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HIV /AIDS CLINICAL TRIALS : A STATISTICAL REVIEW

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ABSTRACT

The HIV pandemic has grown to become one of the greatest infectious disease threats, to human health and to socio-economic stability that the world has ever encountered. It is imperative that the epidemic is controlled as rapidly as possible through prevention of new infections. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people to improve health. When the objectives or the endpoints of clinical trials for HIV/AIDS are carefully defined then Statistics will be very useful not only in designing the trial and formulating hypothesis but also in providing guidance in the analysis of the data on completion of the trial and to enhance the credibility of the results. This article mainly reviews the analysis of HIV/AIDS clinical trials. Concepts such as meta-analysis, analysis in the case of incomplete data and Bayesian analysis in the context of HIV/AIDS have also been covered.

Key Words : *AIDS, Bayesian analysis, CD4 Cells, Clinical Trials, HIV, Meta analysis.*

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1. Introduction

Human Immunodeficiency Virus (HIV) is the virus that is widely believed to cause Acquired Immune Deficiency Syndrome (AIDS). HIV infects the defense cells of the immune system of the human body called CD4+ T lymphocytes and gradually reduces them in number, thus, making an individual susceptible to a wide range of opportunistic infections such as cancer and tuberculosis. As the viral load in the blood rises and the CD4 count falls, it indicates the advancement of immunosuppression and AIDS. The four modes of HIV transmission are – (i) unprotected sexuality (ii) contaminated blood transfusion (iii) infected injecting equipments (iv) infected mother-to-child transmission.

The HIV pandemic continues to engulf the world even 25 years after the initial identification of this infection. The disease has already killed millions, shortened life expectancy, created orphans and has slowed down the rate of growth of the Gross National Product of many heavily affected countries. Hooper (1999) states that since 1981, when the condition was first recognized in American homosexuals, upto the present, the origin of the epidemic had always intrigued people. The UNAIDS/WHO AIDS update (2005), states that there are 40.3 million persons living with HIV/AIDS, and in India alone the cases recorded by National AIDS Control Organisation are about 5.15 million. In absolute figures, India stands second to South Africa which has an estimated 5.3 million HIV infections.

2. Clinical Trials

Health vaccines are widely considered as one of the greatest achievements in public health, having had a dramatic impact on the prevalence of several infectious diseases. Since the 1940's, clinical trials have become critical for evaluating new vaccines as well as other prevention and treatment strategies in combating human diseases. Today, the randomized clinical trial is the important standard for providing scientific evidence regarding the efficacy of a vaccine.

Clinical trial is a study conducted on human volunteers to answer specific health questions. Carefully designed clinical trials are the fastest and safest way to find treatments that work on people and improve health. All such trials have guidelines about who can participate. Some research studies require participants with illness while others need healthy participants. But the names of the participants remain confidential.

Clinical trials are carried out on the basis of new ideas from researchers, after it is tested in the laboratory on animals. The experimental treatments with most promising results are moved into clinical trials, where more information is gained about the treatment, its risks and how well it may work. The treatments are often compared with the control group which receives a placebo instead of an active drug or treatment.

Clinical trials are conducted for different purposes and are classified as treatment trials, prevention trials, diagnostic trials, screening trials and quality of life trials.

The ethical and legal codes that govern medical practice apply to clinical trials as well. Most clinical research is government regulated with built-in safeguards to protect the participants. As a trial progresses, researchers report the results at scientific meetings, medical journals and to government agencies.

In general, the different phases of preventive vaccine trials are the following :-

i) Preclinical studies - The earliest stage of vaccine development begins with investigation of vaccines in animals (in vivo) and in laboratories (in vitro). In these studies, the assessments are typically viewed as tests of biological concepts with attention paid more to qualitative than to quantitative outcomes. Preclinical studies in laboratories include assessment of quality control of the manufacturing process and validation of immunogenicity assays to be used in subsequent clinical trials.

ii) Phase I trials – Researchers test an experimental drug (vaccine) on a small group of people (about 10 to 100). Assessment of safety is often the primary objective, participants are usually healthy adults at low risk of acquiring the infection or disease of interest. Depending on the setting, enrolment may be limited to include only individuals having prior infection with the pathogen of interest.

