Mathematical biology and medical statistics: contributions to the understanding of AIDS epidemiology

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Some of the many ways in which mathematical biology and statistics have been used in investigating the acquired immunodeficiency syndrome (AIDS) epidemic are reviewed. Aspects of the spread of the disease via social and sexual networks are discussed. The different kinds of data involved are critically compared. Some studies of the incubation period are briefly reviewed and some comments made on the role of adherence to therapy.

1 Introduction

The impact of infectious disease on the developing world was dramatically reduced in the twentieth century by mass immunization and the use of antimicrobial drugs. However, the emergence of new pathogens, including the human immunodeficiency virus (HIV) and drug-resistant strains of previously controlled diseases (e.g. tuberculosis), has called into question the future control of infections. Since the identification of acquired immunodeficiency syndrome (AIDS) in 1982,1 considerable progress has been made in the development of drugs to treat HIV-infected patients, initially AZT and other nucleoside reverse transcriptase inhibitors and more recently protease inhibitors and non-nucleoside reverse transcriptase inhibitors. At the same time six major prevention strategies have been pursued: mass media campaigns, peer education programmes, treatment of other sexually transmitted infections, condom social marketing, safe blood provision, and needle exchange/bleach provision.

In the familiar settings of clinical trials and randomized controlled intervention trials, statisticians have, of course, made major contributions to the evaluation of both drug treatments and prevention programmes and in the identification of risk factors associated with infection. Mathematical biologists, on the other hand, began by analysing the transmission dynamics of the HIV virus, estimating quantities such as the doubling time of the AIDS epidemic and the demographic impact of high AIDS incidence. However, the challenges posed by the HIV/AIDS epidemics required the development of new methodology to address the impact of factors such as

- the long and variable incubation period of the disease;
- the variation in infectiousness throughout the disease; and
- heterogeneity in sexual activity

on the patterns of the epidemics, often combining the approaches of different disciplines. Collaborations between medical statisticians and mathematical biologists have been
particularly fruitful. Technical advances, for example in the measurement of viral load in blood and tests for HIV drug resistance in patients receiving antiretroviral treatment, have provided increasingly powerful data for analysis and hypothesis testing. Many recent analyses are only possible due to ongoing improvements in computational power, facilitating many things including Markov Chain Monte Carlo sampling and numerical integration sufficiently quick to allow dynamical models without closed-form solutions to be fitted using maximum likelihood techniques. The statistical and mathematical HIV/AIDS literature is growing so quickly and developing in so many directions that it would be impossible to give a comprehensive summary in anything short of a book. Thus, in this paper we have chosen to highlight a few key areas of interest to both statisticians and mathematical biologists, as well as to the wider community of HIV/AIDS epidemiologists.

2 Understanding the spread of disease: partnerships and networks

The risk of acquiring HIV or any other sexually transmitted infection depends both on the sexual behaviour of the susceptible individual and the distribution of infection within the population. Early studies of behaviour linked heightened individual risk to incomplete condom use, numbers of sexual partners and types of sexual acts. However, mathematical modelling has illustrated that going beyond individuals to the analysis of sexual mixing patterns (who forms partnerships with whom) and the wider sexual network yields greater insight into the transmission dynamics within populations. Since HIV can, of course, also be transmitted through injecting drug use, consideration has also been given to the wider risk network incorporating both sex and drug use partnerships. Those, especially haemophiliacs, who have been infected by contaminated blood products have also been intensively studied, in part because in many cases the date of infection can be reasonably closely estimated but here the issue of networks does not arise.

The importance of network structure is not surprising when the transmission process is broken down into the two dynamical processes of partnership formation/dissolution and within partnership transmission from infected to susceptible individuals. This two-stage process causes considerable complications in the mathematical analysis of transmission dynamics compared to systems with homogeneous mixing or fixed networks. A particularly important feature of the network is the level of concurrency, where one of the partners has more than one partner simultaneously.

