

Concepts of Time in Clinical Research

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The study of events in time is fundamental to biomedical research and public health surveillance. Clinicians have an intuitive appreciation for the relevance of time to health and disease, and patients invariably ask questions relating to time for which clinicians need answers. An appreciation of the picture of health and disease over time is equally fundamental to public health. Research designs that incorporate time have long been in use; the cohort study, which involves follow-up of persons over time, is the fundamental design. Analysis of longitudinal data, generated by cohort studies and related approaches, has been enhanced by new statistical methods that are appropriate to data collected over time from repeated observations. In the next millennium, new and increasingly complex questions will undoubtedly require investigation. The research designs and analytic methods used to address clinical questions in time will continue to evolve and will provide better, sharper answers.

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Clinicians have an intuitive appreciation for the relevance of time to health and disease. Each day brings snapshots of individual patients: their current health and a profile of the factors that predict risk for disease. As these snapshots accumulate, the clinician is witness to the development of disease, the unfolding of natural history, and the consequences of interventions for prognosis. Patients invariably ask questions relating to time for which clinicians need answers: “How long until I am better?” “How long will I need this therapy?” “How long will I live?” Patients also want to know about their future risks for disease and whether these risks can be decreased. The time frames of reference for many questions may differ for patients and clinicians because patients seek answers to their immediate questions and clinicians maintain a long-term perspective.

Time inherently flows through the natural history of disease, from its onset to its end. Clinicians may be less aware of the temporally dynamic processes that originally lead to the development of disease. Many risk factors for disease are fluid in time: age, diet, smoking, work experiences, and the quality of the environment, for example. We now know that many of the devastating chronic diseases that are the leading causes of death in developed countries are the end stages of lengthy processes of change and deterioration. For example, chronic obstructive pulmonary disease usually arises after decades of

lung function loss caused by cigarette smoking (1), the most common types of cancer are thought to occur after multiple genetic changes in a cell lead to unrestrained replication (2), and the origins of coronary artery disease can be traced back to childhood (3). Infectious diseases, although often acute in onset, may have lengthy natural histories, and lines between “acute” and “chronic” diseases have blurred as we have learned that some chronic diseases may be caused by infection (4). An understanding of these processes is crucial to reducing morbidity and mortality through primary prevention (by minimizing or eliminating risk factors) and secondary prevention (by screening).

An appreciation of the picture of health and disease over time is equally fundamental to public health. For centuries, government organizations have recorded births and deaths and have monitored the size of the population. Together, these data constitute the numerators and denominators for fundamental measures of population health: the total mortality rate and the infant mortality rate. We now also track the incidence of some diseases—that is, the occurrence of new cases—and calculate the incidence rate. For example, in the United States, we have maintained a national registry of incident cancer cases (the Surveillance, Epidemiology, and End Results [SEER] program of the National Cancer Institute) (5) since 1973, and soon almost all cases of cancer will be registered nationally. The SEER program alerted us to the increased incidence of non-Hodgkin lymphoma and documented the dramatic improvement in survival rates for men with testicular cancer. We systematically monitor rates of death and disease as part of our national surveillance strategy. Surveillance may show benefits of prevention (for example, decreasing incidence of lung cancer and decreasing mortality rates in U.S. men [5]) or problems that need further evaluation as a basis for intervention (for example, the recent unexplained increase in asthma prevalence [6]).

The temporal dimensions of biomedical research should reflect the multiple axes of time that are relevant to a particular disease (**Figure 1**). For the clinician, the age of the patient is always relevant because it determines the underlying risk for disease and death. Survival time is another key variable: When measured from the time of diagnosis it is the basic standard of prognosis, and when measured from the start of treatment it tracks the consequences of therapy. Calendar time may also be of

interest as diagnostic and therapeutic methods become more effective over time. For causes of disease, the time since exposure began, the age at which exposure began, and the duration of exposure may all be relevant. Exposure may occur continuously, stop and start, or occur instantaneously. From the population perspective, changes in rates of disease over time are central to surveillance, and the characteristics of the population itself may change over time as well.