iii) Phase II trials – The experimental vaccine or drug under study is given to a larger group of people (about 100 to 500) with the primary objective of further characterization of safety and immunogenicity. Typically randomized, double-blind and placebo-controlled Phase II trials enroll individuals from the target population.

iv) Phase III trials - This phase is employed for vaccine candidates that are safe and immunogenic in Phases I & II, the experimental study drug or treatment is given to a larger group of people (about 1000 to 1,00,000) with the objective of estimating the efficacy of a vaccine in the population of interest.

Hudgens et.al. (2004) are of the opinion that vaccine efficacy has the form

$$VE = 1 - RR,$$

where RR denotes the relative risk of disease in vaccinees as compared to placebo recipients.

$$\text{i.e. } RR = R_v / R_p,$$

where R_v and R_p denote the risk in the vaccine and placebo arm respectively.

Given that a risk ratio must be non-negative it follows that VEE lies in $(-\infty, 1]$ with a value of '1' indicating complete protection and '0' representing no effect and a negative value conveying an increase in risk due to vaccination.

v) Phase IV studies – (For vaccines that prove efficacious in Phase III trials and result in licensure). Subsequent Phase IV or post licensure studies are typically implemented to look at safety and vaccine effectiveness.

The ultimate goal for HIV vaccine development is to find an approach that can prevent infection in an exposed individual or lead to clearance of infected cells to avoid persistent infection. Most vaccines are effective because they limit the replication and spread of the pathogen. A more realistic initial goal for HIV vaccine development is to achieve a dampening of the initial viremia in an infected individual, maintenance of a low viral load and prevention of progression to AIDS. Thus, altering the disease course in individuals could potentially have a large impact on the spread of HIV within a population.

According to Graham (2001), the determinants of epidemic spread can be expressed as $R_o = \beta \times c \times D$; where R_o is the reproductive rate of the epidemic or a measure of spread, β is the transmission efficiency of the agent, c is the frequency of new partners or new transmission opportunities and D is the duration of transmission.

If $R_o > 1$, the epidemic will spread and if $Ro < 1$, the epidemic will diminish. Effective vaccination has the potential to change both β and D and education and traditional public health approaches can alter c.

Bonhoeffer et al. (2003) have formulated a model called the Central Virus-Load Relation (CVLR) which specifies that the steady state load of infected cells is given by the product of three factors:

i. $1/\delta$ - the reciprocal of the death rate of infected cells

ii. σ - the fraction of infected cells progressing to a state of active virus production and

iii. F – the net rate of production of new susceptible target cells.

Therefore a large variation in atleast one of these factors would result in a large variation of the steady-state infected-cell load observed in different patients. The following is the description of CVLR:

If T denotes the population susceptible target cell i.e. the activated CD4+ T cells and I denotes the population of cells that are actively producing virus (infected cells), then the dynamics of these populations are given by

$$\frac{dT}{dt} = F - H \tag{2.1}$$

$$\text{and } \frac{dI}{dt} = \sigma H - I\delta, \tag{2.2}$$

where F is the net rate of target cell production, H is the rate of loss of susceptible target cells due to infection, δ is the death rate of infected cells and σ is the fraction of the infected cells progressing to active virus production.

During chronic infection, these dynamics are in steady state i.e. $\frac{dT}{dt} = \frac{dI}{dt} = 0$.

In this state, equ (2.1) becomes, $\frac{dT}{dt} = F - H = 0$, i.e. H and F are equal, and equ (2.2) becomes, dI = σH - Iδ = 0 , i.e. σH = Iδ i.e. $I_{ss} = \sigma H / \delta$ and since H and F are equal, we get

$$I_{ss} = \sigma F / \delta \tag{2.3}$$

3. Statistical Analysis of HIV Clinical Trials

Semi-parametric and non-parametric methods with incomplete data

An important problem in clinical trials is that complete follow up may not be available on all subjects. The reasons for incomplete data in clinical trials are

i) Administrative censoring, where investigators choose to analyse the data before all subjects have completed the study. Examples include interim monitoring

and early termination of the study. The latter may occur due to a variety of reasons, such as delayed recruitment, inadequate funding, safety concerns, or compelling early evidence of efficacy or lack of efficacy. In these circumstances, O'Brien et al. (2005) have suggested that it is reasonable to assume that the missing data are 'missing completely at random' (MCAR).

ii) Decisions by participants to discontinue their participation in the trial.

