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Non-AIDS related mortality in the human immunodeficiency virus infection

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Summary

The author presents an example of how non-AIDS related mortality may influence the apparent progression from HIV infection to AIDS. In HIV infected subjects, non-AIDS mortality modifies the incidence counts of AIDS cases. These modifications appear particularly important in groups of subjects with high levels of non-AIDS related mortality. For example, in Italian intravenous drug users, hypothesising a constant, non-AIDS related mortality hazard of 0.01 $year^{-1}$, expected AIDS counts result asymptotically reduced by more than 10 per cent.

1. Introduction

Non-AIDS related mortality in subjects infected with HIV may reduce AIDS incidence counts. By consigning to other fates a fraction of the subjects destined do develop AIDS, non-AIDS mortality may influence the estimates of HIV infection curves based on AIDS counts; i.e. estimates obtained by backcalculation (Brookmeyer, Gail, 1986, 1988; Brookmeyer, Damiano, 1988; Taylor, 1989; Centers for Disease Control, 1990; Rosenberg, Gail, 1991).

Intravenous drug users (IVDUs), and elderly subjects, may present significant non-AIDS related mortality. Thus, analysing data from these subjects, it is important to recognize non-AIDS mortality as a possible cause of underestimation of the numbers of previously infected.

Key words: AIDS, backcalculation, human immunodeficiency virus, intravenous drug users

We present a model-based example about the influence of non-AIDS related mortality on HIV infection to AIDS progression. Also, we present a possible way to account for non-AIDS related mortality in advanced applications of backcalculation.

2. Materials and methods

In Italian IVDUs (and male homosexuals), Mariotto *et al.* (1992) have estimated the parameters of a compartmental model concerning the progression of the HIV infection, from the asymptomatic status to AIDS. They adopted a tri-compartmental model (Klein *et al.*, 1984), assuming the progression as an asymptomatic – AIDS related complex – AIDS, three-stage process (Figure 1, top diagram). The transition times 1) from seroconversion to AIDS related complex (ARC), and 2) from ARC to AIDS, were described by Weibull distributions, with respective hazard functions

$$\begin{aligned} h_1(t) &= \rho\lambda_1(\lambda_1 t)^{\rho-1} \ , \\ h_2(t) &= \rho\lambda_2(\lambda_2 t)^{\rho-1} \ . \end{aligned} \tag{1}$$

The estimated values of ρ, λ_1, and λ_2 were 1.194 (±0.100), 7.221 (±1.276) $\times 10^3$/ month, 3.691 (±0.600) $\times 10^2$/month, respectively. Expressed as a system of differential equations, this "base" model is

$$\begin{cases} y'_1(t) = -h_1(t)\, y_1(t) \\ y'_2(t) = \ h_1(t)\, y_1(t) - h_2(t)\, y_2(t) \\ y'_3(t) = \qquad\qquad h_2(t)\, y_2(t) \end{cases} , \tag{2}$$

$$y_1(0) = N_0;\ y_2(0) = 0;\ y_3(0) = 0 \ ,$$

where, according to a continuous approximation (Bailey, 1975), y_i represents asymptomatic subjects ($i = 1$), subjects with ARC ($i = 2$), and subjects with AIDS ($i = 3$). Also $y_1(0)$, $y_2(0)$, and $y_3(0)$ are the conditions at seroconversion time $t_0 = 0$.

In the above model, we may easily introduce an element representing "generic" mortality. For example, we may assume for non-AIDS related mortality a constant hazard, d, equal for asymptomatic subjects and subjects with ARC. If we indicate as 4 the compartment of infected subjects that died before developing AIDS, the model (see also Figure 1, middle diagram) will be