Despite considerable development and analysis of mathematical models of networks, drawing inferences from the analysis of sexual network data remains particularly difficult. The collection of reliable data on individual sexual or drug use behaviour requires particular care, for example, in assuring subjects of confidentiality and minimizing non-response. However, the problems of sampling bias, (possibly non-ignorable) non-response, and measurement error are considerably more difficult when subjects are asked to report their partners’ behaviour. Attempts to reconstruct entire sexual networks have been beset by the non-identification of partnerships (e.g. Woodhouse et al.; Ghani et al.). Thus, an important area of recent work is the development of moment closure methods using pair approximations for higher-order correlations, since the identification of pairs and singletons is considerably easier than network reconstruction.
There are possible links, unexplored so far as we are aware, with the extensive literature on social networks; see, for example, Wasserman and Faust.\textsuperscript{15}

When the focus of interest is on the infectivity of HIV, then partnerships provide sufficient data for analysis without consideration of the extended network. Assuming that the probability of transmission of viruses remained the same at each contact, HIV-1 was found to be more infectious than HIV-2.\textsuperscript{16} Methods were further developed by Jewell and Shiboski\textsuperscript{17} to allow for heterogeneity across partnerships. Evidence that infectivity varies, in a pattern similar to viral load levels, with increased levels following the infection of the primary partner, decreasing to lower levels for several years afterwards, was obtained from the analysis of roughly 400 couples.\textsuperscript{18} More recently, Quinn \textit{et al.}\textsuperscript{19} studied a similar number of couples and were able to confirm that viral load predicts HIV infectivity.

### 3 Within-host dynamics

Once transmission of the virus has taken place, the virus and the immune system begin a long-term battle having complex dynamics within a single infected individual, the host. The lower limit of detection of techniques for measuring HIV viral load in plasma\textsuperscript{20,21} and other tissues, such as lymph nodes, has dropped dramatically in the last decade.\textsuperscript{22} Highly sensitive viral load tests yield data with increased power to test hypotheses about the within-host dynamics.

The early phase of HIV infection, characterized by acute symptoms and high viremia, is followed by a clinically latent phase that varies in duration but is typically several years. During this time, the virus is not dormant but actively infects CD4+ T cells causing a gradual decline in CD4 cell count. Essentially empirical statistical analyses of CD4 decline, using techniques such as multilevel models, have described the variability between patients attributable to the virus (HIV-1 or HIV-2\textsuperscript{23}) or to host genotype.\textsuperscript{24} Measurement or sampling error is appreciable in these studies. However, the predictions that can be made from these models about, for example, effective treatment regimes are limited in the absence of models of the interaction between virus and the cells of the immune system.

Insight into the eventual collapse of the immune system despite the apparent low rate of viral replication was provided by simple steady state models of infection, cell death and replacement.\textsuperscript{25,26} The disease process is so closely approximated by a steady state equilibrium that it is the perturbations brought about by treatment of HIV-infected patients with highly active antiretroviral treatment (HAART) that has facilitated much biomathematical insight into the disease process. Such models have described the development of genetic variation within the virions in a single patient as well as giving some understanding of the pathogenesis of AIDS.

Works of Wei \textit{et al.}\textsuperscript{25} and Ho \textit{et al.}\textsuperscript{26} provide excellent examples of the integrated study of biomathematical models and patient data producing greater insights into the disease process than purely theoretical or purely descriptive analyses of the laboratory data would have produced on their own. In these settings statistical estimation and hypothesis testing based on dynamical models offer considerable benefits over those based on more traditional purely empirical statistical modelling especially because of the non-linear nature of the disease process (see Wu \textit{et al.};\textsuperscript{27} Ding and Wu\textsuperscript{28}).
The most important single quantity describing the within-host dynamics is the basic reproduction number, typically denoted by $R_0$, of the virus. If $R_0$ is greater than one, then in a deterministic framework, the population of virions will increase, though possibly quite gradually at first. Similarly, in stochastic models, the virus population will most likely grow if $R_0$ is greater than one, but there is a non-zero probability that the population will become extinct. The non-linearity of the system compresses the most critical area of parameter space leading to the potential for considerable underestimation of the effectiveness of interventions if the non-linearity is not accounted for. This situation is, in this sense, similar to the evaluation of vaccine efficacy, in which it has been demonstrated that estimates of vaccination effectiveness based on individual effectiveness are not good measures of the effects of the protection conferred to the entire population (for example, see Haber et al.\textsuperscript{29}).

4 Data sources including the role of large observational database

Randomized controlled trials are widely regarded as gold-standard studies providing evidence of the highest standard. When compliance is high, such designs ensure that the treatment under study is the only systematic difference between the two groups of patients being compared. Observational studies, on the other hand, are vulnerable to confounding. While known confounders can be adjusted for in estimating treatment effects, results from non-randomized studies must be interpreted in light of the potential for unknown confounders and the inclusion of patients’ and physicians’ preferences in treatment selection.

