000 German hemophiliacs are HIV-positive (Koerper, 1989).

A key epidemiologic descriptor of infectious disease is the time it takes from infection to the diagnosis of the disease or the incubation period (Sratwell, 1950). In the context of AIDS, we refer to the incubation period as the time elapsed from HIV seroconversion (that is detection of antibodies by serological tests) to the onset of a clinical condition defining the AIDS (Centers for Disease Control, 1987).

Estimating the progression from HIV infection to full-blown AIDS is of particular importance for patient counselling, for deciding if and when to administer treatment, for monitoring the success of therapy, and for health planning (Chiarotti, 1994). Estimates of progression to AIDS among haemophiliacs have recently been produced both in Italy and in other countries based on data from national or multinational cohort studies (Goedert et al., 1989; Darby, 1990). Chiarotti et al. (1992) has presented and discussed the effects of some parametric estimation procedures of seroconversion time on the analysis of progression to AIDS, using data for Italian haemophiliacs. Chiarotti et al. (1994) estimated the median incubation time between human immunodeficiency virus (HIV) infection and onset of acquired immunodeficiency syndrome (AIDS), using three parametric models and six estimates of seroconversion time for 732 HIV-positive haemophiliacs enrolled in the Italian registry of patients with congenital coagulation disorders.

Papadopulos-Eleopulos et al. (1995) carefully examined the association between the acquired immune deficiency syndrome (AIDS) and haemophilia and found that many patients with haemophilia have become HIV

infected and/or developed the AID clinical syndrome as a direct result of the transfusion of factor VIII preparations contaminated with this particular virus. But despite the many claims that HIV causes AIDS in hemophiliacs (Centers for Disease Control, 1986; Institute of Medicine, 1988; Weiss and Jaffe, 1990; Chorba, 1994) not much work has been done on the morbidity or mortality of HIV- positive hemophiliacs. The present study has therefore focused on the estimation of mortality of HIV patients and the progression from HIV infection to full-blown AIDS for a cohort of hemophilia patients.

In epidemiologic studies of an infectious disease, two important objectives are to identify risk factors for infection and risk factors for progression to clinical disease once infected. Brookmeyer et al. (1989) developed analytic methods for identifying risk factors both for infection and for onset of clinical disease once infected, when the time of infection can be determined within an interval. Here, a two-stage parametric regression model was proposed for jointly estimating the effects of covariates on risk of infection as well as risk of progression to clinical disease once infected, where the two stages refer to infection (Stage 1) followed by onset of clinical disease (Stage 2). There are two types of covariates: X_1, which modify risk of infection, and X_2, which modify risk of disease once infected; some covariates may be included in both X_1 and X_2. The risk of AIDS depends on two types of covariates. The first type (X_1) are covariates that modify risk of HIV infection. The hemophiliacs were at the risk of HIV infection because some lots of replacement clotting factor had been infected. Covariates that could affect risk of infection among haemophiliacs include the hemophilia treatment centre or geographic region because some regions may have received infected lots earlier than others, and the amount and type of clotting factor received. The second type of covariates, X_2, which are sometimes called cofactors, are those that modify risk of onset of clinical AIDS following infection. These covariates may include age, prior health status, and possibly dose of inoculum received. Some covariates may be common to both X_1 and X_2.

The objective of this paper is to estimate the probability of dying in the stage of HIV in a year without passing to the state of AIDS (that is, HIV mortality rate). Secondly, a double decrement life table has been constructed. This device consists essentially of two decrements: HIV positive hemophiliacs either depart from the AIDS-free group by eventually developing AIDS or by dying from other causes; those who eventually develop AIDS either remain alive with it until they die from it or die from other causes. The distribution of incubation period of AIDS is based on a two-stage parametric regression model proposed by Brookmeyer et al. (1989). An application has been presented for a cohort of hemophiliacs in USA who Putting $\lambda = 0.07696$, $T = 31$ (the incubation period of AIDS (Becker et al., 1991) is usually abnormally long even to the extent of 30 years or even more) and taking $i = (0,1,2, \quad ,30)$ in (2), we can obtain the HIV mortality rate denoted by $Q_i\ (i = 0,1,2,\ldots\ldots,30)$ between i to $(i+1)$ year of age from the date of infection of HIV, which are presented in Table 1 (Probability of dying in the stage of HIV by years).

were infected with the AIDS virus.

