DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO
ATTENTION OF

June 8, 1992

Human Use Review and
Regulatory Affairs Office

SUBJECT: IND 16666 - Ribavirin (Virazole)
(Serial No. 011)

Director
Division of Anti-Infective Drug Products (HFD-815)
Center for Drug Evaluation and Research
Office of Drug Review II
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

Enclosed in triplicate is a report entitled "Final Report Analysis of a Clinical Trial Ribavirin and the Treatment of Lassa Fever." The data were collected by the Centers for Disease Control under their IND 17186, however, since the U.S. Army Medical Research and Development Command provided funding for the study, we felt it appropriate to submit the report to our IND 16666.

Please contact (b)(6) if any questions arise concerning this submission.

Sincerely,

(b)(6)

Medical Service Corps
Chief, Human Use Review and
Regulatory Affairs Office

Enclosure

Copy Furnished:

U.S. Army Medical Materiel Development Activity,
ATTN: SGRD-UMP

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATION (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: March 31, 1990.
See OMB Statement on Reverse

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Office of The Surgeon General, Department of the Army

2. DATE OF SUBMISSION
- 8 JUN 1992

3. ADDRESS (Number, Street, City, State and Zip Code)
Commander, U.S. Army Medical Research and Development Command
ATTN: SGRD-HR
Fort Detrick, Frederick, Maryland 21702-5012

4. TELEPHONE NUMBER *(Include Area Code)*
(b)(6)

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Ribavirin (Virazole, 1-B-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide)

6. IND NUMBER *(If previously assigned)*
16,666

7. INDICATION(S) *(Covered by this submission)*
Lassa Fever

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐PHASE 1 ☐PHASE 2 ☒PHASE 3 ☐OTHER_____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

NDA 18,859 [Virazole (ribavirin) lyophilized aerosol administration]
IND 17,111 (ribavirin aerosol)
IND 9,076 (ribavirin oral and injectable)
IND 16,666 (Lassa and Hemorrhagic Fevers)
IND 27,296
IND 17,186 (Centers for Disease Control)
DMF 5,544 (Ribavirin, Eastman Kodak Company)
DMF 6,212 (Carter-Glogau Laboratories, Inc.)

10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

SERIAL NUMBER
0 1 1

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)

☐INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENTS(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐NEW PROTOCOL	☐CHEMISTRY/MICROBIOLOGY	☐INITIAL WRITTEN REPORT
☐CHANGE IN PROTOCOL	☐PHARMACOLOGY/TOXICOLOGY	☐FOLLOW-UP TO A WRITTEN REPORT
☐NEW INVESTIGATOR	☒CLINICAL	

☐RESPONSE TO FDA REQUEST FOR INFORMATION ☐ANNUAL REPORT ☐GENERAL CORRESPONDENCE

☐REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐OTHER_____ (Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW, REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐TREATMENT IND 21 CFR 312.35(b) ☐TREATMENT PROTOCOL 21 CFR 312.85(a) ☐CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:

FORM FDA 1571 (10/89) PREVIOUS EDITION IS OBSOLETE.

12. **CONTENTS OF APPLICATION**

This application contains the following items: ***(check all that apply)***

- ☐ 1. Form FDA 1571 [21 CFR 312.23(a)(1)]
- ☐ 2. Table of contents [21 CFR 312.23(a)(2)]
- ☐ 3. Introductory statement [21 CFR 312.23(a)(3)]
- ☐ 4. General investigational plan [21 CFR 312.23(a)(3)]
- ☐ 5. Investigator's brochure [21 CFR 312.23(a)(5)]
- ☐ 6. Protocol(s) [21 CFR 312.23(a)(6)]
  - ☐ a. Study protocol(s) [21 CFR 312.23(a)(6)]
  - ☐ b. Investigator data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - ☐ c. Facilities data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing and control data [21 CFR 312.23(a)(7)]

  Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]
- ☐ 8. Pharmacology and toxicology data [21 CFR 312.23(a)(8)]
- ☐ 9. Previous human experience [21 CFR 312.23(a)(9)]
- ☒ 10. Additional information [21 CFR 312.23(a)(10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

N/A

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

N/A

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE
(b)(6)	(b)(6)

18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR Fort Detrick, Frederick, MD 21702-5012	(b)(6)	June 4, 1992

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Section 1001.)

DEPARTMENT OF THE ARMY
US ARMY MEDICAL MATERIEL DEVELOPMENT ACTIVITY
FORT DETRICK, FREDERICK, MARYLAND 21702-5009

REPLY TO
ATTENTION OF:

SGRD-UMP (70-1r) 4 June 1992

MEMORANDUM FOR Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, Maryland 21702-5012

SUBJECT: "Final Report Analysis of a Clinical Trial Ribavirin and the Treatment of Lassa Fever," Dated 7 February 1992

1. Reference: Ribavirin IND 16,666

2. Enclosed are four copies of subject report, each attached with the signed FDA Form 1571. One copy is for your files, and three are to be forwarded to the FDA.

3. The subject report was based on data collected by the Centers for Disease Control under their IND #17186. However, since the U.S. Army Medical Research and Development Command funded this study, it would be appropriate to submit the analysis under The Surgeon General's sponsored IND (# 16666) for the same protocol. Therefore, it is recommended that, in your cover letter to the FDA, you state our reasons for submission of subject report.

4. Please provide this office with a copy of your forwarding letter and the FDA's response so that we may keep our record complete.

5. The point of contact is (b)(6), (b)(6).

6. USAMMDA - Developing Quality Medical Products for Soldiers.

FOR THE COMMANDER:

(b)(6)

4 Encls

Project Manager
Pharmaceutical Systems

-8 JUN 92 11 17

RECEIVED
U.S. ARMY MEDICAL DEPT.

FINAL REPORT
ANALYSIS OF A CLINICAL TRIAL
RIBAVIRIN AND THE TREATMENT OF LASSA FEVER

Submitted To

Sherikon, Inc.
92 Thomas Jefferson Drive
Suite 130
Frederick, MD 21702

Under Contract No. DAMD17-89-C-9160

This document was prepared for Birch & Davis Associates, Inc., by David Bodycombe, Task Manager, and Hillard Davis, Analyst.