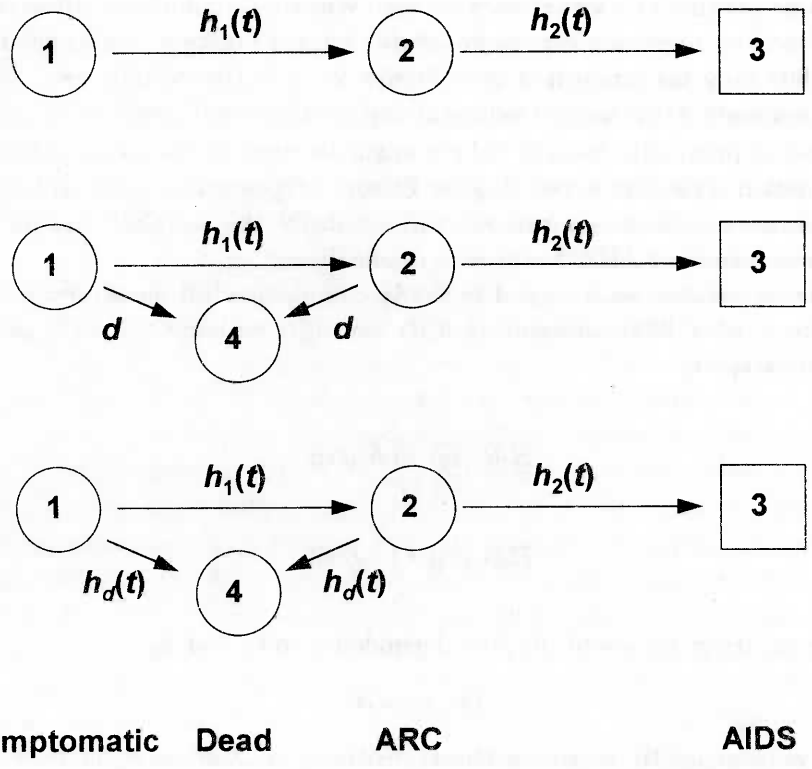

Figure 1. In a diagrammatic form, alternative models for the progression from the asymptomatic status to AIDS, with and without non-AIDS related mortality (see text for more explications).

$$\begin{cases} y'_1(t) = -\{h_1(t) + d\}\, y_1(t) \\ y'_2(t) = \quad h_1(t)\, y_1(t) \qquad -\{h_2(t) + d\}\, y_2(t) \\ y'_3(t) = \qquad\qquad\qquad\quad h_2(t)\, y_2(t) \\ y'_4(t) = \qquad d y_1(t) \qquad\quad + d y_2(t) \end{cases} \tag{3}$$

$$y_1(0) = N_0;\ y_2(0) = 0;\ y_3(0) = 0;\ y_4(0) = 0\ .$$

Since we consider AIDS as an end point, we may disregard generic mortality in subjects with AIDS. (We use however the surrogate time of AIDS diagnosis as the time of AIDS "development".)

Advanced backcalculation applications require an explicit expression of the hazard function for AIDS (Rosenberg *et al.*, 1992). Many incubation models (implicitly bi-compartmental) presented in the literature (Rosenberg *et al.*, 1992),

and the tri-compartmental model proposed by Mariotto *et al.* (1992), in which a unique parameter ρ was chosen for both Weibull distributions, allow the computation of an algebraic expression of this hazard function (see Appendix). Other models may be integrated (see Figure 2), and the results used to tabulate approximate AIDS hazard values at various time intervals from seroconversion. These approximate hazard values might be used in the place of algebraically computed ones (the curve "h_{+d}" in Figure 3 represents an example). However, algebraic expressions represent without doubt the simplest and most flexible way to introduce AIDS hazards in applications.

In particular, with regard to the tri-compartmental model proposed by Mariotto *et al.* (1992), integrating $h_1(t)$ and $h_2(t)$ with respect to a generic time interval $t_1 - t_2$

$$\begin{aligned} H_1(t_1, t_2) &= \int_{t_1}^{t_2} h_1(t)dt \\ H_2(t_1, t_2) &= \int_{t_1}^{t_2} h_2(t)dt \end{aligned} \quad , \tag{4}$$

and omitting, for simplicity, the dependence on t_1 and t_2,

$$H_i(t_1,t_2) \equiv H_i \quad , \tag{5}$$

we may explicitly calculate the transition probabilities p_{ij} of passing during $t_1 - t_2$ from the compartment i to the compartment j:

$$\begin{aligned} p_{11} &= \exp(-H_1) \\ p_{12} &= h_1\{\exp(-H_1) - \exp(-H_2)\}/(H_2 - H_1) \\ p_{13} &= 1 - p_{11} - p_{12} \\ p_{21} &= 0 \\ p_{22} &= \exp(-H_2) \\ p_{23} &= 1 - p_{22} \\ p_{31} &= 0;\ p_{32} = 0;\ p_{33} = 1 \end{aligned} \quad . \tag{6}$$