METHODOLOGY

Computation of probability of dying in HIV

The latest statistics of the global HIV and AIDS were published by UNAIDS in November 2009, and refer to the end of 2008. The newly infected population with HIV of the world is 2.7 million (UNAIDS, 2009) and the number of deaths due to HIV/AIDS is 2 million by the end of 2008. Therefore, the death rate due to HIV (Grover and Das, 2005) can be taken as

$$\text{Death rate} = \frac{\text{Total number of death cases due to HIV}}{\text{Total Population living with HIV}} = \frac{2,000,000}{27,000,000} = 0.07407$$

per person per year which roughly gives the mean hazard rate (λ) due to HIV as

$$\lambda = -\log\left(1 - \text{death rate}\right) = (-\log 0.92593) = 0.07696$$

Defining the random variable X as the age of death due to HIV counted from the date of infection with HIV, the density function of X is given by

$$f(x) = \frac{\lambda\ e^{-\lambda(T-x)}}{1-e^{-\lambda T}} \qquad (1)$$

for $0 \le x \le T$ and $\lambda > 0$ where $f(x)$ is a proper probability density. $f(x)$ is chosen as a truncated exponential distribution truncated at T (the upper limit of the time of death due to HIV) with the property of increasing probability of deaths with advancing x.

The proportion of deaths denoted by Q_i during i to (i+1) year due to HIV is given by

$$Q_i = \frac{e^{-\lambda T}}{1-e^{-\lambda T}} \left[e^{\lambda(i+1)} - e^{\lambda i} \right] \qquad (2)$$

Incubation period distribution from a cohort study of hemophiliacs

Brookmeyer et al. (1989) developed a two stage model for AIDS and applied it to a study of hemophilia-associated AIDS. This National Cancer Institute Multicenter Hemophilia Cohort Study consisted of a cohort of hemophiliacs who were active patients on January 1, 1978, at one of the three treatment centers (Hershey, New York, and Pittsburgh) in the United States. In the cohort, there

Table 1. Probability of dying in the stage of HIV by years.

Age interval from the date of infection of HIV (i to i+1)	Q_i
0-1	0.00811
1-2	0.00875
2-3	0.00946
3-4	0.01021
4-5	0.01103
5-6	0.01191
6-7	0.01287
7-8	0.01389
8-9	0.01501
910	0.01621
10-11	0.01750
11-12	0.01900
12-13	0.02042
13-14	0.02205
14-15	0.02381
15-16	0.02572
16-17	0.02777
17-18	0.03000
18-19	0.03240
19-20	0.03499
20-21	0.03778
21-22	0.04081
22-23	0.04408
23-24	0.04760
24-25	0.05141
25-26	0.05552
26-27	0.05997
27-28	0.06476
28-29	0.06994
29-30	0.07554
30-31	0.08158

were 458 hemophiliacs. Of these, only 296 were infected with HIV after January 1, 1978. No information on the date of infection was available for the remaining 162 hemophilia patients. The analysis produced an estimate of the incubation period distribution, $1 - S(t; X_2, \beta)$, defined as the cumulative probability of developing AIDS at or before t years from seroconversion. The estimated cumulative distribution of incubation period for hemophiliacs is given by:

$$1-S(t;X_2\beta)=1-\exp(-0.0021t^{2.516})$$

(t measured in years), and the incubation period distribution is obtained as shown in Table 2 (Incubation Period Distribution).

A double decrement life table of HIV hemophilia population

A double decrement life table (Figure 1.Double decrement table for the incidence of AIDS) has been prepared for a cohort of 296 hemophiliacs (Brookmeyer and Goedert, 1989) with the following two decrement states:

(1) Due to death in the HIV state without passing to the state of AIDS (State 1)
(2) Transition from HIV to the state of AIDS (State 2)

Computation of HIV Hemophilia Population

The life table starts with a cohort of $l_0 = 296$ seropositive hemophiliacs. Let Q_i be the probability of dying for an HIV hemophilia patient during i to $i+1$ years following the onset of seropositivity without passing to the state of AIDS and $P_i = 1 - Q_i$ be the complementary probability of survival. Similarly, p_i be the probability that an HIV hemophilia patient will pass to the state of AIDS during i to $i+1$ year. Then $q_i = 1 - p_i$

Table 2. Incubation period distribution.

