A modeled time-varying density function for the incubation period of AIDS

Marc Artzrouni
Department of Mathematical Sciences, Loyola University, New Orleans, LA 70118, USA

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Abstract. Building on the Weibull distribution, we develop a modeled time-varying density function of the incubation time between exposure to HIV infection and full-blown AIDS. This approach leads to a series of cohort-specific density functions that take into account the increasing impact of new therapies such as zidovudine (AZT). The resulting modeled density functions are studied in detail, particularly with regard to their modes and medians. The mode is sensitive to changes in the period incubation time distribution, with even a possibility of a bimodal distribution for certain combinations of the parameters that determine the rate at which the period median incubation time changes. An important substantive result is that when a period median incubation period slowly increases to some leveling off value, say \( m(x_c) \), then it is surprisingly early on that cohorts of infected individuals have a median incubation period very close to that ultimate value \( m(x_c) \).

Key words: Human immunodeficiency virus (HIV) – Acquired immunodeficiency syndrome (AIDS) – Incubation period – Weibull distribution

1 Introduction

Efforts at the mathematical modeling of the various aspects of the HIV/AIDS epidemic continue at an accelerated pace (Castillo-Chavez 1990). In particular, the distribution of incubation times between infection with HIV and full-blown AIDS has received a lot of attention in the last few years (see Lui et al. 1986, Lui et al. 1988, Medley et al. 1987, Bachetti and Moss 1990, De Gruttola and Lange 1989, Blythe and Anderson 1988, among others). In the early phase of the epidemic it was quite natural to consider that the distribution of incubation times was characterized by one density function that did not change through time. (Different functions or parameter values were considered for different modes of transmission, however.) It is difficult enough to estimate parameters when conditions do not change through time, and making such an assumption was quite reasonable at the beginning of the epidemic.

However, one question that is beginning to gain attention is that of a possible lengthening in the incubation period of AIDS. This is occurring as a
result of new treatments that delay the progression from HIV infection to AIDS. The example of zidovudine (AZT) is the first one that comes to mind. Epidemiologists have indeed begun to speculate on the impact that AZT may have on the AIDS epidemic in settings where AZT is becoming widely available (Anderson et al. 1991, Gail et al. 1990, Brookmeyer and Liao 1990, Brookmeyer 1991, Solomon and Wilson 1990). Some have already noted peculiarities in the incubation distribution for cohorts of infected individuals using AZT (Schechter et al. 1989). Others have investigated the impact of a variable incubation period in the context of a dynamic model of HIV transmission (Thieme and Castillo-Chavez 1991).

In view of these developments, it seems appropriate to contemplate the question of a time-varying model of incubation times distribution. Concretely, this means that a density function \( p(x) \) of incubation times will have to be indexed, in some way, by time.

In the simple case of a time-invariant incubation period, the quantity \( p(x) \, dx \) is the probability that an individual will develop AIDS when his infective age is in the interval \([x, x + dx]\). (The infective age is the length of time an individual has been infected with HIV.) In order to address the question of a time-varying density function \( p(x) \) we will make use of the hazard rate \( \mu(x) \) of developing AIDS; \( \mu(x) \, dx \) is the conditional probability of converting from HIV infection to AIDS at infective age \([x, x + dx]\) for a person who is known not to have converted before infective age \( x \). The hazard rate is

\[
\mu(x) = \frac{p(x)}{1 - \int_0^x \rho(s) \, ds}.
\]  

A number of models for \( p(x) \) have been proposed (the Weibull, log-normal, normal distributions, etc.). We will focus here on the Weibull, partly because the hazard rate \( \mu(x) \) for the Weibull density has a simple expression. The Weibull density \( p(x) \), parameterized by the median incubation period \( m \) and the shape parameter \( \beta \) is

\[
p(x) = \beta (\ln 2) m^{-\beta} x^{\beta - 1} \exp[-(\ln 2)(x/m)^\beta]
\]  

and the corresponding hazard rate \( \mu(x) \) is

\[
\mu(x) = \beta (\ln 2) m^{-\beta} x^{\beta - 1}.
\]  

For future reference we note that a Weibull density \( p(x) \) with median \( m \) and shape parameter \( \beta \) has a mode equal to \( m[(\beta - 1)/((\beta \ln(2))]^{1/\beta} \). We call this latter quantity \( H(m, \beta) \).

We now assume that the risk of developing AIDS changes with time; \( p(x) \) then becomes a function of the infective age \( x \) and of the time \( \tau \) at which an individual became infected with HIV. Equivalently, \( p(x) \) is a function of \( x \) and of the time \( t \) at which the conversion from HIV to AIDS occurs. Indeed, for a fixed infective age \( x \), it is equivalent to index time with respect to the time of infection \( \tau \) or with respect to the time of conversion \( t \) since \( t = \tau + x \); given \( x \) we know \( \tau \) as soon as we know \( t \) and vice-versa. In the sequel, the Greek \( \tau \) will always refer to a time of infection whereas \( t \) will refer to the time of conversion to AIDS.

We now let \( p_c(x, \tau) \) be the density function of the incubation period for a cohort of individuals infected at time \( \tau \). (The subscript "c" is to emphasize that \( p_c(x, \tau) \) refers to a cohort of individuals who became infected at the same time \( \tau \).)