O'Brien et al. (2005) perceived that the most commonly used method for dealing with this problem is the use of 'Last Observation Carried Forward' (LOCF). For this method, to provide unbiased estimates and valid tests, one must assume that the last observation has the same expectation as the value that would have been observed at the last scheduled follow up, an assumption that is implausible in most trials. In the case of progressive diseases such as dementia, it was found that if a placebo treated patient fails to complete the study, LOCF will essentially give the placebo treatment credit for halting progression of dementia from the point of last follow up to the end of the trials, which could result in an important loss of power if incomplete follow up is more common in the placebo group. A completers analysis (analysis using only data from subjects who complete a trial) avoids this bias, but appears to be rarely used owing to the loss of power associated with failure to use information available from non-completers.

O'Brien et al. (2005) have also mentioned the use of Mixed-effects Model Repeated Measures (MMRM) methodology, which was studied extensively by Mallinekroat et al. (2001, 2003), to deal with the problem mentioned above. The MMRM method fits a model with terms for treatment group, visit and interaction. Although this approach has satisfactory operating characteristics, it appears to be rarely used. The reasons for this are yet to be investigated, but may reflect the relative simplicity of the LOCF and Completers procedures and the corresponding ease of communication to non-statisticians, or lack of familiarity with the necessary software.

Meta-analysis

Meta analysis is a set of statistical procedures designed to accumulate experimental and correlational results across independent studies that address a related set of research questions. Unlike traditional research methods, meta-analysis uses the summary statistics from individual studies as the data points. By accumulating results across studies, one can gain a more accurate representation of the population relationship than is provided by the individual study estimators. The power to test the effect of a new treatment is increased by meta-analysis by pooling results from a number of clinical trials. Usually, meta-analysis is based on trial of the parallel group design, but some trials assessing the treatment of interest may use other

designs. Both parallel and cross-over trials provide estimates of the same treatment effect, but the between-subject comparison of parallel trials is replaced by a within-subject comparison in cross-over trials.

Hughes et al. (1998) have evaluated the initial changes in CD4 cell count as a surrogate endpoint for clinical outcome in HIV infected patients, using Meta-analysis of all relevant Phase II and III randomized clinical trials undertaken by the adult AIDS clinical trials group. Individual patient data were obtained from each clinical trial and the difference between a pair of treatments in their effect on clinical outcome (AIDS or death) during 2 years of follow-up was evaluated. The proportion of treatment effect explained (PTE) was the proportion of this difference explained by the change in CD4 cell count 6 months after starting treatment, evaluated using proportional hazards models. A weighted average PTE across treatment comparisons was obtained. The association between the difference between treatments in clinical outcome, expressed as hazard ratio, and the difference in mean change in CD4 cell count was evaluated using regression analysis. There were 15 clinical trials involving 24 treatment comparisons. The weighted average PTE for both progression to AIDS or death was 0.16 [95% confidence interval (CI), 0.07-0.26] and for death was 0.10 (95% CI, 0.00-0.20). There were significant associations between treatment differences in effect on AIDS or death, and on death alone, and the difference in mean change in CD4 cell count. The small PTE suggest that other mechanisms of drug action not captured by initial change in CD4 cells are important. CD4 cell count is a weak surrogate endpoint, but has some value as an aid for screening treatments for drug development or preliminary regulatory approval.