Age interval from the date of infection of HIV (i to i+1)	Incubation period (p_i)	$q_i = (1-p_i)$
0-1	0.00210	0.99790
1-2	0.00984	0.99016
2-3	0.02083	0.97917
3-4	0.03363	0.96637
4-5	0.04708	0.95292
5-6	0.06003	0.93997
6-7	0.07135	0.92865
7-8	0.08011	0.91989
8-9	0.08558	0.91442
910	0.08737	0.91263
10-11	0.08552	0.91448
11-12	0.08035	0.91965
12-13	0.07258	0.92742
13-14	0.06304	0.93696
14-15	0.05266	0.94734
15-16	0.04231	0.95769
16-17	0.03270	0.96730
17-18	0.02428	0.97572
18-19	0.01733	0.98267
19-20	0.01188	0.98812
20-21	0.00782	0.99218
21-22	0.00493	0.99507
22-23	0.00299	0.99701
23-24	0.00173	0.99827
24-25	0.00096	0.99904
25-26	0.00051	0.99949
26-27	0.00026	0.99974
27-28	0.00013	0.99987
28-29	0.00006	0.99994
29-30	0.00002	0.99998
30-31	0.00001	0.99999

be the probability that an HIV hemophilia patient will not pass to the state of AIDS during i to $i+1$ year. Then, the HIV hemophilia population at age 'n' is given by:

$$l_n = l_0 \prod_{i=0}^{n-1} \{1 - Q_i\}.q_i \qquad \text{for } n \geq 1 \qquad (3)$$

Now from (3), we obtain the successive values of HIV hemophilia population $\{l_n\}$ by using HIV mortality rate (Q_i values) from Table 1(Probability of dying in the stage of HIV by years) and the probability of an HIV hemophilia patient not passing to the state of AIDS (q_i values) from Table 2 (Incubation Period Distribution). These are presented in Table 3 (HIV hemophilia population at the beginning of a year starting with a cohort of 296 newly infected hemophilia HIV patients).

Decrements in the cohort of HIV hemophilia patients

Using the life table, an alternative estimate of the probability of hemophilia HIV between i to (i+1) year can be obtained by the formula given as

$$Y_i = \left| \frac{l_i - l_{i+1}}{l_i} \right| \times \left| \frac{Q_i}{p_i + Q_i} \right| \qquad (4)$$

Again, we can see that Y_i and Q_i values are almost the same $\forall i$ (I=1,2,…).

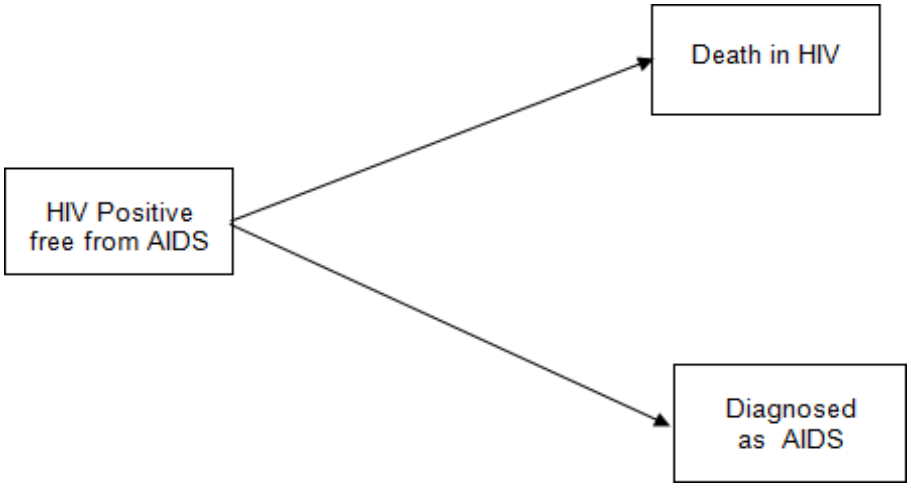

Figure 1. Double decrement table for the incidence of AIDS.

Table 3. HIV Hemophilia population at the beginning of a year starting with a cohort of 296 newly infected hemophilia HIV patients.

No. of year of age from the date of infection of HIV (i)	HIV Hemophilia population
0	296
1	293
2	288
3	279
4	267
5	251
6	234
7	214
8	194
9	175
10	157
11	141
12	127
13	116
14	106
15	98
16	91
17	86
18	81
19	77
20	74
21	70
22	67
23	64
24	61
25	58
26	54
27	51
28	48
29	45
30	41
31	38

We can also obtain:

(i) The number of hemophilia deaths in HIV during i to (i+1) years

$$= (l_i - l_{i+1}) \times \left(\frac{Q_i}{p_i + Q_i} \right) \quad (5)$$

(ii) The number of births of hemophilia AIDS from HIVs during i to (i+1) year

$$= (l_i - l_{i+1}) \times \left(1 - \frac{Q_i}{p_i + Q_i} \right)$$

$$= (l_i - l_{i+1}) \times \left(\frac{p_i}{p_i + Q_i} \right) \quad (6)$$

The resulting double decrement of hemophilia HIV patients with increasing age is shown in Table 4 (Decomposition of the decrement in the cohort of hemophilia HIV patients by their deaths and the births of AIDS).