The potential benefits of clinical databases, as contrasted both with randomized trials and with specific observational studies, may include:

- large size;
- coverage of a wider patient population than those eligible for participation in clinical trials; and
- extended follow-up periods.\textsuperscript{30}

However, the extent to which this potential is realized depends critically on the quality of the data entered. For example, to ensure comparability, Phillips \textit{et al.}\textsuperscript{31} analysed three databases which used standardized procedures for data collection and follow-up, as well as a consistent definition of AIDS.

It has quite often been reported in other contexts that treatment effects estimated from non-randomized, observational studies differ from those estimated from randomized controlled trials. Although the conventional view is that estimates from observational studies will tend to be larger than those from randomized trials,\textsuperscript{32–35} non-randomized treatment allocation and even inadequately concealed random allocation have been associated with relative inflation of estimated effects by a factor of 1.6, deflation by a factor of 4.2 and even inversion of the estimated effect.\textsuperscript{36}

However, a recent study comparing meta-analyses of randomized controlled trials with meta-analyses of observational studies (cohort or case–control studies) concluded that ‘well-designed’ observational studies produced comparable results to clinical trials on the same topic.\textsuperscript{37} Similar results were found when individual randomized controlled trials were compared with individual observational studies.\textsuperscript{38} Although an earlier systematic
review led to the conclusion that results from randomized and observational studies did not inevitably differ,\textsuperscript{39} the reports by Concato \textit{et al.}\textsuperscript{37} and Benson and Hartz\textsuperscript{38} caused a flurry of discussion.\textsuperscript{40,41}

While randomized trials and carefully planned cohort and case–control studies are of established effectiveness, the possible role of patient databases as a research tool is attracting some attention. Issues here concern the quality, completeness and comparability of information in such databases, as well as whether they contain sufficiently focused information to address the delicate issues of potential confounders, sequential treatment allocation, etc. that are difficult enough to contend with in a specifically planned investigation. Such databases are, however, likely to have a valuable role in hypothesis generation. Also when such databases are set up, perhaps for managerial purposes, it is certainly wise to consider their potential as research tools, in particular about assessing apparent treatment effectiveness in a routine medical setting.

For a broad review of data collection issues with particular reference to disease surveillance, see Solomon and Isham.\textsuperscript{42}

5 Adherence

Considerable attention has been paid to the study of patient adherence (compliance) to prescribed antiretroviral therapy. Highly active antiretroviral therapy (HAART) has, in recent years, led to a marked decrease in HIV-related morbidity and mortality. However, as HAART typically involves multiple drugs and many daily doses (often in excess of 25 pills per day\textsuperscript{43}), perfect adherence is a very difficult task indeed. Mathematical models of adherence to therapy and disease progression have given insights into the power of drug selection pressure to encourage the accumulation of drug-resistant mutations leading to therapeutic failure. Statistical studies of adherence have sought to explain the variation in patients’ adherence patterns and to investigate epidemiologically the links between adherence and clinical outcome.

Mathematical models of pharmacokinetics combined with HIV viral replication provide insights into the conditions which favour the emergence of drug-resistant viral strains as well as the failure to eliminate wild-type virus.\textsuperscript{44–49} When the pharmacokinetic and pharmacodynamic models are linked directly to adherence behaviour, then these models can provide insights into which patterns of non-adherence are particularly likely to foster therapeutic failure.\textsuperscript{48}

Studies of adherence have estimated levels of individual patient adherence using indirect measures including self-report, pharmacy prescription filling records, physician estimates, attendance of clinic appointments and pill counts, as well as more direct measures of biological markers, drug plasma concentrations and electronically recorded dosing histories. Medication-event monitors electronically record the date and time whenever the medication container is opened, revolutionizing the collection of adherence data, still subject to the assumption that opening the container corresponds to ingestion of a single prescribed dose.

Significant associations have been found between estimates of patient adherence and mortality directly\textsuperscript{50} as well as other measures of clinical outcome (viral load,\textsuperscript{51–55} CD4 cell count\textsuperscript{55–59} and Karnovsky score\textsuperscript{60}). Review of the antiretroviral adherence literature
suggests no clear boundary beyond which imperfect adherence is adequate to gain the full benefit of antiretroviral therapy, and thus cautions against simple classification of patients as ‘adherent’ and ‘non-adherent’.