This paper provides both a perspective on the central role of time in clinical and population research and an introduction to the statistical methods used to explore and optimally use data that are collected over time. It describes key measures of disease occurrence in time and the observational study designs (the cohort study and its variants) that explicitly incorporate the passage of time into the follow-up of participants. Clinical trials—experimental studies that include randomization and a comparison group—also involve follow-up of participants in time. Although the core longitudinal study designs for clinical and epidemiologic research are not new, biostatistical methods that fully allow for the effects of time have been developed and applied only in recent decades. Use of these methods is illustrated by examples of their application to the many clinical and public health questions that have been raised about HIV infection and AIDS.

Tracking the Occurrence of Disease

The fundamental measures of disease occurrence are indicators of the rate of disease onset at a particular point in time. The incidence rate describes the risk for transition from being free of a particular disease to having it, although a clear transition point may not be identifiable for some

chronic diseases. The mortality rate is a similar measure of the risk for death (7). The prevalence rate is the proportion of a population that has a disease at a particular time. When assessed repeatedly, these measures take on the added dimension of calendar time.

As disease rates are tracked over time, the population is dynamic in its structure, with younger persons aging and some risk factors, such as smoking, increasing and decreasing over time. When interpreting temporal trends in disease rates, researchers may see variations that reflect age, period, and cohort effects. Wade Hampton Frost, the first professor of epidemiology at the Johns Hopkins School of Hygiene and Public Health (and, for that matter, in the United States), has been credited with developing a cohort analysis of data on vital statistics to separate these effects. This age- and birth-cohort analysis tracked specific patterns of tuberculosis mortality rates in Massachusetts from 1880 to 1930 (Figure 2) (8). His graphical presentation successfully disentangled age and cohort effects. In a previous analysis of cross-sectional mortality rates, Frost had incorrectly assumed that tuberculosis incidence involved a “postponement of maximum risk” to older ages; in this analysis, however, he found that the mortality rates from tuberculosis in later life reflected those in early life. Nine years earlier, in 1930, Andvord (9) had published a similar but overlooked analysis of tuberculosis mortality rates. Today, we use specific statistical methods to more formally separate the effects of age, period, and cohort (10).

The same types of data and analyses of rates remain in use today. Recent reports, for example, have addressed infectious disease mortality rates throughout the century (11), trends in liver cancer mortality rates (12), and incidence of cardiogenic shock (13). The recent perplexing and alarming in-

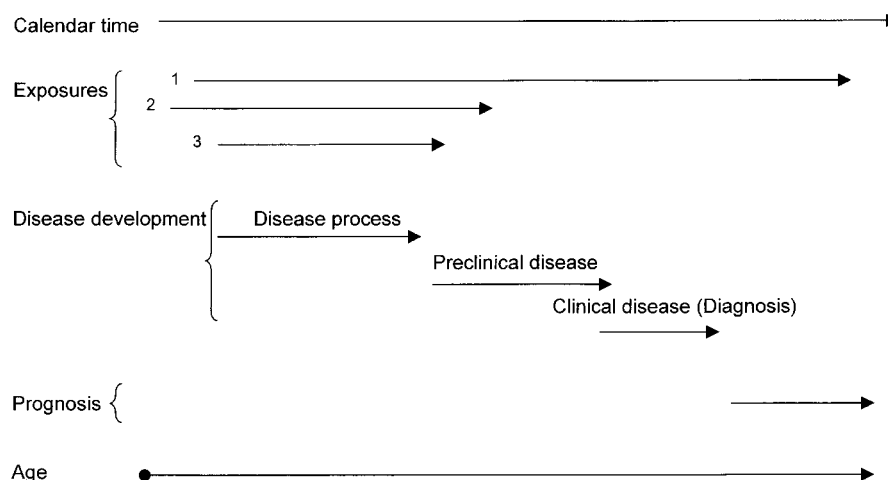


Figure 1. Hypothetical etiologic exposure and phases of disease over time and age.