February 7, 1992

CONTENTS

EXHIBITS

CHAPTER I

INTRODUCTION

CHAPTER I

INTRODUCTION

The clinical efficacy of ribavirin in treating Lassa fever is assessed based upon an analysis of the results of a nearly 15-year clinical trial that was conducted in Sierra Leone (West Africa) by the US Centers for Disease Control (CDC) and the Sierra Leone Ministry of Health. This introduction briefly reviews the epidemiology and clinical characteristics of Lassa fever, provides a brief history of the clinical trial, and offers a rationale for the study. Chapter II provides a discussion of the both the clinical trial methodology and the data analysis plan. Chapter III presents the trial results and study conclusions are stated in Chapter IV.

1. EPIDEMIOLOGY OF LASSA FEVER

Lassa fever is a severe and often fatal viral disease that is endemic to West Africa. It is one of a family of arenaviruses for which rodents represent the primary reservoir and vector of transmission. Unlike other arenaviruses, however, Lassa fever can also be spread from person to person. Infection rates may reach 10 to 20 percent per year, with one in 20 infections requiring hospitalization. Until recently, the prognosis for hospitalized Lassa patients was grim, with a reported 15 to 20 percent case fatality rate in febrile patients.[1,2,3]

2. CLINICAL PROPERTIES AND TREATMENT OF LASSA FEVER

Lassa fever is characterized by high fever and accompanying headache, myalgia, and malaise. In the severest cases, patients may develop hemorrhage and facial edema, ultimately succumbing to irreversible shock. Diagnosis is generally based on isolation of the virus from blood, urine, or throat washings and serologically by IFA titer. Lassa-convalescent plasma has, until recently, been the only method with which to treat the disease, other than symptomatically.

The synthetic nucleoside ribavirin, a guanosine analogue, has been shown to inhibit the replication of both DNA and RNA viruses in vitro, representing a potentially promising treatment alternative.

3. HISTORY OF THE CLINICAL TRIAL

Beginning in 1977, a Lassa fever collaborative study involving researchers from the CDC and the Sierra Leone Ministry of Health was conducted in rural Sierra Leone, West Africa. The fundamental objective of the study was to determine which subgroups of patients treated with ribavirin have the best outcome (survival rate). Since its initiation, the study has engaged the participation of more than 2,000 subjects. Patient recruitment will continue until the drug is exhausted.

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[1] Joseph B. McCormick, et al., "A Case-Control Study of the Clinical Diagnosis and Course of Lassa Fever," *The Journal of Infectious Diseases*, 155(1987):445.

[2] Abram S. Benenson, ed., *Control of Communicable Disease in Man*, American Public Health Association, (1985):201.

[3] Joseph B. McCormick, et al., "Lassa Fever: Effective Therapy with Ribavirin," *The New England Journal of Medicine*, 314(January 1986):20-26.

4. REASON FOR THE CURRENT STUDY

Preliminary results presented by McCormick, et al.[4] covered only part of the total span of data collection for this clinical trial. The purpose of the present effort is to extend this initial work on the clinical efficacy of ribavirin to cover the period of data collection through 1991. The study addresses five key questions:

- Is the drug correlated with a beneficial outcome?
- Has the drug non-beneficial effects on non-disease conditions?
- Are there any other relevant statistics to strengthen the case of the drug application?
- Are there differences within/between the nine different treatments?
- Are there any correlations of the drug with concomitantly used drugs?

The preparation and analysis of the clinical trial data were undertaken as a joint effort by Sherikon, Inc. of Frederick, Maryland, and by Birch & Davis Associates, Inc., of Silver Spring, Maryland, through a contract with the United States Army Medical Materiel Development Activity, Fort Detrick, Maryland.

[4] Ibid., p. 445.

CHAPTER II

METHODOLOGY

CHAPTER II

METHODOLOGY

The analytic approach to this study has been adapted from the FDA publication *Guidelines for the Format and Content of the Clinical and Statistical Sections of New Drug Applications*. The present effort is confined to the preparation and analysis of precollected data and is not intended to completely fulfill the requirements of a formal clinical trial.

The remainder of this chapter briefly reviews the field data collection methodology and the development of the study data file, including a description of the data elements and data cleaning and verification procedures; a discussion of the analytical objectives; and an overview of the analytical approach.

1. DESCRIPTION OF THE CLINICAL TRIAL METHODOLOGY

Although a written protocol was not available for planning the data analysis, the study methodology has been previously described.[1,2] To maintain the integrity of the present document, a synthesis of these prior reports is provided in this section.

The efficacy of ribavirin and convalescent plasma were assessed longitudinally among hospitalized patients in rural Sierra Leone. The study was hampered by problems common to medical care in less developed regions, including the limited availability of trained medical staff, drugs, equipment (including laboratory), and water and electricity. The absence of adequate roads as well as the high cost of petroleum made transportation of laboratory specimens and supplies difficult, particularly during the rainy season. While serologic studies of Lassa fever and certain basic clinical laboratory tests could be conducted onsite, virus isolation and more complex assays were carried out at the maximum-containment clinical laboratory at the CDC in Atlanta.

Potentially eligible study patients included hospitalized adults with a febrile illness (oral or axillary temperature $\geq 38°C$). Adults in this case represented anyone older than 14 years of age. Approximately 8.2 percent of study patients were determined not to be adults--most enlisted during the last five years of data collection. Given the limited number of available beds, admissions were typically those who appeared most severely ill to the admitting physician regardless of presumptive diagnosis. Admitted eligible patients were questioned and examined by Lassa Fever Project staff. Blood and urine specimens were collected every two to four days for analysis.

Cases were defined to be those patients meeting one or more of the following criteria:

- Isolation of the Lassa virus from serum or other body fluid or organ
- Seroconversion to Lassa virus as measured by immunofluorescent-antibody (IFA) test with antibody titers rising from $< 1:4$ to $\geq 1:16$

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[1] Joseph B. McCormick, et al., op. cit., p. 20.

[2] Joseph B. McCormick, et al., "A Case-Control Study of the Clinical Diagnosis and Course of Lassa Fever," *The Journal of Infectious Diseases* 155(March 1987):445-455.