Thus, the hazard function for AIDS, $h(t)$, dependent on the time from seroconversion, may be obtained as the ratio of the probability density of developing AIDS at time t, $h_2(t)p_{12}(0,t)$, and the probability of not to have developed AIDS up to time t, $\{1 - p_{13}(0,t)\}$:

$$h(t) = h_2(t)p_{12}(0,t) \,/\{1 - p_{13}(0,t)\} \quad . \tag{7}$$

To introduce non-AIDS related mortality in practical applications of backcalculation, we must complete the above model in a convenient way, preserving, if

possible, the possibility of an explicit computation of the hazard function for AIDS. To be specific, we may obtain algebraically solvable transition probabilities, if we model transition times to non-AIDS death according to a Weibull distribution with the same parameter ρ of Weibull distributions describing asymptomatic-ARC and ARC-AIDS transition times (see Appendix). So, non-AIDS mortality may be introduced according to the hazard

$$h_d(t) = \rho\lambda_d\,(\lambda_d t)^{\rho-1} \quad . \tag{8}$$

The model (Figure 1, bottom diagram) will be

$$\begin{cases} y_1'(t) = -\{h_1(t) + h_d(t)\}\, y_1(t) \\ y_2'(t) = \quad h_1(t)\, y_1(t) \quad - \{h_2(t) + h_d(t)\}\, y_2(t) \\ y_3'(t) = \quad h_2(t)\, y_2(t) \\ y_4'(t) = \quad h_d(t) y_1(t) \quad + h_d(t)\, y_2(t) \end{cases} \tag{9}$$

$$y_1(0) = N_0;\ y_2(0) = 0;\ y_3(0) = 0;\ y_4(0) = 0 \quad .$$

Integrating $h_d(t)$ between t_1 and t_2,

$$H_d(t_1,t_2) = \int_{t_1}^{t_2} h_d(t)dt \quad , \tag{10}$$

and omitting its arguments,

$$H_d(t_1,t_2) \equiv H_d \quad , \tag{11}$$

the transition probabilities may explicitly expressed as

$$\begin{aligned} p_{11} &= \exp(-H_1 - H_d) \\ p_{12} &= H_1\{\exp(-H_1 - H_d) - \exp(-H_2 - H_d)\}\ /(H_2 - H_1) \\ p_{13} &= H_1H_2[\exp(-H_1 - H_d)\ /\{(H_1 - H_2)(H_1 + H_2)\} + \\ &\quad 1/\{(H_1 + H_d)(H_2 + H_d)\} + \exp(-H_2 - H_d)/\{(H_2 - H_1)(H_2 + H_d)\}] \\ p_{14} &= 1 - p_{11} - p_{12} - p_{13} \\ p_{21} &= 0 \\ p_{22} &= \exp(-H_2 - H_d) \\ p_{23} &= H_2\{1 - \exp(H_2 + H_d)\}\ /(H_2 + H_d) \\ p_{24} &= 1 - p_{21} - p_{22} - p_{23} \\ p_{31} &= 0;\ p_{32} = 0;\ p_{33} = 1;\ p_{34} = 0 \\ p_{41} &= 0;\ p_{42} = 0;\ p_{43} = 0;\ p_{44} = 1 \end{aligned} \tag{12}$$

Again, the unconditioned AIDS hazard may be explicitly calculated as

$$h(t) = h_2(t)p_{12}(0,t)\ /\{1 - p_{13}(0,t)\} \quad . \tag{13}$$

In Italy, non-AIDS related mortality in male and female IVDUs is 10 and 20 times greater than in the general population, respectively (Commissione Nazionale per la Lotta contro l'AIDS, 1992). To evaluate the importance of generic mortality on AIDS incidence data recorded in IVDUs, we hypothesized the presence of a constant, competitive non-AIDS-related mortality hazard (rate), assumed to be 0.01 $year^{-1}$. Then, we solved the systems of differential equations presented above (Fox, Mayers, 1987). Besides the model with a constant non-AIDS related mortality hazard, a model in which hazard was obtained according to a Weibull distribution was considered (the constant hazard refers to an exponential distribution of death times). In this Weibull-derived hazard function, the parameter λ_d was chosen so as to minimize the differences with respect to the constant hazard model. This was accomplished by minimizing the squared differences between the values of the Weibull distribution and those of the exponential distribution involved in the constant hazard model, calculated over the first 15 years from seroconversion (Marquardt, 1963).

3. Results

Figure 2 presents, as a function of the time from seroconversion, the expected asymptomatic, ARC, AIDS and death cases obtained by numerically integrating the various systems of ordinary differential equations presented. In particular, it shows the "base" model, without non-AIDS related mortality (continuous line), and the models in which non-AIDS mortality was introduced according to an exponential distribution (constant hazard; dashed line) and to the Weibull, distribution (dotted line).