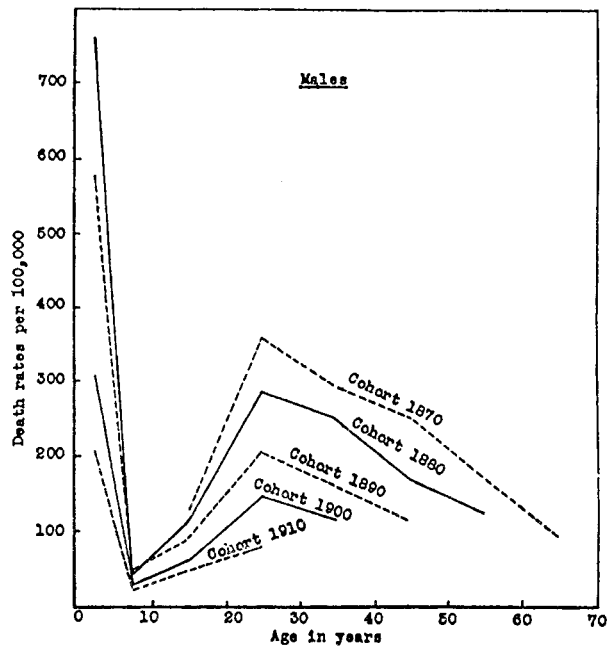


Figure 2. Age- and birth-cohort analysis of specific patterns of tuberculosis mortality rates in men in Massachusetts, 1880 to 1930 (8). Reprinted with permission from the *American Journal of Epidemiology*.

crease in asthma incidence was identified by tracking time trends of mortality and prevalence (6). Data on incidence over time, however, were notably lacking because it is difficult to count incident cases of asthma.

Describing the Prognosis of Disease

Prognosis—the outcome of disease over time—is determined by following persons with a disease and monitoring recovery or death. The follow-up study design, which is called the cohort study, has its origins in the need for information on length of life and the course of disease. The earliest life tables, developed in the 17th century by Graunt and Halley from cross-sectional mortality counts, were intended to project deaths with aging, inherently acknowledging the passage of time. A life table organizes information on survival of participants on the time axis of interest, which is often age, time since diagnosis, or time since treatment. Farr, a British statistician and public health official, used the life table as an indicator of population health (14). Actuaries also used life tables to project the risks incurred by insured persons, and a century ago the experience of insurance policyholders was pooled across many companies to provide a view of mortality rates associated with various diseases (15, 16). At about the same time, the cohort design was used in several studies to track mortality rates of persons with tuberculosis who were discharged from sanatoriums after receiving therapy. In one of the earliest

of these studies, Brown and Pope (17) traced more than 1000 persons who were discharged from the Adirondack Cottage Sanitarium in Saranac Lake, New York (which would later become the famed Trudeau Sanatorium). They compared patient survival rates in their life table with those in a life table that Farr had prepared using data from the entire British population. Sartwell (18) noted that this study represents the first application of the life-table method in a clinical follow-up study.

In 1938, Pearl (19) published a study in *Science* that described the survival rates of 6813 men in east Baltimore, Maryland. The survival curves for persons who did not smoke, for those who smoked moderately, and for those who smoked heavily offered one of the first indicators of the now well-documented propensity for premature death in persons who smoke (Figure 3). To quote Pearl, “In this sizable material the smoking of tobacco was statistically associated with an impairment of life duration, and the amount or degree of this impairment increased as the habitual amount of smoking increased” (19).

Although the life table describes prognosis, clinicians frequently need to answer questions about the determinants of prognosis and the effect of therapy. In 1958, Kaplan and Meier (20) offered a simple