- An IgG titer (by IFA) ≥ 1:256 on admission and a Lassa antigen-specific IgM titer (by IFA) ≥ 1:4

As the trial progressed, it became clear that patient survival was related to their serum aspartate aminotransferase (AST) level and to viremia. Consequently, at one point a more restricted group of patients was studied consisting of those that met the prior criteria and had an admission AST level of ≥ 150 international units (IU). Cases were randomly assigned to treatment groups. Controls consisted of febrile adult medical patients who may have had IgG antibody but otherwise failed to meet the criteria listed above.

The types of treatments that were employed also changed over time. This analysis covers the following range of treatments:

- Treatment 1--No treatment
- Treatment 2--IV Ribavirin followed by oral dose
- Treatment 3--Ribavirin + plasma
- Treatment 4--Plasma alone
- Treatment 5--Ribavirin 25-30mg loading dose
- Treatment 6--Ribavirin 34mg loading dose
- Treatment 7--Ribavirin 33mg loading dose followed by ¼ dose
- Treatment 8--Ribavirin 17mg loading dose followed by ⅛ dose
- Treatment 9--Ribavirin + prostacyclin
- Treatment 10--Patients for which no drugs were available

Some of these treatments were started and not completed either because the drug was not available or for other reasons.

2. DATA FILE DEVELOPMENT

The data available to the analysis team consisted of a FoxPro database on 2,154 eligible admissions as well as copies of the original data collection forms that included marginal notes. A complete data dictionary is provided in Appendix A.

2.1 Types Of Data That Were Included In The Study Database

Four major types of data were collected: (1) demographic, (2) clinical, (3) laboratory, and (4) outcome. Key data items are as follows:

- Demographic--Major demographic variables included age, gender, and patient's weight at time of admission. Age could be an important predictor variable, with younger Lassa fever patients potentially experiencing a less severe form of the disease than adults.[3]

- Clinical--Pregnancy status, treatment regimen, days between onset and admission, days between admission and treatment, and days between onset and discharge were among the major clinical data items collected. It is thought that pregnant women often experience a more severe case of the disease.[4] The effect of inducing labor in pregnant Lassa fever patients is thought to affect outcome by increasing the survival of the mother. Also, it is thought that patients receiving treatment earlier in the course of the disease have a better chance of survival than those who receive the treatment later.[5] Both of these issues were addressed in the data analysis.

- Laboratory--Immunofluorescent-antibody (IFA); serum aspartate aminotransferase (AST or SGOT); and hematocrit at admission, during the hospital stay, and at discharge were among laboratory tests that were regularly reported. Viremia was also assessed but on a less regular basis. Viremia and IFA were measures that were used to diagnose a Lassa case, and SGOT and viremia were used to measure the severity of the case. A small number of IgM, IgG, and liver touch prep (conducted at autopsy) specimens were also collected; these aided in the diagnosis of Lassa fever cases.

- Outcome--The measure used for outcome was survival, i.e., discharged alive or dead. The code "discharged against medical advice" was included in the database and could have affected the determination of outcome; however, this code occurred for only seven patients.

[3] T. P. Monath. "Lassa Fever: Review of Epidemiology and Epizootiology," *Bulletin of the World Health Organization* 52(1975): 577-592.

[4] Karl M. Johnson, "Lymphocytic Choriomeningitis Virus, Lassa Virus (Lassa Fever), and Other Arenaviruses," In: Gerald L. Mandell, R. Gordon Douglas, Jr.; John E. Bennett (eds.) *Principals and Practice of Infectious Diseases, Third Edition*. (Churchill-Livingston, 1990):1329-1336.

[5] Joseph B. McCormick, et al., op. cit., p. 20.

2.2 Data Verification

An extensive data verification effort preceded the data analysis. Corrections covered the following:

- Logical errors and inconsistencies between fields
- Entering missing data

Handwritten marginal clinical notes from the patient data sheets or their audits were used when feasible to complete missing fields or to verify the recorded data. Exhibit II-1 shows the percentage of key data elements that were verified through the use of additional supporting information.

Duplicate records were purged from the database. The computerized record was verified against the original record and corrected where necessary. Nearly 1,000 new records were entered into the database and verified. After all the data entry had been completed, it became evident that a large amount of information was still missing. At the request of the Government, all records were reexamined and relevant information from the handwritten marginal notes of the medical staff and the study team were added to the computerized record. Two additional relational databases were developed from the existing database, one for diagnosis and one for treatment. The final database contained records on 2,154 patients.

Exploratory data analysis[6] was conducted to facilitate the identification and removal of outliers. Outliers fell outside of the specified boundaries that are termed "fences" in exploratory data analysis. The boundaries of these fences are defined as follows:

lower fence = lower hinge - (1.5*Hspread)
upper fence = upper hinge + (1.5*Hspread)

where the hinges mark the 25 percent and 75 percent quartiles and the Hspread represents the range between these two points.

If a value was identified as an outlier, it was coded as missing.

As a further refinement, durations between disease onset and admission as well as between admission and treatment were limited to 90 days; and admission SGOTs that exceeded 29,999 were set to missing even though they were not identified as outliers.

2.3 Additional Data Fields

In addition to serving as a source of information for verifying the data that were coded on the patient data sheets, handwritten notes were also used as the source of additional supplementary fields that were available for analysis. These additional fields are listed in Appendix B.

[6] J. W. Tukey, *Exploratory Data Analysis*, Addison-Wesley (1977):1.

3. DATA ANALYSIS PLAN OVERVIEW

The analysis plan for this study is provided as Appendix C. While the approach specified in the plan was followed closely, it was necessary to make some modifications to reflect attributes of the actual data. These analytical modifications are as follows:

- Identification of cases--There were numerous instances (210 cases) where a Lassa fever diagnosis was either not made or included in the database. It was possible to establish the diagnosis in some of these cases through other means. A Lassa fever case was confirmed if it had any of the following traits:

  - The CDC confirmed that the patient had Lassa fever

  - The patient had an IFA reading of 30 or more; or had a positive viremia, IgG, IgM; or had a positive liver touch prep.