RESULTS

Table 3 (HIV Hemophilia population at the beginning of a year starting with a cohort of 296 newly infected hemophilia HIV patients) gives the HIV hemophilia population at different ages.Table 4 (Decomposition of the decrement in the cohort of hemophilia HIV patients by their deaths and the births of AIDS) shows the resulting double decrements of hemophilia HIV patients with increasing age. The analysis shows that the decrement in hemophilia HIV population is increasing initially and is highest in the 7th and 8th intervals. After that a decreasing trend is observed as age increases and from the end of the 18th interval, the loss in the cohort of hemophilia HIVs remains relatively constant, fluctuating between 3 and 4. A similar constant trend is observed by examining the number of deaths in the cohort of hemophilia HIV patients. The highest proportion (100%) of the decrement in the cohort is due to State 1 and occurs after the completion of 21 years from the date of infection with HIV to the end. However, the births of hemophilia AIDS patients increase monotonically with the advancement of age in the beginning after infection with HIV. It reaches a peak at the 7th and 8th intervals and then decreases. Figure 2 (Composition of 296 HIV hemophiliacs to AIDS double decrement table) shows the changing proportions in States 1 and 2 for this example.

DISCUSSION

The natural history of human immunodeficiency virus (HIV) infection in persons with haemophilia is not well established and may differ from that in other acquired immunodeficiency syndrome (AIDS) risk groups (Goedert et al., 1986; Ekert, 1987; Turner, 1987). Differences in the route and frequency of exposure to HIV, differences in the prevalence of potential cofactors for the development of AIDS (e.g., coexistent infections), and differences in routine medical care could lead to a variation in disease progression and ultimate outcome, such as death. For some time, scientists had known that hemophiliacs were at high risk of hepatitis, a group of viral diseases that can be transmitted by contaminated blood and blood products. Though, not usually fatal, hepatitis is serious.

In 1982, food and drug administration (FDA) licensed a vaccine to protect against hepatitis B. But for AIDS, there is no cure and no vaccine. People living with hemophilia are at enormously high risk of HIV infection, because they require regular transfusions of clotting factors in order to maintain a normal blood clotting system. From the late 1970s to the mid-1980s, about half of all people with hemophilia became infected with HIV through blood products. Many of these people have developed AIDS. Currently, 10 to 15% of persons with hemophilia are infected with HIV. The AIDS epidemic has placed great health, economic, ethical and emotional burdens on affected families and the wider bleeding disorders community (http://www.aids.about.com).

Hence, this study is motivated by the most perilous risk factor for HIV infection and the disease AIDS of hemophilia patients. Also, the estimates of HIV deaths and AIDS births for this community, obtained in this chapter, are of great practical importance and can lead to great benefits to the society by helping the scientists to exploit new techniques and discoveries for reducing the risk of AIDS infection among hemophiliacs.

A methodology has been developed here to estimate HIV mortality rate and then a double decrement life table analysis with two decremental forces of HIV patients, viz., mortality due to HIV and conversion to AIDS has been constructed for a cohort of hemophilia patients. The incubation period distribution is based on the joint analysis of the effect of covariates on both risk of infection and risk of AIDS once infected (Brookmeyer and Goedert, 1989). Joint estimation is needed because the time interval in which seroconversion occurred was wide for a large number of hemophiliacs. Using the data from National Cancer Institute Multicenter Hemophilia Cohort study for hemophilia-associated AIDS, we obtained the birth of AIDS patient following the diagnosis of HIV infected hemophilia and the death of hemophilia patient following the infection of HIV in the United States.

In the present study, it is showed that the highest decrement (20 cases) in the cohort is observed during 7th to 8th year from the date of infection with HIV. The largest death of hemophilia HIV (4 cases) occurred in 26th and 30th intervals. The birth of hemophilia AIDS attained the peak (17 cases) in absolute terms at the 7th and 8th

Table 4. Decomposition of the decrement in the cohort of hemophilia HIV patients by their deaths and the births of AIDS.