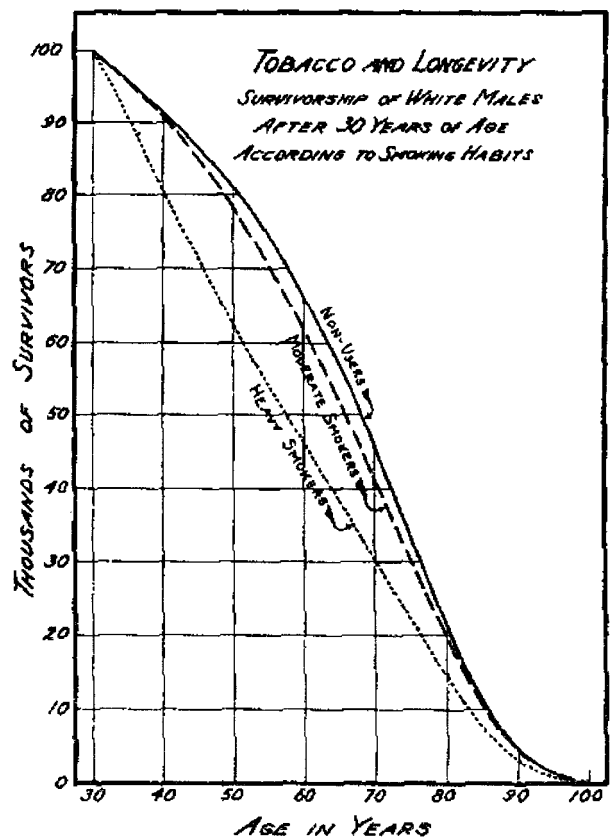


Figure 3. Survivorship lines of life tables for white men in three categories of tobacco use (19). Reprinted with permission from *Science*.

method for estimating survival curves; Kaplan–Meier curves are a pictorial representation of the survival experience of a patient group. The log-rank test offers an equally simple method for statistical testing of differences in survival between groups (21). Questions about prognosis are usually multivariate, however, because many determinants are involved; some examples are age, sex, number of disease conditions, and type of therapy. In 1972, Cox (22) offered a solution to this problem in his seminal paper on regression methods for time-to-event data, thereby providing the conceptual basis for the proportional hazards regression model. The proportional hazards model estimates the effect of a specific factor on survival while controlling for the potential confounding effects of other factors. One of the strengths of this model is that no assumption must be made about risk for disease in the reference group because the effect of treatment is assessed relative to the reference group. Today, proportional hazards models can be easily implemented with computer software, and they are widely used throughout the clinical literature.

One example, the International Cooperative Pulmonary Embolism Registry, was established to characterize mortality rates after pulmonary embolism (23). Data from 2454 patients with acute pulmonary embolism were analyzed by using the Kaplan–Meier method and showed a mortality rate of 17.4% 3 months after diagnosis. Risk factors for death were examined with proportional hazards models; independent effects of age, clinical diagnoses, and pattern of clinical presentation were found.

Markers of prognosis, which reflect intermediate disease stages that occur before the final outcome, have increasingly become a focus of investigation. Such “surrogates” can be biomarkers that are measured in biological materials; for example, the level or rate of change in the number of CD4 cells in the blood might be used as a marker of prognosis in patients with AIDS. Contemporary studies of prognosis often include collection of specimens for determination of biomarker values, and statistical methods have been proposed for analysis of data on biomarkers (24).

Finding Risk Factors for Disease

The notion of a risk factor for disease inherently incorporates time. The presence of the risk factor informs us about the future risk for disease, and the relative risk estimates the predictive strength of the factor. Risk factors are identified by using epidemiologic study designs: the cohort study and the case–control study. The cohort study directly incorporates time. Participants are enrolled, their risk factors are

characterized, they are followed over time, and the events of interest are monitored. A cohort study can be done prospectively, stretching into the future, or retrospectively, drawing on past documented events. In a case–control study, risk factors are assessed in persons who have the disease of interest and in appropriate controls; these factors can be past exposures to risk factors (such as cigarette smoking) or fixed personal characteristics (such as genotype). The time element is not explicit, as in the cohort design, but implicit: Actions of the risk factors are assumed to be antecedents of disease. Case–control studies, like cohort studies, estimate the relative risk, but they do not directly measure the absolute rate of disease. Hybrid study designs—the nested case–control study and the case–cohort study—combine the two designs to increase efficiency (25).

The contemporary era of research on risk factors for disease dates to the mid-20th century. Landmark case–control and cohort studies that were initiated to identify the causes of increasing rates of heart disease and lung cancer provided strong evidence on smoking and other risk factors. In 1950, for example, the results of five case–control studies linking smoking to lung cancer were published (26, 27). A study by Wynder and Graham (28) was begun by Wynder while he was a medical student. In a recent commentary, Wynder (29) wrote that he quickly became convinced that smoking was a cause of lung cancer because almost all of the initially interviewed case-patients smoked. In the United Kingdom, Doll and Hill (30) completed an equally convincing case–control study of lung cancer. However, because of skepticism about the case–control design, they designed a prospective cohort study of British physicians that continues to this day (30, 31). The study’s design was straightforward: It involved follow-up for death in approximately 40 000 physicians who periodically completed questionnaires on their smoking habits. After only a few years of follow-up, the findings of the case–control studies were confirmed. With 40 years of follow-up now completed, the data show the ways in which risks with smoking vary on several time axes: increasing with longer duration of smoking, decreasing with continued cessation, and increasing over calendar time (32).