Analysis of Uncontrolled Treatment Changes in HIV Clinical Trials

Some clinical trials involving subjects with HIV allow a change or cross-over, of treatments when particular criteria are met. For example, after it was established that the drug Zidovudine (ZDV), previously known as AZT, was effective in delaying the progression of AIDS among subjects with CD4 cell count below 500/mm^3, one study required subjects with CD4 cell counts above 500/mm^3 who were taking a placebo, to change to ZDV treatment when their counts fell below 500/mm^3. Another example is concerned with an ongoing trial that compares combinations of drugs to treatment with single drug. In this study, a cross-over to a new treatment is required if a person's CD4 count declines to below 50% due to both ethical considerations and patient/physician's perception that the regimen initially assigned has failed, all subjects change treatment when they meet the cross-over criterion.

The CD4 cell count is used both as the marker of disease progression to determine when a person should cross-over and also to assess the benefits of changing treatment (increase in the CD4 cell count suggest beneficial treatment activity). Substantial within subject variability of the CD4 cell counts in HIV infected patients suggests that this regression effect may be considerable. Thus, the challenge for analysis is to separate out the effect of switching treatment from the effect of regression to the mean.

Lin and Hughes (1996) focus on the application of an extension of a likelihood-based methodology that allows appropriate estimation of the effect of switching treatments using subjects data from before and after the treatment switch. The specific application uses data from the examples, which have been mentioned above, i.e. to assess the effect on the CD4 cell count of introducing ZDV after taking placebo when a subject's count first fell below 500/mm^3. A particular advantage of this study is that the clinical trial involved a blinded comparison of ZDV to placebo. Subjects in both treatment arms were required to change from their initially assigned regimen to open label ZDV when their counts fell below 500/mm^3. As the subjects changing from blinded ZDV to open label ZDV had no real change of treatment, we can obtain an estimate of the regression to the mean effect directly from this group. Subtracting this regression to the mean effect from the change observed in the group that switched from placebo to ZDV then provides a direct estimate of the effect of introducing ZDV. Comparison of this estimate with that from the model based approach (which uses data only from subjects who switched from placebo to ZDV) allows an assessment of how well the model based approach performs in practice and hence its utility in other applications which typically, do not have an external estimate available for the regression to the mean effect.

Comparison of the plots for the two groups shows how difficult it is to distinguish treatment effects, which are modest in size, against the background variability and against the effects of the selection. For both groups, the mean CD4 cell counts have a very similar profile over time prior to time zero. After time zero, the pattern of mean CD4 cell counts differs between the two groups. The jump immediately after time zero for the immediate group reflects the size of the regression to the mean effect. Consequently, the differences between the two means at successive points after time zero provide a heuristic and assumption free estimate of the effect on CD4 cell count associated with the introduction of treatment for the deferred ZDV group which is adjusted for the selection effect.

Bayesian analysis of HIV clinical trials

Bayesian analysis is a statistical procedure which endeavors to estimate parameters of an underlying distribution based on the observed distribution. It begins with a

'priori distribution' which may be on anything, including an assessment of the relative likelihoods of parameters or the results of non-Bayesian observations. In practice, it is common to assume a uniform distribution over the appropriate range of values for the prior distribution.

Given the prior distribution, data are collected to obtain the observed distribution. Then the likelihood of the observed distribution is calculated, as a function of parameter values, this likelihood function is then multiplied by the prior distribution and normalized to obtain a unit probability over all possible values. This is called the *posterior distribution*. The mode of the distribution is the estimate of the parameter.

Hughes (1993) has explained the role of Bayesian analysis in reporting clinical trials with emphasis on the prior belief as aid for interpreting results. He has made use of the following simple logistic model to analyse data of trials having mortality as their primary endpoint, for the probability π of dying during follow up,

$$\ln\left[\frac{\pi}{1-\pi}\right]=\alpha+\beta x\ ;$$

where x = 0, if a patient receives placebo, x = 1, if the active treatment is administered to the patient, β is the log odds ratio of dying in the treatment relative to placebo group and α is the log odds ratio of dying in the placebo group.

Hughes has assumed an uniform non-informative prior distribution for α which is independent of β. On a log odds scale, this gives all values of α equal probability *a priori* and so $P(\alpha)$ has an (improper) uniform distribution. For simplicity, the marginal post-trial density function for given the trial's data y, is obtained using Bayes' theorem:

$$P(\beta\,|y)=k\int l(y|\alpha,\beta)P(\beta)d\alpha\ ; \qquad (3.1)$$

where $(y|\alpha,\beta)$ is the likelihood function based on the logistic model, $P(\beta)$ is the prior distribution for the treatment effect, and k is the constant so that the $P(\beta|y)$ integrates to unity over the range of β.