Another important area is the investigation of social and psychological factors associated with patient non-adherence with the aim of raising awareness of such factors by practitioners attending HIV-infected patients. Although the specific problems raised by adherence to antiretroviral therapy are recent, the findings of intervention studies of patients on other chronic medication regimes (including the treatment of asthma, cardiovascular disease and hypertension) suggesting multifactorial, interdisciplinary approaches to increasing patient adherence may be relevant in the development of effective HIV/AIDS treatment strategies.

Adherence can also play a role in randomized clinical trials, with poor adherence generally causing ‘as treated’ and ‘per protocol’ analyses to be biased and have very low power. For a general review of these issues, see the symposium papers edited by Goetghebeur and van Houwelingen. In general, before elaborate methods are used, it is important to examine the relevance of the detailed assumptions to the specific study under analysis. JM Robins and his coworkers have developed and applied powerful methods to these issues; see, for example, Robins and Hern-Ant et al. A major complication arises whenever the reasons for poor adherence are associated with the outcome variable of interest. In this case, the factors predicting adherence act as confounders and may bias estimates of treatment effects.

Finally, although there has been considerable discussion of the effects of non-adherence on the interpretation of clinical trials and therapeutic success generally, there has been little attention paid to the effects that poor levels of adherence can have on preventive vaccine efficacy trials. Clearly, the collection and thoughtful analysis of accurate and detailed data on the patient adherence to increasingly complex treatment regimes facilitate estimation of the causal effects of chemotherapy (and similarly vaccination) on disease.

6 Incubation period

A key aspect of any epidemic is the distribution of incubation period. When both the initiating contact and the incidence of symptoms are clearly defined and observable, estimation of the distribution raises no special problems, once an effectively random sample of subjects is available. For AIDS, however, there are major difficulties. The initiating event, whether it is regarded as the contact at which infection is started or the time of seroconversion, is rarely directly observable. Furthermore the ‘end point’, whenever it is progression to full-blown AIDS, is subject to changes of definition, uncertainties of diagnosis and in more recent years systematic changes arising from improved treatment regimens. The last point also applies to studies of time from infection to death.

Estimation of the distribution of incubation time thus depends on the availability of a cohort of subjects either with a single known incidence of exposure to risk or for whom repeated blood samples are available establishing the last date of HIV-negativity and the first date of positivity. The latter case thus determines an interval censored incubation time, assuming of course that there are no errors in testing. The first possibility of a single
known incidence of exposure is applicable to patients receiving a single transfusion of possibly infected blood. The second applies to haemophiliacs for whom regular blood samples are available over a period and to particular intensive studies of high risk cohorts. Thus in some studies incubation time is measured from the first known instance of sexual contact with an individual established to be seropositive.

We shall not attempt to review all studies of incubation period. We shall outline one early analysis and then sketch the conclusions from a major recent analysis bringing together data from 38 studies.

One of the first analyses of incubation time in the relatively early years of the AIDS epidemic analysed data from CDC Atlanta, Georgia. Medley et al.,73,74 estimated the distribution of incubation period from individuals who had received a single infusion of possibly contaminated blood. At that stage there were virtually no individuals who had been at risk for more than 4 or 5 years. Since this was almost certainly just the beginning part of the distribution, non-parametric analysis was useless and a series of parametric analyses was made using different assumptions of distributional form. This combined with some assumptions about incidence of infectivity led to a formal maximum likelihood analysis. The main conclusions were estimated median incubation times of 8 years for adults under 60 years of age with a reduced value for older individuals and very young children.

Babiker et al.,75 on behalf of a Collaborative Group including the CASCADE EU Concerted Action, brought together data from 38 studies in Europe, North America and Australia in which the date of seroconversion could be approximately estimated. There were about 13 000 patients in all, of whom nearly 4000 developed AIDS indicator disease. Patients suffering from Karposi’s sarcoma were excluded.

The main technique of analysis was log Poisson regression in which time and age at seroconversion were both divided into 5 year time bands. A technical complication was the presence of left truncation. For example, a patient becoming HIV positive in 1990 and entering a study in 1995 would not have been included had they died in, say, 1993. This aspect is dealt with by entering the individual in the risk set for calculations only after 1995; see, for example, Cox and Oakes.76 The most striking conclusion was a strong dependence of incubation time on age at seroconversion. Thus the estimated median incubation time varies from 12.5 years in the 15–24 year age group to 7.9 years in the 45–54 year age band. There was no evidence that mode of transmission affected incubation time, once age at infection was allowed for. No parametric representations of incubation time were reported.