Note the effect of non-AIDS mortality on AIDS incubation (y_3/N_0). Asymptotically, over 10 per cent of the subjects destined to develop AIDS, die before developing it (11.3 per cent and 11.9 per cent in the case of the constant and Weibull-derived hazard, respectively). Results obtained introducing the Weibull-derived hazard were very similar to those obtained introducing the constant one.

Figure 3 shows the "base" AIDS hazard (main plot, continuous line "h") and its components, "h_1" and "h_2" in the upper inset. Also, this figure presents non-AIDS related mortality hazards, the constant one (lower inset, dashed line "d") and that Weibull-derived (lower inset, dotted line "h_d"), as well as the effect of their introduction on the hazard for AIDS (main plot, dashed line "h_{+d}" and dotted line "h_{+h_d}", respectively).

We applied the above, "base" model, as well as the model with non-AIDS related mortality (Weibull-derived), to backcalculate the HIV infection curve of IVDUs in the Italian region Lombardia, adjusting AIDS data for reporting delay, and including treatment effects and changes in surveillance definition (Rosen-

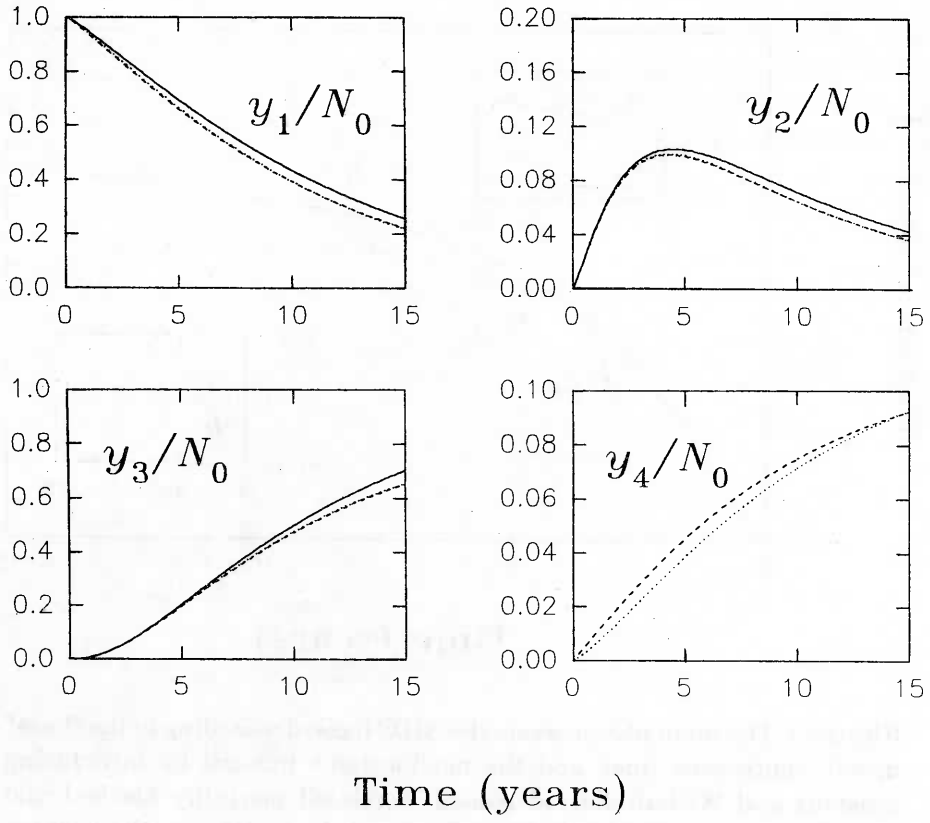

Figure 2. As a function of the time from seroconversion, the expected asymptomatic subjects (y_1), subjects with ARC (y_2) and AIDS (y_3), and non-AIDS related deaths (y_4), normalised with respect to the number of subjects initially seroconverted (N_0). Data have been obtained by numerically integrating the ("base") model without non-AIDS related mortality (continuous line), and the model with a constant non-AIDS related mortality hazard (dashed line) or with a Weibull-derived one (dotted line).

berg, Gail, 1991; Rosenberg *et al.*, 1992). HIV infection curves estimated according to both models peak during 1986. The minimum size estimate of the numbers of previously infected subjects, up to 31 December 1992, was 11,929 subjects without considering non-AIDS related mortality, and 12,428 by considering non-AIDS related mortality, a difference of more than four per cent.