Other landmark cohort studies that were implemented in the late 1940s and early 1950s include the Framingham study, a study of Japanese atomic bomb survivors, and a U.S. Public Health Service study of Colorado Plateau uranium miners. Dawber (33) described the origins of the Framingham study, which was begun in a population sample to test multiple hypotheses about the cause of cardiovascular disease. Results from the study associated smoking, cholesterol level, and hypertension with risk for cardiovascular disease.

Table. Analytical Methods for Cohort Studies: Epidemiology of HIV Infection in Homosexual Men (Multicenter AIDS Cohort Study, 1984–1997)

Aim	Method	Study (Reference)
To determine prevalence of infection (seroprevalence)	Logistic regression	Chmiel et al. (43)
To determine incidence of infection (seroconversion)	Poisson regression	Kingsley et al. (44)
To determine immunosuppression (CD4 cell count)	Regression for continuous correlated data	Margolick et al. (47)
To determine incubation (seroconversion to AIDS)	Log-normal regression and juxta-analysis: incident plus prevalent subcohorts	Mellors et al. (48)
To determine markers and disease progression (viral load and CD4 cell count and progression to AIDS and death)	Cox regression and regression trees	Muñoz and Xu (45)
To determine time of survival from AIDS to death	Cox regression	Muñoz et al. (46, 53, 54)
To determine incidence of specific AIDS diagnosis by period	Poisson regression	Taylor et al. (55)
To determine risk factors for fast progression to AIDS	Conditional logistic regression	Fahey et al. (49)
To determine the effects of high-risk behavior	Regression for categorical correlated data	Enger et al. (51)
To determine the effectiveness of AIDS therapies	Cox regression with staggered entries	Mellors et al. (48)
To examine long-term survivors and determine the pathogenesis of HIV infection	Nested studies based on markers	Jacobson et al. (56)
		Muñoz et al. (57)
		Phair et al. (50)
		Gange et al. (58)
		Muñoz and Hoover (59)
		Detels et al. (52)
		Muñoz et al. (60)
		Gange et al. (61)

The study of atomic bomb survivors involved reconstruction of the radiation doses received from the blast and follow-up for death and cancer incidence (34). This study documented a quick increase in the incidence of acute leukemia, which peaked 7 years after the blast (in 1952) and then decreased. By 1960, solid tumors were occurring frequently among the survivors; the excessive occurrence was shown to be proportional to the radiation dose.

Unlike atomic bomb survivors, who received a single dose of radiation, underground uranium miners receive constant exposure to radon as they work. Consequently, their cumulative exposure varies over time, as does the rate of exposure. The Public Health Service study tracked radon exposure of the miners over time and found a strong but time-dependent association between radon exposure and risk for lung cancer (35, 36).

The cohort and case-control study designs remain the fundamental designs for identifying risk factors for disease. Clinical trials, however, may be used to test preventive strategies that have their origins in observational evidence. For example, the Nurses' Health Study, a prospective cohort study of approximately 100 000 U.S. nurses, has provided information about diet and other risk factors for cancer and cardiovascular disease (37, 38). The cohort design is also appropriate for characterizing disease outcomes and determinants of favorable and unfavorable outcomes. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT), for example, assessed determinants of prognosis after critical care; one unexpected outcome was increased risk for death among recipients of a right-heart catheter (39). Studies of outcomes among persons enrolled in managed care organizations are usually done with the cohort design.