  Thus, out of 2,154 patients in the final data set, 1,853 were classified as having Lassa fever and 153 as not having Lassa fever; the rest had an unknown disease status. The assessment of treatment effects was confined to only those patients classified as having Lassa fever.

- Determination of illness severity--Since patients with high levels of SGOT are known to have higher case fatality rates than those with lower SGOTs[7], SGOT levels (< 150 and ≥ 150) were used to stratify patients for the analysis. If a group had a greater proportion of patients in the higher SGOT stratum, then such a group would be expected to have a less favorable result regardless of the treatment. Thus, all results are reported separately for the less severely ill ($<$ 150 SGOT) versus the more severely ill ($\geq$ 150 SGOT) patient groups. Given the importance of this variable, it should be noted that admission SGOT was missing in one-third of all patient records.

The remainder of the discussion considers other aspects of the analysis, such as the selection of study variables, the analytical techniques employed, the use of adjustment factors and controls, and the potential limitations of the analytical approach.

3.1 Selection Of Variables

A subset of those variables that are most likely to affect clinical outcomes was selected from among all available variables. These variables were:

- Patient age
- Patient sex
- Patient weight
- Pregnancy status

[7] Joseph B. McCormick, et al., "Lassa Fever: Effective Therapy with Ribavirin," op. cit., p. 23.

- Days between disease onset and admission
- Days between admission and treatment
- Days between onset and discharge
- Lassa fever diagnosis
- Treatment administered
- Admission SGOT
- Admission viremia
- Admission hematocrit
- Survival status

3.2 Analytical Techniques

Frequency distributions and cross-tabulations were employed to describe the patient population in terms of demographics, clinical status, and survival. X^2 tests of independence were conducted to determine if the treatment groups differed significantly in terms of such key characteristics as age, gender, patient weight, and laboratory values. Statistically significant associations suggested the need to impose control for these variables in the assessment of treatment efficacy. For example, if younger patients had a higher survival rate than older ones, the treatment group with an excess of younger patients would be expected to have a better outcome, in spite of treatment efficacy. X^2 tests were also used to distinguish between multiple treatment groups.

While X^2 tests are useful for demonstrating association, they tell nothing about the strength of these relationships. The strength of the relationships between continuous study variables was assessed through examination of the correlation matrix. Where high correlations exist ($\geq .8$), one of the pair could potentially be eliminated and, thus, simplify the analysis.

3.3 Use Of Adjustment Factors And Controls

The Analysis Plan specifies that a proportional weighting scheme would be used to adjust the data based on the distribution of verified data elements. This would occur whenever high error rates could introduce the potential for bias. Unfortunately, while it was possible to determine where verification had introduced changes, it was not possible to accurately characterize the nature of these changes and, thus, to devise proportional weights. Where the potential for bias exists, an effort was made to determine its overall impact on the findings.

The literature suggests that such factors as age, pregnancy status, and certain immunologic values could affect outcome. The descriptive component of the analysis explored a range of variables for their potential effects. Where potential effects were noted, we established statistical controls. For example, since we used SGOT as a measure of the severity of the disease, results were reported for those with SGOTs less than 150 and SGOTs greater than 150.

Since multiple prognostic variables could affect treatment outcomes, methods suitable for the simultaneous control of multiple variables were employed. Multiple logistic regression proved to be a superior statistical tool in this process since the dependent variable, survival, is dichotomous rather than continuous. The logistic model is as follows:

$$\log\left(\frac{p}{1-p}\right) = c_0 + c_1x_1 + c_2x_2 + \ldots + c_{m_n}$$

where p represents the probability of survival (the log odds of surviving), c_0 through c_n represent logistic coefficients, and x_1 through x_n represent prognostic variables. A positive logistic coefficient for treatment would suggest that the probability of surviving on treatment would be greater than remaining untreated. Further, the exponential function of the logistic coefficients can also be used as an indicator of relative risk, the odds of surviving after controlling for other prognostic factors.

3.4 Potential Limitations Of This Approach

The quality of the data represent the principal study limitation. Examination of the data shows frequent missing and outlier values for some of the data items. For example, more than half of the patient weight values were missing. The numbers of missing values are documented in the presentation of results.

Noncompliance with the drug regimen poses an important complicating factor. Noncompliance reflects the inability of staff to correctly follow the prescribed treatment regimen and/or the patient's failure to adhere to this regimen. Possible reasons for noncompliance include withdrawal and failure to complete the required drug dosage. The status of withdrawals from the trial is summarized in the adjacent text box. For a large number of patients, the withdrawal status could not be determined. Characteristics of the 34 noncompliant patients who died are listed in Appendix D along with all other patients who died. Of 807 Lassa patients with a known outcome in a drug treatment group, 11 percent missed doses and 8 percent missed consecutive doses. In addressing these regimen failures, we chose the "pragmatic" approach that was suggested by Pocock[8]:

WITHDRAWAL STATUS	
DIED	34
LACK OF RIBAVIRIN	12
NOT LASSA	8
OTHER	19
UNKNOWN	15
TOTAL DISCONTINUED	88
TOTAL CONTINUED	446
TOTAL UNKNOWN	1,620
GRAND TOTAL	2,154

> ... all eligible patients, regardless of compliance with protocol should be included in the analysis of results whenever possible

This approach is referred to as "analysis by intention to treat."

[8]Stuart J. Pocock, *Clinical Trials: A Practical Approach*, John Wiley & Sons(1983):182.

Another concern is how patients were assigned to treatment groups. It appears that those patients judged to be the most severely ill on admission were more likely to be treated and to be given higher doses. The effect of this treatment bias would be a higher case-fatality rate for the treatment group in spite of the possible efficacy of the treatment.

The available numbers of observations also proved to be a limiting factor in the assessment of treatments other than groups I (no treatment) and II (ribavirin only). Generally, in X^2 testing, no expected cell values should be less than 1 and no more than 20 percent should be less than 5.[9] Where the observed frequencies were too small for the sampling distribution of the X^2 distribution to be approximated, it was, in some cases, possible to substitute the Fisher's exact test. In other cases, especially when the numbers of subgroups were large and cell frequencies small, analysis was not possible. The following two treatments that included only two patients each were excluded from consideration entirely: (1) intravenous ribavirin followed by oral ribavirin and (2) oral ribavirin followed by intravenous ribavirin.