Using the non-informative prior for β in which $P(\beta)$ has an (improper) uniform distribution, the posterior distribution known as the standardized likelihood distribution is

$$P(\beta\,|y)=k\int l(y\,|\alpha,\beta)d\alpha\ ; \qquad (3.2)$$

Clinicians have their own beliefs about the possibility that a treatment will have a beneficial effect. These beliefs may be based on results from other trials or on their own experiences with the treatments or related treatments. If a treatment is to became established in clinical practice, then data from a trial needs to affect such beliefs so that clinicians are convinced of its worth. Hughes (1993) has used two models M_0 and M_1, where M_0 represents that the treatment has no effect neither beneficial nor detrimental and M_1 represents that the treatment had an effect, though not necessarily beneficial, whose magnitude he was unsure. A simple prior belief distribution was constructed to capture the uncertainty between the two models M_0 and M_1. In the former, there is no treatment effect, so $\beta = 0$ with probability 1. The latter allows treatment effects with non-informative (uniform) prior describing prior beliefs. Taking the prior beliefs in models M_0 and M_1, as p_0 and $(1-p_0)$ respectively. The odds for M_0 model versus M_1 model is $\lambda = \frac{p_0}{1-p_0}$. Thus the pooled prior from the two models is a mixture distribution having the point of no effect with probability mass p_0 and for other effects, uniform with total probability mass $(1-p_0)$. Thus the post-trial probability distribution $P(\beta \mid y)$ is then proportional to

$$P(\beta \mid y, M_0)P(M_0 \mid y) + P(\beta \mid y, M_1)P(M_1 \mid y).$$

Using the Bayes factor B_{01}, defined as the ratio of posterior to prior odds for model M_0 versus M_1, i.e.

$$B_{01} = \frac{P(M_0 \mid y)/P(M_1 \mid y)}{p_0/(1-p_0)}$$

$$\text{i.e. } \lambda B_{01} = P(M_0 \mid y)/P(M_1 \mid y)$$

$$\therefore P(\beta \mid y) = \frac{\lambda B_{01}}{1+\lambda B_{01}} P(\beta \mid y, M_0) + \frac{1}{1+\lambda B_{01}} P(\beta \mid y, M_1) \qquad (3.3)$$

This is a mixture distribution having a spike with probability mass $(\lambda B_{01}) \div (1+\lambda B_{01})$ at the point of no treatment effect and elsewhere following the shape of the standardized likelihood distribution with probability mass $(1) \div (1+\lambda B_{01})$. Thus a clinician's post-trial beliefs can be related to their pre-trial belief p_0 that there is no treatment effect. Also, any clinical trial report should provide information in a form that can convince clinicians of a treatment's worth or otherwise. Bayesian analyses can be valuable aids in achieving this. Graphical displays of post-trial probability distributions allow clinicians to assess for themselves the likely size of effect and also illustrate sensitivity of interpretation to a range of prior beliefs.

In specific context of clinical trials, Carlin and Sargent (1996) mention Spiegelhalter et al (1993, 1994) suggestion of implementing an approach using 'clinical' prior, representing the prior feelings of the trials investigators, a 'sceptical' prior, reflecting the opinion of person that doubts the treatment's effectiveness, and a 'non-informative' prior, a neutral position that leads to posterior summaries formally equivalent to those produced by standard maximum likelihood techniques. This is a 'forward' approach to prior robustness.

Carlin and Sargent (1996) also mentioned the prior partitioning approach of Carlin and Louis (1996) as a backward approach and have done an extension on a point null hypothesis and a two-sided alternative for a treatment effect θ, by taking an interval null hypothesis. This is very useful for clinical trials work since such a setting involves an indifference zone $[\theta_L, \theta_U]$, within which one is indifferent as to the use of treatment or placebo. For example, we might take $\theta_L = 0$ and $\theta_U > 0$ if there were increased costs or toxicities associated with the treatments.