Advances in biostatistical methods for analysis of longitudinal data have enhanced the informativeness of cohort studies (40–42). Longitudinal data are often “messy” and therefore pose substantial challenges to the analyst. Some factors (for example, smoking) may change during follow-up, and observations may be incomplete for some study participants. In addition, many clinical problems must be approached with multivariate data analysis so that the effects of one factor can be separated from those of other factors. Methods are now available to process the diverse outcome measures used in clinical research and to handle repeated observations with missing data, which occur frequently when study participants are seen at regular clinic visits but some visits are missed. These methods extend to analysis of disease incidence and include outcome events that occur more than once (such as infection) and continuous measures that may be observed repeatedly during a study (such as blood pressure).

An Example: The Multicenter AIDS Cohort Study

The Multicenter AIDS Cohort Study (MACS) was implemented in 1984 and 1985 as a prospective cohort study of 4954 homosexual men in four cities. Participants are examined and provide blood samples every 6 months, and seroconversion, onset of AIDS, and death have been closely tracked. Although MACS was initially established to characterize risk factors for and the natural history of AIDS, it has provided information on the effects of therapeutic interventions and reductions in high-risk behaviors. The **Table** lists key publications and the analytic methods that were applied as the follow-up

data grew and the methods evolved. One of the initial reports from MACS (43) addressed determinants of prevalent infection at the time of enrollment. This analysis was cross-sectional and did not explicitly incorporate time. As follow-up data accumulated, incidence of infection was documented, and a 1991 publication described predictors of incidence by using Poisson regression (44).

Subsequent reports from MACS have addressed the natural history of HIV infection and AIDS. The incubation period was characterized by combining information from prevalent and incident cases (45, 46). The CD4 cell count is a marker of immunodeficiency, and the rate at which the CD4 cell count decreases is a useful intermediate marker of disease progression. Using serially collected CD4 cell counts, the MACS investigators described rates at which counts decreased and predictors of more rapid decreases (47); viral load was eventually shown to be a key determinant of a decrease in CD4 cell count (48). Determinants of prognosis were assessed by using proportional hazards regression (49), and as follow-up was extended, the effects of AIDS treatments were examined by comparing survival in different calendar periods (50, 51).

One of the most recent reports from MACS illustrates the usefulness of rich longitudinal data

sets for addressing time-related questions. By analyzing MACS data in time periods—1984 to 1990 (little or no therapy), 1990 to 1993 (monotherapy), 1993 to mid-1995 (combined therapy), and mid-1995 to mid-1997 (potent antiretroviral therapy)—Detels and colleagues (52) assessed the effects of the distinct therapies administered in each of these periods. This analysis was possible because MACS spanned four eras of therapy. The outcome measures were time from seroconversion to development of AIDS (**Figure 4**), time from seroconversion to death, and change in CD4 cell count. Strong effects of calendar period were found: The most recent time period showed that more time passed before development of AIDS (**Figure 4**) and death, and a substantial improvement was also seen in the rate at which CD4 cell count decreased.

Figure 4 provides survival curves for the development of AIDS during the four therapeutic eras on a time axis defined by years since seroconversion. In any given calendar period, men entered the study at different stages of infection. A maximum of only 5 years of follow-up was possible during the earliest calendar period (1984 to 1990); up to 13 years of follow-up were possible for patients who developed disease during the last calendar period (mid-1995 to mid-1997). During the most recent