Finally, the confirmation of the diagnosis of Lassa fever was not instantaneous. Some patients died before such a final assessment could be made. This introduced additional possibilities for bias. It was, however, possible to reclassify some cases based upon post admission positive viremias and IFA titers as well as through liver touch preps that were conducted on autopsies. Using this approach, 22 patients were converted from the non-Lassa fever to the Lassa fever category.

[9] W. G. Cochran, "Some Methods of Strengthening the Common X^2 Tests," *Biometrics*, 10(1954):417-451.

EXHIBIT II-8

VALIDATION OF DATA ITEMS

DATA ITEM	PERCENT VALIDATED
AGE OF PATIENT	46.8
PATIENT WEIGHT	30.8
DATE OF ONSET OF DISEASE	59.9
DATE OF ADMISSION TO HOSPITAL	68.5
DATE OF DISCHARGE FROM HOSPITAL	68.0
DISEASE DIAGNOSIS	33.9
TREATMENT ADMINISTERED	55.0
ADMISSION SGOT	60.3
ADMISSION VIREMIA	0.6
ADMISSION HEMATOCRIT	64.7

CHAPTER III

FINDINGS

CHAPTER III

FINDINGS

The results of this study are presented in two sections. The first section gives a description of the study population in terms of demographics, clinical indicators, laboratory values and outcomes. The second presents results regarding the efficacy of the treatments.

1. DESCRIPTIVE ANALYSES

Descriptive data pertinent to patient demographics, clinical indicators, laboratory values, and outcomes are shown in Exhibit III-1. Data are arrayed according to treatment status (treated/untreated), disease status (diseased/nondiseased), and treatment group. Exhibit III-2 shows data for the same variables arrayed by specific treatments.

1.1 DEMOGRAPHIC AND CLINICAL PROPERTIES OF THE DATA

The characteristics of the patient population were considered in terms of age, sex, body weight, pregnancy status, interval in days between onset of disease and hospital admission, interval in days between admission and treatment, interval in days between onset and discharge, maximum IFA, admission SGOT, admission viremia, and admission hematocrit. Differences between specific treatment groups were also determined with respect to demographic and clinical characteristics. Discussions appropriate to each of these variables follow.

- Age--Over 40 percent of all patients were in the 20-29 age group. The less than 15 year old group (children) comprised approximately eight percent of the total. The age distribution is similar for diseased, non-diseased, treated and untreated patients. There were, however, proportionately nearly twice as many children in the non-diseased patient group and half as many in the treated patient group. The data were relatively complete, with most ages known for the population. A much larger proportion of children were represented in treatment group V and, to a lesser extent, in treatment groups VII and X.

- Gender--Females represent approximately 54 percent of the total patient population compared to 46 percent males. A slightly wider disparity existed between the males and females (58 versus 42 percent) among the treated patients. Males were a majority in treatment groups II, VII, VIII, IX, and X

- Body weight--Approximately one-half of the patients had body weights between 50 and 69 kilograms. Since body weight is usually a function of age, i.e., older people are taller and are usually heavier than their younger counterparts, this measure is probably strongly correlated with age. A better prognostic indicator of body weight would associate it with height. However, height was not collected. Also, body weight was reported for only about 25 percent of the patients. Although included in our analyses, the body weight variable should be interpreted cautiously.

- **Pregnancy status**--Among all females between the ages of 15 and 44 years, 11.3 percent were pregnant. The non-diseased patient group included proportionately twice as many pregnant females. In the treated population these differences were even greater--20.6 were pregnant, compared to 4.0 percent in the untreated population. Among treatment groups, most of the pregnant women were given treatments IV, VI and IX. A higher proportion of pregnant patients could have important implications for treatment efficacy since it is believed that pregnant women are particularly susceptible to high case fatality rates if labor is not induced.

- **Days between onset and admission**--The mean time between the onset of Lassa fever and admission into the hospital was 7.1 days, with a minimum of zero days and a maximum of 79 days. The reliability of this measure is unknown since it was based on a clinical history which is dependent on the patient or some other person's recollection of events. There is no statistical basis for distinguishing between the treatment status groups or disease status groups in terms of this variable.

- **Days between admission and treatment**--The average number of days between admission and treatment was 1.5 days for all patients and similar for both the disease status and treatment status groups. Treatment occurs fairly quickly with approximately 49 percent of patients receiving treatment on the day they were admitted and 71 percent treated in less than two days.

- **Days between onset and discharge**--The number of days between onset and discharge was a measure of the severity of the case and the concomitant convalescent time. The exceptions to this were those patients who died before discharge and those who left the hospital against medical advice. Overall, the average time period between onset and discharge was 17.8 days. There was little to distinguish between groups in terms of disease or treatment status with respect to this variable. There were differences in time period between the treatment groups, with IX showing the highest percentage discharged in less than 10 days (35.3 percent). Treatment group III had by far the fewest short duration stays, with less than three percent in this category. Treatment group III showed the highest percentage discharged after 20 or more days (54 percent) while treatment group VIII had proportionately the fewest patients in this category (12.5 percent). A short time interval does not necessarily reflect treatment efficacy--treatment group IX also had the highest case fatality rate (82.4 percent).

- **Maximum immunofluorescent antibody (IFA)**--IFAs were used as a diagnostic tool to measure the level of antibodies to Lassa fever. Among the treated patients, 30.1 percent had a coded score of less than 30 which indicated levels not high enough to use this measure alone as a basis for diagnosis. Among untreated patients, the comparable figure was 5.7 percent.

- **Admission SGOT**--Admission SGOTs, a measure of disease severity, varied widely between treated and untreated groups generally as well as among specific treatment groups. As noted in Chapter II, SGOTs of 150 or more are believed to be indicative of greater illness severity. The mean value for the admission SGOT, 737.6, would suggest that many patients were severely ill. However, the data are highly skewed with 50 percent of the study patients having SGOTs of 150 or less. The mean has been skewed strongly to higher values due to a large number of SGOTs greater than 10,000. Among the treated patient group, 65.6 percent had an SGOT of 150 or more compared to 22.5 percent of the untreated group. Among the specific treatment groups, the percent of patients with readings less than 150 varied between 84.3 percent (for

controls) and 0 percent. Given the observed differences in severity between treatment groups, SGOT levels should be controlled when making comparisons.