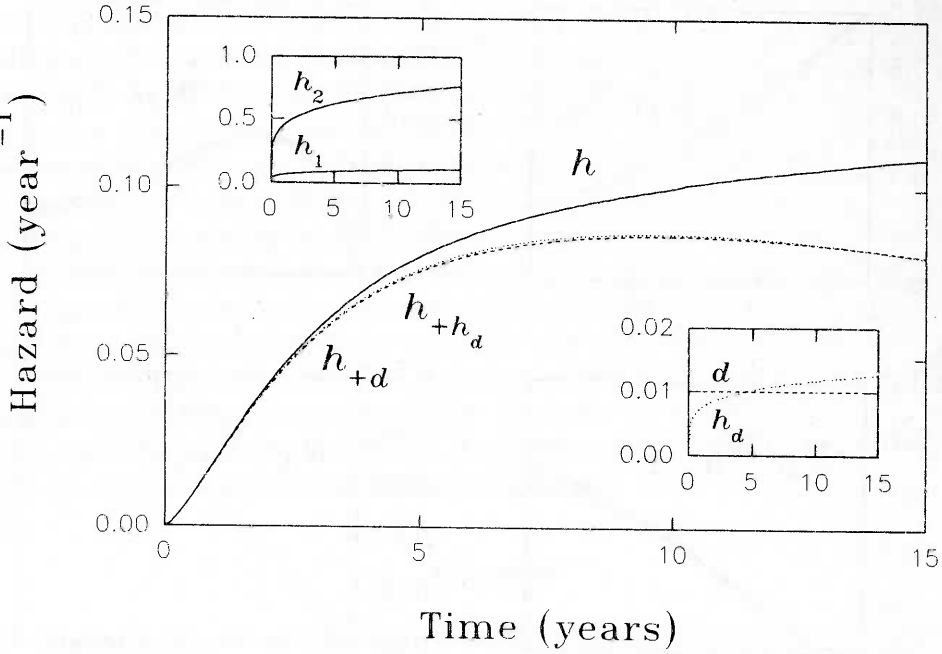

Figure 3. The main plot presents the AIDS hazard according to the "base" model (continuous line), and the modifications induced by introducing constant and Weibull-derived non-AIDS related mortality (dashed and dotted lines, respectively). In the upper inset, h_1 and h_2 are the hazards to move from the asymptomatic status to ARC, and from ARC to AIDS, respectively. The lower inset presents the non-AIDS related mortality hazards, the constant one (dashed line) and the Weibull-derived one (dotted line).

4. Discussion

Non-AIDS related mortality has to be recognized as a possible, important element contributing to the underestimation of HIV infection. This is even more important in countries as Italy in which prevailing cases are IVDUs, and non-AIDS related mortality in IVDUs appears particularly high. Also, estimations of HIV infection in elderly subjects appear as another case in which to compensate for non-AIDS related mortality may be very important.

We have to choose with care theoretical models of AIDS incubation to be used as parts of practical techniques as backcalculation. In particular, practical models

have to provide algebraic expressions for the hazard function. In the two families of models presented in Appendix, transition probabilities may be derived from matrix exponential functions. One family is that of models in which all hazards are constant with respect to the time from seroconversion. The other, is the interesting family of models in which all hazards are derived from Weibull distributions with the same parameter ρ.

Frequently, model choices involve compromises, and assumptions connected with the limits of the chosen models have to be analysed in depth to be accepted. An important limit of the models presented in this paper may be the dependence of the non-AIDS related mortality from the time of seroconversion. For example, we propose a Weibull-derived, non-AIDS related mortality hazard as an approximation of a constant one. Practical results were similar. However, according to the Weibull-derived model, at, or shortly afterward the seroconversion, an individual is subject to no, or to a very low risk of death with respect to a pre-existing, generic mortality. This appears as a very unnatural assumption. However, immediately after the seroconversion, the risk of AIDS is also relatively low, and few cases are missed in relation with this "inappropriate" assumption. Also, both models appear as rough, first approximations of the reality. Thus, it is probably not worthwhile to worry about the choice of one or the other model, if a practical utilization is in discussion.

Thus, modelling the progression from HIV infection to AIDS as a multi-step process may make easier to integrate defined patterns of non-AIDS related mortality. Multicompartmental models, being more flexible than simpler ones, are able to describe AIDS incubation in presence of important exogenous influences. Finally, the important practical implications of backcalculation results justify a moderate increase in model complexity.