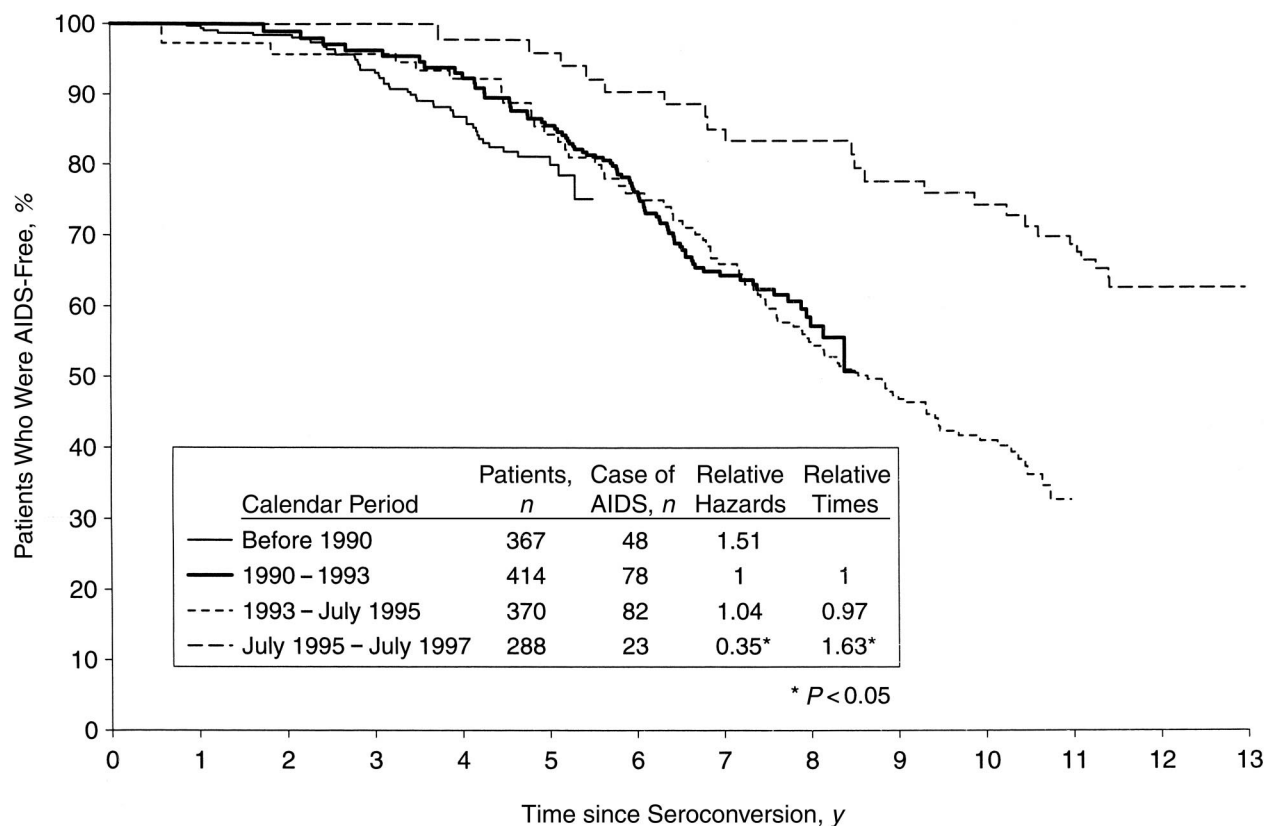


Figure 4. Extended Kaplan-Meier curves, relative hazards, and relative times to AIDS from HIV seroconversion in calendar periods during which different types of antiretroviral therapy were used (52). Adapted with permission from JAMA. 1998;280:1497-503; copyright 1998, American Medical Association.

calendar period, it is evident that more time passed between HIV infection and development of AIDS.

Figure 4 also provides the relative hazard for developing AIDS by calendar period and relative AIDS-free survival times. The relative hazard describes the change in risk for AIDS in relation to the reference calendar period (1990 to 1993), and the relative AIDS-free survival times characterize increments in survival time without AIDS.

The relative hazard from the Cox proportional standards model shows a reduced risk for AIDS in the most recent time period compared with all three earlier time periods and a 63% increase in AIDS-free survival time. The benefits of therapy relative to the outcome of death were estimated with the same methods, and the findings were similar. In addition, CD4 cell counts decreased more slowly during the last time interval. These analyses provide convincing evidence of the benefits of potent antiretroviral therapy and two clinically meaningful estimates: the relative hazard and the relative survival time.

Conclusions

The study of events in time is fundamental to biomedical research and public health surveillance. Research designs that incorporate time have long been in use; analysis of longitudinal data has been enhanced by new statistical methods that are appropriate to data collected over time. In the next millennium, new and increasingly complex questions will undoubtedly require investigation. The research designs and analytic methods used to address clinical questions in time will continue to evolve and will provide better, sharper answers.

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Time is . . . one damn thing after another; an endless succession of events; time is a measure of change, the separation of events; time is a fleeting illusion. Time is.

Michael Shallis
*On Time: An Investigation into Scientific Knowledge
 and Human Experience*
 New York: Schocken Books; 1983:13

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