Age interval from the date of infection of HIV (i to i+1)	Decrement in hemophilia HIV population	No. of deaths of hemophilia HIV	No. of births of hemophilia AIDS
0-1	3	2	1
1-2	5	2	3
2-3	9	3	6
3-4	12	3	9
4-5	16	3	13
5-6	17	3	14
6-7	20	3	17
7-8	20	3	17
8-9	19	3	16
9-10	18	3	15
10-11	16	3	13
11-12	14	3	11
12-13	11	2	9
13-14	10	3	7
14-15	8	2	6
15-16	7	3	4
16-17	5	2	3
17-18	5	3	2
18-19	4	3	1
19-20	3	2	1
20-21	4	3	1
21-22	3	3	0
22-23	3	3	0
23-24	3	3	0
24-25	3	3	0
25-26	4	4	0
26-27	3	3	0
27-28	3	3	0
28-29	3	3	0
29-30	4	4	0
30-31	3	3	0

intervals and then decreases. From Figure 2 (Composition of 296 HIV hemophiliacs to AIDS double decrement table) the trends of hemophilia HIV deaths and hemophilia AIDS births exhibit that the decrement of the cohort of hemophilia HIVs is more affected by State 2 in the beginning then decreases, but after reaching the22nd interval, hemophilia patients co infected with HIV are not converting to the stage of AIDS.

Thus, a careful examination reveals that the HIVpositive hemophiliacs were at higher risk of onset of clinical AIDS than the risks of death due to other causes in the state of HIV for the first 17 years from infection with HIV. With progression of time the loss in the population of HIV positive haemophilia was controlled because more severe cases of hemophilia could receive more frequent and larger doses of replacement clotting factors.

Furthermore, the progression to AIDS occurred in the beginning due to severe condition of hemophilia at the entry of the cohort. Again towards the end of the study period, HIV infected hemophiliacs died of a cause other than going to the stage of AIDS. Thus, our findings provide a novel mechanism for understanding the deaths of HIV hemophiliacs without going to the stage of full blown AIDS. It also provides important information on the births of AIDS patients from a cohort of HIV infected hemophiliacs, thus, trying to give a better picture to identify the hemophilia AIDS population. Many real-life data-analytic problems involve modelling complexphenomena. In this paper, we present quite simple model of an essentially complex phenomenon: the spread of HIV infections and the development of AIDS amongst hemophiliacs in USA. Our purpose in this work

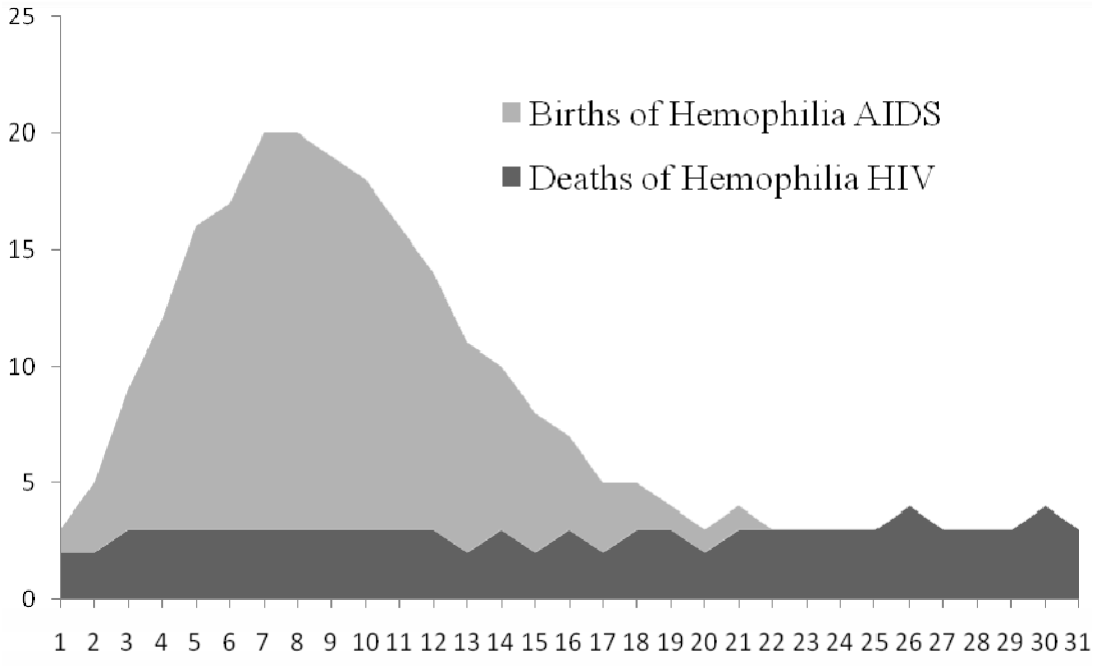

Figure 2. Composition of 296 HIV hemophiliacs to AIDS double decrement table.

is to present an illustration and discussion of this methodology, to demonstrate its power for the analysis of complex data. We also focus on the application of the concepts by the researchers for the analysis of data relating to other countries.

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