The ***Prior Partitioning Approach*** – considers the point null testing scenario put forth by Sargent and Carlin (1994), i.e. $H_0 : \theta = \theta_0$ verses $H_1 : \theta \neq \theta_0$. Without loss of generality if $\theta_0 = 0$. Suppose there is an observation x that has density $f(x \mid \theta)$, where θ is the unknown scalar treatment effect parameter. Let π denote the prior probability of H_0 and G (θ) the prior cumulative distribution (CDF) of θ conditional on $\{\theta \neq 0\}$. Then the complete prior CDF for θ is $F(\theta) = \pi I_{[0,\infty]}(\theta) + (1-\pi)G(\theta)$ where I_s is the indicator function of the set S. The posterior probability of the null hypothesis is therefore given by

$$P_G(\theta = 0 \mid x) = \frac{\pi f(x \mid 0)}{\pi f(x \mid 0) + (1-\pi)\int f(x \mid \theta) dG(\theta)}. \qquad (3.4)$$

For a given prior distribution G and some $p \in (0,1)$, we stop the experiment and reject the null hypothesis if $P_G(\theta = 0 \mid x) \leq p$. Elementary calculations show that characterizing the class of priors { G } is equivalent to characterizing the set H_c, defined as

$$H_c = \left\{ G : \int f(x \mid \theta) dG(\theta) \geq c = \left(\frac{1-p}{p}\right)\left(\frac{\pi}{1-\pi}\right) f(x \mid 0) \right\} \qquad (3.5)$$

Results regarding the features of H_c, were established and then these results were used to obtain sufficient conditions for H_c to be non-empty for classes of priors that satisfy various moment and percentile restrictions.

Turning to the interval null hypothesis $H_0 : \theta \in [\theta_L, \theta_U]$ and $H_1 : \theta \notin [\theta_L, \theta_U]$, if π denotes the prior probability of H_0 and $G(\theta)$ corresponds to the prior CDF of θ given θ does not belong to the interval $[\theta_L, \theta_U]$. Making the simplifying assumption of a uniform prior over the indifference zone, the posterior probability of H_0 is computed by Bayes rule as

$$P_G(\theta \in [\theta_L, \theta_U] \mid x) = \frac{\int_{\theta_L}^{\theta_U} f(x \mid \theta)\left[\frac{\pi}{\theta_U - \theta_L} I_{[\theta_L, \theta_U]}(\theta) + (1-\pi) g(\theta)\right] d\theta}{\int f(x \mid u)\left[\frac{\pi}{\theta_U - \theta_L} I_{[\theta_L, \theta_U]}(u) + (1-\pi) g(u)\right] du} \qquad (3.6)$$

In the decision, the priors G that lead to rejection of H_0 are those for which the above equation is less than or equal to some prespecified probability p. Since $g(\theta)$ has no support on the interval $[\theta_L, \theta_U]$, this is equivalent to describing the set

$$H_c = \left\{ G : \int f(x \mid \theta)\, dG(\theta) \geq c = \left(\frac{1-p}{p}\right)\left(\frac{\pi}{1-\pi}\right)\frac{1}{(\theta_U - \theta_L)} \int_{\theta_L}^{\theta_U} f(x \mid \theta)\, d\theta \right\} \qquad (3.7)$$

Sargent and Carlin (1994) restrict the class of candidate G's some what by considering only those for which $P_G(\theta \leq \xi_L) = a_L$ and $P_G(\theta > \xi_U) = a_U$, for some fixed ξ_L, ξ_U where a_L and a_U lie in the unit simplex. That is, they require that the prior CDF G passes through the points (ξ_L, a_L) and $(\xi_U, 1-a_U)$. They also assume that $\max(\xi_L, a_L) \leq \min(\xi_L, a_U)$ and $f(x \mid \theta)$ is a unimodal function of θ for fixed x that vanishes in both tails. Owing to the asymptotic normality of the observed likelihood function, the final assumption is approximately true for large datasets. These assumptions lead to expressions for $sup_G \int f((x \mid \theta)\, dG(\theta)$ and $inf_G \int f(x \mid \theta)\, dG(\theta)$, where inf and sup are over the restricted class of G described above. The supremum expression can be used to determine whether any priors G exist that enable stopping to reject the null hypothesis. Similarly, the infimum expression may be useful in determining whether any G enable stopping to reject the alternative hypothesis H_1.