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Appendix

A system of ordinary differential equations, as those described in the text, may be written as a "vector equation" $Y'(t) = W(t)Y(t)$, with initial conditions $Y(t_0) = Y_0$.

Defining

$$A(t) = \int_{t_0}^{t} W(t)dt,$$

we may obtain the solution of the system above as $Y(t) = e^{A(t)}Y_0$, provided that $W(t)$ and $A(t)$ are commutative, or $W(t)A(t) = A(t)W(t)$. Defined $E(t) = e^{A(t)}$, an equivalent assumption is that $E'(t) = A'(t)E(t)$. In particular, this will be true if $W(t)$ is a constant matrix W, i.e. the hazards introduced in the models derive from exponential distributions.

When $W(t)$ is composed by Weibull-derived hazards with the same parameter ρ, $w_{ij}(t) = \sum_u k_{iju}h_u(t) = \sum_u k_{iju}\rho\lambda_u(\lambda_u t)^{\rho-1}$, where k_{iju} are the appropriate constants for the u-th term in the ij-th element. Thus, $A(t)$ is composed of elements

$$a_{ij}(t) = \int \sum_u k_{iju}h_u(t) = \int \sum_u k_{iju}\rho\lambda_u(\lambda_u t)^{\rho-1} = t^\rho \sum_u k_{iju}\lambda^\rho = t^\rho b_{ij},$$

where b_{ij} are constants, and $E(t) = e^{A(t)} = e^{t^\rho B}$.

Applying the definition of a matrix exponential,

$$E(t) = \sum_{k=0}^{\infty} \frac{(t^{\rho}B)^k}{k!} = \sum_{k=0}^{\infty} \frac{t^{\rho k}B^k}{k!} = \left[\sum_{k=0}^{\infty} \frac{t^{\rho k}}{k!} b_{ij}^{(k)}\right] ,$$

and

$$E'(t) = \left[\sum_{k=0}^{\infty} \frac{t^{\rho k}}{k!} b_{ij}^{(k)}\right]' = \left[\sum_{k=1}^{\infty} \frac{\rho k t^{\rho k-1}}{k!} b_{ij}^{(k)}\right] = \left[\sum_{k=1}^{\infty} \frac{\rho k t^{\rho-1+\rho(k-1)}}{k!} b_{ij}^{(k)}\right] =$$

$$= \rho t^{\rho-1} \left[\sum_{k=1}^{\infty} \frac{k t^{\rho(k-1)}}{k!} b_{ij}^{(k)}\right] = \rho t^{\rho-1} \left[\sum_{k=0}^{\infty} \frac{t^{\rho k}}{k!} b_{ij}^{(k+1)}\right] = \rho t^{\rho-1} \sum_{k=0}^{\infty} \frac{t^{\rho k}B^{k+1}}{k!} =$$

$$= \rho t^{\rho-1} \left(\sum_{k=0}^{\infty} \frac{t^{\rho k}B^k}{k!}\right)B = \rho t^{\rho-1} B\left(\sum_{k=0}^{\infty} \frac{t^{\rho k}B^k}{k!}\right) .$$

Since $A'(t) = (t^{\rho}B)' = \rho t^{\rho-1}B$, then $E'(t) = A'(t)E(t)$. So, when $W(t)$ is composed by Weibull-derived hazards with the same parameter ρ, $W(t)$ and $A(t)$ are commutative: we may solve the system as $Y(t) = e^{A(t)}Y_0$, and search for an eventual algebraic expression of this solution. Admitting different initial conditions to obtain this solution is equivalent to obtain the transition probabilities to be used in the AIDS hazard computation.

Śmiertelność nie związana z AIDS przy zakażeniu HIV

Streszczenie

W pracy pokazano w jaki sposób śmiertelność nie związana z AIDS może wpływać na ocenę postępu od zakażenia HIV do AIDS modyfikując liczebność przypadków AIDS. Modyfikacja ta wydaje się szczególnie istotna dla grup pacjentów o wysokim poziomie śmiertelności. Na przykład we Włoszech, w grupie osób stosujących narkotyki dożylnie, przy założeniu stałego ryzyka śmiertelności nie związanej z AIDS równego 0.01 rok^{-1}, oczekiwane liczebności przypadków AIDS zostały zredukowane asymptotycznie o ponad 10 procent.

Słowa kluczowe: AIDS, obliczenia wsteczne, dożylne stosowanie narkotyków