Exhibit III-3 describes differences between high and low admission SGOT patient groups in terms of selected patient characteristics. What should be immediately clear from this table is that admission SGOT is missing for approximately one-third of all patients. Given that the unknowns have a distinct profile in terms of the selected variables, they seriously impugn findings that can be drawn from the data. Ostensibly, the high SGOT group is somewhat more likely to be:

- Male
- Pregnant if female
- Treated more quickly once admitted

- **Admission viremia**--A positive viremia is a strong indicator of whether or not the patient has Lassa fever. The higher the value, the more likely a person will have the disease. Of all the patients for whom specimens were collected and assessed, 14.1 percent had levels between 3 and 19. Among untreated patients, 32.9 percent had readings between 3 and 19 and 62.9 percent had readings greater than 19. This compares to 7.2 percent of the treated patients with readings between 3 and 19 and 91.4 percent with readings greater than 19. This evidence suggests that the disease was less severe in the untreated cases. Unfortunately, less than 14 percent (n=298) of the patients were given this laboratory test.

- **Admission hematocrit**--Admission hematocrits were completed on 69.3 percent of the patients. The average hematocrit for all patients was 36.9. Among treated patients the average was 37.0 compared to 36.6 for the untreated patients. The majority of patients in all treatment groups had a reading of 30 or more. There is no firm basis for distinguishing between patient groups with respect to hematocrit.

1.2 OUTCOME ASSESSMENT

Treatment outcome was measured in terms of survivorship. Several aspects of treatment outcome were explored: (1) the effect of year recruited into the study, (2) association with prognostic variables, (3) the effect of pregnancy, (4) treatment compliance, and (5) concomitant medications. Each of these topics is discussed separately below.

- **The effect of time on outcome**--As noted in the introduction, this study covers patient recruitment between 1977 and 1991. To determine if trends existed among the total, treated, and untreated patients, the case fatality rate was arrayed by year recruited into the study (Exhibit III-4). Case fatality rates varied widely from year to year. The greatest case fatality rates occurred, especially among the treated group, during the latter years of the study. Whether this is because patients with a more virulent strain of Lassa fever were being treated at different times or whether some other factor was operative cannot be determined from the data. However, the SGOT level of patients in the later study years was higher among the treated patients than during the earlier years.

- **Correlations between variables**--To examine the relationship between demographic, clinical, laboratory and outcome variables, a Pearson correlation coefficient matrix was computed (see Exhibit III-5). The Pearson correlation coefficient measures the linear relationship between two measures. Positive correlations indicate a positive association between the two measures, i.e., if one measure is high the other is likely also to be high.

  Of the variables arrayed in the matrix, survival relates most strongly to admission SGOT, viremia, interval in days between onset and discharge, patient weight, pregnancy status, and date of admission. It does not apparently relate to age, gender, days between onset to admission, or days between admission to treatment. This suggests which variables are important to control for when assessing treatment effects. If a correlation is statistically significant it is indicated by asterisks in the exhibit. These results have face validity since high viremias and high SGOTs are expected to be associated with poor outcomes and higher lengths of stay may reflect the fact that the patient has survived to be discharged alive. The positive association between pregnancy and survival is somewhat perplexing since the literature suggests the opposite. This issue is further discussed below.

- **The effects of pregnancy and induced labor on outcome**--Pregnancy is considered a high risk factor for women with Lassa fever. Women with Lassa fever who have induced labor are thought to have a greater survival rate than those who do not. Exhibit III-6 shows how the 82 pregnant women who were actually diagnosed as having Lassa fever were distributed among the treatment groups along with their case fatality rates.

  Pregnant women were assigned to all treatment groups except groups V and VIII. The untreated group had a case fatality rate of 21.1 percent, a significantly ($p < 0.05$) lower rate than the combined treatment groups. Arguably, as prior findings suggest, the untreated women could be less severely ill. However, when the level of disease severity is controlled, pregnant women continue to experience a relative risk of dying that is approximately twice that of their nonpregnant peers.

  Analysis of induced labor and survival status by severity of disease did not yield sufficient observations for untreated women who sought induced labor ($n = 2$). Similarly, only two women in the lowest severity group of treated patients had induced labor. Among the 24 treated women in the highest severity group who had induced labor, the case fatality was 41.7 percent, a rate nearly identical to that experienced by all pregnant women in the highest severity category (42.6 percent). This evidence suggests that induced labor may be of limited therapeutic value.

- **The effects of compliance on outcome**--The effects of protocol compliance on outcome were difficult to measure since this information was not reported for most of the cases. As noted earlier, only 88 out of the 2,154 cases had this information. For some patients, missed doses and consecutively missed doses were known, but the reason for missing the dose was not given. Given the paucity of available data, we have chosen to exclude this variable from further analysis.

- **The effect of concomitantly used drugs on outcome**--Information on other drugs used was limited. Although 650 out of the 2,154 patients were indicated to have taken concomitant medications during their participation in the study, an accounting of the types and number of

doses could not be achieved. For this reason, we have chosen to not consider concomitant drug use further in this analysis.

2. TREATMENT EFFICACY AND POTENTIALLY ADVERSE EFFECTS

The following discussion is organized into two sections. The first addresses the efficacy of treatments in diseased patients. The second section considers the effects of treatment on patients who may not have had Lassa fever but who were treated anyway.

2.1 Efficacy Of Treatment

The effectiveness of the eight drug treatment groups are compared to the pooled control groups in Exhibit III-7. The percentage of survivors for all treatment groups is less than for controls, reaching statistical significance for treatment groups II (ribavirin only) and IV (plasma only). When the p-values are adjusted for multiple testing by multiplying them by the number of tests conducted (e.g., eight), only treatment group II remains marginally significant.