Very similar conclusions resulted when time to death rather than time to AIDS was used as end point. No analysis of time from seroconversion to death was included.

A separate earlier investigation of the UK haemophiliac cohort77 showed that those becoming seropositive had about 10 times the mortality rate of those not seroconverting, the latter group retaining the historical mortality rate. The higher mortality was very largely due to AIDS-related causes. This is all quite strong direct evidence of the causal effect of seroconversion, an aspect that has occasionally been questioned. An alternative explanation would have to postulate seroconversion as an irrelevant side-effect of an event, transfusion with contaminated blood or some event statistically associated with that, having some quite different pathway to AIDS.

Bunting,78 in a careful study of an MRC cohort from south-west Uganda, showed in particular that analyses of survival postulating a Poisson process of infection between the
last negative sample and the first positive gave results negligibly different from those assuming seroconversion at the midpoint.

General studies of time from AIDS to death are limited by the difficulties of diagnosing AIDS and by the likely effects of treatment, especially in more recent studies. Information can be obtained, however, from the extensive accounts of randomized trials which we do not attempt to review in this paper. Early studies by Reeves\textsuperscript{79} using UK data, and Rothenberg \textit{et al.}\textsuperscript{80} using data from New York City, showed virtually identical results. There was a concentration of frequency of about 0.08 near zero, presumably to diagnoses of AIDS close to death or post-mortem and, after that, a distribution very close to an exponential distribution of mean 15 months. One interpretation of the exponential distribution is via death consequent on vulnerability to randomly occurring infections.

7 A fundamental equation

If incidence of infection occurs in a time-dependent Poisson process of rate $\rho_1(t)$ and the probability density function $f(\cdot)$ of incubation time is fixed in time, then cases occur in a Poisson process of rate $\rho_C(t)$, where

$$\rho_C(t) = \int_{-\infty}^{t} \rho_1(u) f(t-u) \, du$$

There is the mild assumption that the incubation period of any subject is independent of other aspects of the process. This equation\textsuperscript{81–83} can be used in various ways. Essentially given any two of the three functions involved the third can in principle be determined by convolution to find $\rho_C(t)$ and by the more delicate procedure of deconvolution in the other two cases.

Generalizations of the equation are possible to allow for rates and incubation periods that are, for example, age-dependent.

The applications of this equation to AIDS have assumed the incubation distribution known and have either used estimates of the function $\rho_C(t)$ to derive estimates of the infectivity process or have used the method as a base for prediction of the rate of incidence of new cases.

In some ways surprisingly these calculations have, so far as we know, all been done non-parametrically, although deconvolution in particular is sensitive to errors of specification and it is easy to get nonsensical answers such as negative estimated rates, so that some imposed smoothness is needed. See, in particular, Isham,\textsuperscript{82} who studied some aspects analytically.

The equation above can be rewritten as

$$\rho_C(t) = E\{\rho_1(t - X)\}$$

where the random variable $X$ denotes an incubation time and the expectation is over its distribution. If $\rho_1(\cdot)$ varies slowly over the effective support of the distribution of $X$, an assumption unlikely to hold for AIDS, we can write this approximately as
\[ \rho_C(t) = \rho_1(t - \mu) + \sigma^2 \rho_1''(t - \mu)/2 + \sigma^3 \gamma_3 \rho_1'''(t - \mu)/6 + O(\sigma^4) \]

where \( \mu, \sigma \) are the mean and standard deviation of incubation period and \( \gamma_3 \) is the standardized third cumulant. Thus, even if the cubic term in \( \sigma \) is ignored, estimation of \( \rho_C(t) \) depends appreciably on estimating the second derivative of \( \rho_1(\cdot) \) or in a non-parametric setting some equivalent thereof.

Conversely the solution of the differential equation for \( \rho_1(\cdot) \) in terms of \( \rho_C(\cdot) \), an approximate version of the deconvolution problem, is in effect by reversion of the series expansion

\[ \rho_1(t) = \rho_C(t + \mu) - \sigma^2 \rho_C''(t + \mu)/2 + \sigma^3 \gamma_3 \rho_C'''(t + \mu)/6 + O(\sigma^4) \]

again emphasizing the sensitivity of the method. The methods summarized below used in forecasting the AIDS epidemic thus depend critically on the smoothing techniques used in implementation.