Semi-parametric prior approach is used to obtain more specific results in a prior partitioning and the mixture form used in equation 3.6 is retained. Then

$$h(\theta) = \frac{\pi}{\theta_U - \theta_L} I_{[\theta_L, \theta_U]}(\theta) + (1-\pi)\, g(\theta) \qquad (3.8)$$

Now $g(\theta)$ has to be restricted to some particular parametric family. This approach is referred to as 'semi-parametric' since the parametric form for g does not cover the indifference zone $[\theta_L, \theta_U]$.

Following equation 3.7, requiring $G \varepsilon H_c$ is equivalent to requiring

$$B \leq \left(\frac{p}{1-p}\right)\left(\frac{\pi}{1-\pi}\right);$$

$$\text{where } B = \frac{\frac{1}{(\theta_U - \theta_L)}\int_{\theta_L}^{\theta_U} f(x \mid \theta)\, d\theta}{\int f(x \mid \theta)\, g(\theta)\, d\theta} \qquad (3.9)$$

is the Bayes factor in favour of the null hypothesis. Equ 3.9 not only expresses the Bayes factor as the ratio of the marginal densities under the competing hypothesis, but it is also expressible as the ratio of posterior to prior odds in favour of the null hypothesis. B gives the extent to which the data have revised our prior beliefs concerning the two hypotheses. If we take $\pi = ½$ (equal prior weighting of null and alternative), then a Bayes factor of 1 suggests equal posterior support for the two hypotheses. We require a Bayes factor of 1/19 or smaller to ensure that $P(H_0 \mid x)$ does not exceed 0.05.

4. Sample Study

A sample study was carried out with the aim of finding out the scenario of HIV/AIDS clinical trials in Bangalore. It was decided to conduct the study taking a sample of size ten hospitals in Bangalore. But data could be collected only from five of them. One representative from each hospital filled in a questionnaire which was framed to find out whether the respective hospitals conducted clinical trials and in particular for HIV. If HIV clinical trials are not conducted, what were the requirements and whether they are intending to do so in future.

67% of the hospitals conduct clinical trials, but none of these hospitals conduct HIV/AIDS clinical trials. Some of the reasons for not conducting HIV clinical trials are lack of trained personnel, Willingness of physicians and support team to work on HIV, Active participation of the patients is required , Social stigma attached to the disease etc.

According to the respondents the *facilities/infrastructure required in order to conduct HIV/AIDS clinical trials* are, consent of a good number of HIV positive patients, adequate laboratory facilities, trained personnel to conduct trials, proper documentation and proper data management, ethical committee approval, financial aid, good counselors, free medicines etc.

50% of the respondent hospitals are ***planning to conduct HIV clinical trials in future.*** The sample study revealed that though clinical trials are being conducted in and around Bangalore, there are yet no trials being conducted specifically for HIV/AIDS due to reasons listed above.

5. Discussion

As far as HIV/AIDS prevalence rate is concerned, India is positioned among the top three affected countries, world wide; yet very little statistical research work has been done in this field, in India. Thus, there is a lot of scope for statistical analysis of clinical trials data pertaining to HIV/AIDS in the Indian context.

When compared to clinical trials for other diseases, less statistical work has been carried out in the case of HIV/AIDS and hence this can be an area of study in the days to come, in view of the seriousness of the problem.

Not much meta-analysis has been done so far. This could be taken up in future.

In this article, an attempt has been made to bring forth the concepts of statistical analysis in the field of HIV/AIDS clinical trials. It enumerates a number of statistical techniques used in this field around the world. Concepts such as meta-analysis, analysis in the case of incomplete data and Bayesian analysis in the context of HIV/AIDS have been covered.

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