These results would suggest that treatment is at best ineffective. However, prior evidence indicates that the treated and untreated patient groups differed in terms of disease severity as measured by the admitting SGOT. The treated group were more severely ill and, thus, they would be at a disadvantage in terms of survival. Thus, a meaningful assessment of treatment efficacy should control for admitting SGOT.

Exhibit III-8 shows the result of comparing each of the treatment groups with the untreated groups while controlling for SGOT levels. Results for groups with fewer than 20 observations should be interpreted with caution. Significant results are indicated in the table.

For the most severely ill patients with SGOTs greater or equal to 150, only the case fatality rate for treatment group II was significantly lower (when corrected for multiple testing) than for the untreated patients (treatment group I). This finding reverses those reported above for data where the effects of severity were not controlled. For all treated patients in the most severely ill category, the relative risk of dying was 0.6 times that of untreated patients (difference significant at the 0.01 level). For patients with SGOTs less than 150 the converse was true, with the treated patients showing a relative risk of dying that was 2.8 times that of the untreated patients. This finding would suggest that treatment is most appropriate in more severely ill patients. The severity threshold for effective treatment needs to be better established through further research. Also, the effects of additional factors that might affect outcome must be considered.

In the absence of carefully matched treatment and control groups it was necessary to establish statistical controls for differences in key prognostic indicators such as SGOT. A logistic regression was employed to establish statistical controls. The independent variables employed in the logistic regression model were as follows:

- Age
- Gender
- Time interval between disease onset and admission to the hospital
- Time interval between admission to the hospital and receipt of treatment

- Time interval between onset and discharge from the hospital
- Admission SGOT
- Treatment status

Other variables that might have been used as prognostic variables (viremia, body weight, etc.) had too many missing values to contribute meaningfully and were not used. For this analysis, given the small numbers of observations for other treatment groups, treatment status was handled as a dichotomous variable. Treatment was represented by those treatment groups that yielded the lowest case fatality rates with respect to untreated patients in the high severity patient illness category. These treatments were:

- Treatment II--Ribavirin only
- Treatment III--Ribavirin plus plasma
- Treatment V--Ribavirin 25 to 30mg loading dose
- Treatment VII--Ribavirin 33mg loading dose followed by ¼ dose

The untreated controls were represented by treatment groups I and X.

The results of the logistic modeling effort are summarized in Exhibit III-9. The model permits determination of the effect of treatment after controlling for the prognostic variables. It also permits the quantification of the separate impacts of each variable. The model shows that four logistic coefficients were significant. In two instances the coefficients were negative, meaning that the probability of survival is smaller. For the other two, the opposite was true. The findings are consistent with those reported earlier:

- Treatment is associated with survival
- Longer lengths of stay are associated with survival
- Longer intervals between disease onset and admission are associated with death
- Higher SGOTs are associated with death

Exhibit III-9 also displays the relative risks associated with the prognostic variables. As is clear from this exhibit, the treatment effects of ribavirin appear modest, yielding an increased chance of survival that is only approximately 1.1 times that of untreated patients. Conversely, a relatively high admission SGOT is associated with an odds of surviving that is 61 percent lower than for patients with relatively low SGOTs. A further logistic model was run using a dichotomous variable that replaced SGOT and used the 150 breakpoint for distinguishing between low and high severity. The efficacy of the breakpoint was not established since this variable failed to achieve significance.

2.2 Treatment Effects On Non-Diseased Patients

A total of 149 patients were recruited into the study but were eventually coded as not having Lassa fever. While some, no doubt, represent individuals who were diagnosed in error, others may have had Lassa fever but died or were discharged before a definitive diagnosis could be made.

Exhibit III-10 presents comparative case fatality rates for patients in treated and untreated groups as well as in the two severity of illness groups that were based upon admission SGOT levels. Given the small numbers of observations associated with some treatments, treatment was converted into a dichotomous variable where the treated groups represent all of the treatment categories that yielded the greatest improvement in the previous section (treatments II, III, V, and VII). The non-diseased patients who were treated had a case fatality rate that was nearly four times that of their untreated peers. For diseased patients, these rates were much more similar. However, the case fatality rate was very high among non-diseased patients in the highest severity category--offering support to the hypothesis that non-diseased patients die before a definitive diagnosis can be made. Presumably, if this is true then non-diseased patients should also show shorter lengths of stay. However, when the average interval between onset and discharge of the diseased and non-diseased patient categories was assessed, it was not possible to reject the null hypothesis that the two periods were identical (18.3 versus 19.4 days, respectively). While it is impossible to make definitive statements about the toxic properties of ribavirin from these data, these potentially adverse findings suggest that more careful study is warranted.

EXHIBIT III-1

PERCENTAGE DISTRIBUTION[1] OF PATIENTS BY SELECTED CHARACTERISTICS AND BY PATIENT TYPE

PATIENT CHARACTERISTICS	TYPE PATIENT						
	All Patients	Disease Status			Treatment Status		
		Diseased	Non-Diseased	Unknown	Treated	Not-Treated	Unknown
	(n=2,154)	(n=1,853)	(n=153)	(n=148)	(n=1,020)	(n=1,043)	(n=91)
Age (Years)							
<5	1.5	1.2	4.3	3.8	0.3	2.8	0.0
5-9	3.2	2.7	7.2	7.5	1.0	5.5	2.6
10-14	3.5	3.2	4.3	7.5	2.7	4.4	0.0
15-19	11.4	11.4	12.9	10.0	10.8	11.9	15.8
20-29	41.8	42.3	40.3	32.5	45.3	38.5	34.2
30-39	23.2	23.9	15.1	21.3	25.2	21.1	21.1
40+	15.5	15.4	15.8	17.5	14.8	15.8	26.3
(Unknown)	(133)	(51)	(14)	(68)	(31)	(49)	(53)
Gender							
Male	46.0	45.6	56.4	40.3	42.4	50.3	39.2
Female	54.0	54.4	43.6	59.7	57.6	49.7	60.8
(Unknown)	(32)	(14)	(4)	(14)	(0)	(15)	(17)
Body Weight (Kgs)							
<10	4.7	3.9	9.0	5.0	14.3	4.5	-
10-29	12.2	11.3	17.9	11.7	14.3	12.2	-
30-49	30.3	30.3	26.9	35.0	14.3	30.5	-
50-69	49.6	51.8	43.6	40.0	57.1	49.5	-
70+	3.2	2.7	2.6	8.3	0.0	3.2	-
(Unknown)	(1,531)	(1,368)	(75)	(88)	(1036)	(404)	(91)
Pregnancy Status[2]							
Pregnant	11.3	10.0	20.0	30.3	20.6	4.0	20.0
Not Pregnant	88.7	90.0	80.0	69.7	79.4	96.0	80.0
(Unknown)	(4)	(2)	(0)	(2)	(2)	(0)	(2)
Mean Age ± SEM[3]	28.1 ±0.26	28.3 ±0.27	25.8 ±1.11	26.0±1.38	27.2 ±0.41	28.8 ±0.33	30.2±1.84
Minimum Age	1	1	1	1	1	1	8
Maximum Age	99	99	60	60	90	99	54
Mean Body Weight ± SEM[3]	44.9 ±0.66	45.4 ±0.72	41.4 ±2.11	45.0±2.37	44.9 ±0.66	42.3 ±7.73	-
Minimum Body Weight	3	3	3	5	3	4	-
Maximum Body Weight	86	76	70	86	86	60	91