If, however, it is assumed that \( \rho_1(u) = \rho_1 e^{\lambda u} \), then

\[ \rho_C(t) = \rho_1(t) f^*(\lambda) \]

where \( f^*(\cdot) \) is the Laplace transform of the density \( f(\cdot) \). There is an immediate generalization if the incidence rate is a sum of exponentials. Step function inputs could be handled similarly.

### 8 Impact on methodology

The main emphasis of this paper has been on a few aspects of the contribution of statistical methods to the study of AIDS. Most developments in statistics have arisen directly or indirectly out of specific applications and it is therefore legitimate to turn the question round and to ask: what new methodological developments of general interest have arisen in whole or part from the AIDS epidemic?  

One aspect is the development of mathematical models of the epidemic. There is, of course, a long history of such models initially in the context of malaria. The second edition of the definitive book of Bailey\(^84\) set out the position at that time. Relatively little happened until the 1990s since when, stimulated partly by the direct availability of computerized procedures for solving or simulating more complex models and to no small extent by the special aspects of AIDS, long incubation times and particular exposure patterns, there has been an explosion of work.\(^6\)

In terms of statistical methods there has been more attention focused on the requirements of surrogate response variables especially in clinical trials. Prentice\(^85\) formulated a strong definition of what should be expected of a surrogate response; it seems to be agreed that these conditions are hardly if ever met. For a critical discussion and review, see Fleming \textit{et al.}\(^86\) and for the important additional notion of auxiliary variables Fleming \textit{et al.}\(^85\) Cox\(^88\) distinguished three roles for such variables as viral load, including a much weaker definition of surrogacy than that of Prentice, and sketched different kinds of model that might be appropriate.

Design aspects are crucial in these studies and the challenge is to adapt the general principles of the design of experiments and observational studies to the inevitable constraints, particularly severe in the case of AIDS, arising from ethical and political
sensitivities. Thus in the case of randomized trials of new therapies there have sometimes been major problems in randomizing individuals to control regimes. The use of complex combination therapies raises the possibility of using fractional replication. When, however, treatments are applied in stages, choices and timing of treatment at one stage depending on outcomes at previous stages, great care in analysis and interpretation is crucial unless the conclusions are dramatically clear. There is an extensive recent literature aiming to handle carefully and realistically this and associated issues.

Among observational studies, prevalent cohorts are often encountered. That is, the study population consists of those individuals in some defined group who at some initial time $t_0$ are in a particular state, e.g. are HIV positive or have AIDS. If the time they entered that state is known, we have an example of left truncation to be handled as sketched in Section 6. If, however, the starting time of, say, seroconversion is unknown there are major problems in estimating the relevant distributions and dependencies unless the overall distribution of interest is exponential, which is far from the case here. See Brookmeyer and Gail.

9 Discussion

Even this brief tour through current research in AIDS epidemiology has revealed a wide range of techniques under development and the ongoing contributions of statistical and mathematical researchers. Clearly in such a field, the substantive questions posed by the subject warrant very careful consideration whether they require the development of innovative techniques or simply the prudent application of established methods.

Statisticians, epidemiologists and mathematical biologists have frequently gone further still, in campaigning for the collection of important, but often highly sensitive, data including unlinked anonymous HIV screening and surveys of sexual attitudes and behaviour. Science-based policy recommendations have been made by statisticians, having studied HIV transmission in prison, calling for randomized trials of national drug policies, along the lines of the randomized trial being conducted on badger control strategies aimed at reducing the incidence of bovine tuberculosis in cattle.

What does the future hold? The HIV/AIDS epidemic continues to grow. Demographic models have predicted 500,000 AIDS deaths in South Africa alone in 2010, compared to 100,000 in 2000. Yet there are promising avenues of research. The South African Medical Research Council has recently announced plans to conduct Phase-1 testing of a candidate HIV vaccine, against the dominant subtype of HIV-1 found in Africa and India, in May 2001. Considerable thought has already been given to the issues raised by potential HIV preventive vaccine trials – addressing issues including surrogate end points for measuring vaccine effects on disease progression and secondary transmission, and methods for assessing host immune and viral (genotypic or phenotypic) correlates of vaccine protection against infection or disease.

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