[1] Percentages are based only upon known values and may not sum to 100 due to rounding.

[2] Based upon 926 observations for women aged 15 to 44 years of age of whom 104 were pregnant.

[3] Standard error of the mean.

EXHIBIT III-1

PERCENTAGE OF DISTRIBUTION[1] OF PATIENT BY SELECTED CHARACTERISTICS AND BY PATIENT TYPE

PATIENT CHARACTERISTICS	TYPE PATIENT						
	All Patients	Disease Status			Treatment Status		
		Diseased	Non-Diseased	Unknown	Treated	Not-Treated	Unknown
	(n=2,154)	(n=1,853)	(n=153)	(n=148)	(n=1,020)	(n=1,043)	(n=91)
Days between onset and admission							
0	1.1	1.2	0.7	0.7	0.7	1.7	0.0
1-4	33.4	33.8	32.4	29.2	27.0	39.4	36.1
5-9	43.7	43.1	46.2	48.9	47.9	40.2	33.3
10-14	16.1	16.1	13.1	19.0	18.4	13.2	23.6
15+	5.8	5.9	7.6	2.2	6.0	5.5	6.9
(Unknown)	(51)	(32)	(8)	(11)	(16)	(16)	(19)
Days between admission and treatment							
0	49.3	50.8	48.8	19.6	49.4	25.0	60.0
1	21.8	22.1	17.9	12.2	21.7	50.0	20.0
2	12.1	10.7	15.5	10.1	12.2	25.0	0.0
3	6.4	5.8	8.3	4.7	6.5	0.0	0.0
4+	10.3	10.6	9.5	4.7	10.3	0.0	20.0
(Unknown)	(1,388)	(1,247)	(69)	(72)	(263)	(1,039)	(86)
Days between onset and discharge							
<5	2.1	2.1	1.4	2.7	1.7	2.5	2.8
5-9	11.9	11.7	11.2	13.5	9.0	14.7	11.1
10-14	25.0	25.3	28.0	17.6	19.6	30.6	22.2
15-19	28.9	28.2	35.0	29.1	34.7	23.0	30.6
20-29	24.6	25.0	17.5	25.0	27.4	21.8	25.0
30+	7.5	7.7	7.0	5.4	7.6	7.3	8.3
(Unknown)	(54)	(33)	(10)	(11)	(18)	(17)	(19)
Diagnosis							
Lassa Fever	92.4				97.8	87.4	25.0
Not Lassa Fever	7.6				2.2	12.6	75.0
(Unknown)	(148)				(18)	(87)	(43)
Outcome							
Died	18.0	18.1	16.8	34.3	23.1	14.8	23.8
Survived	82.0	81.9	83.2	65.7	76.9	85.2	76.3
(Unknown)	(35)	(26)	(4)	(5)	(12)	(12)	(11)
Mean Onset-to-Admission ± SEM[2]	7.1±0.13	7.1±0.14	7.3±0.41	7.2±0.60	7.1±0.14	7.3±0.41	7.2±0.60
Minimum Onset-to-Admission	0	0	0	0	0	0	2
Maximum Onset-to-Admission	79	79	31	77	79	31	77
Mean Admission-to-Treatment ± SEM[2]	1.5±0.10	1.4±0.12	1.3±0.21	1.6±0.28	1.4±0.12	1.0±0.41	1.6±0.28
Minimum Admission-to-Treatment	0	0	0	0	0	0	0
Maximum Admission-to-Treatment	32	32	10	13	32	2	13
Mean Onset-to-Discharge ± SEM[2]	17.8±0.21	17.9±0.23	16.8±0.60	17.6±0.89	18.5±0.29	17.0±0.32	18.1±1.31
Minimum Onset-to-Discharge	1	2	1	1	1	2	2
Maximum Onset-to-Discharge	135	135	42	86	134	135	86

1 Percentages are based only upon known values and may not sum to 100 due to rounding.

2 Standard error of the mean.

EXHIBIT III-1

PERCENTAGE OF DISTRIBUTION[1] OF PATIENT BY SELECTED CHARACTERISTICS AND BY PATIENT TYPE

PATIENT CHARACTERISTICS	TYPE PATIENT						
	All Patients	Disease Status			Treatment Status		
		Diseased	Non-Diseased	Unknown	Treated	Not-Treated	Unknown
	(n=2,134)	(n=1,853)	(n=153)	(n=148)	(n=1,020)	(n=1,043)	(n=91)
Maximum Immunofluorescent Antibody (IFA)							
<30	17.0	10.2	93.4	37.8	30.1	5.7	12.1
30-39	7.6	8.4	2.8	0.7	7.2	7.9	7.7
40-49	52.5	56.3	2.8	35.1	43.0	60.0	56.0
50-59	20.9	22.9	0.9	8.8	17.5	24.5	12.1
60+	2.0	2.3	0.0	0.0	2.2	1.9	1.1
(Unknown)	(209)	(136)	(47)	(26)	(147)	(52)	(10)
Admission Serum Aspartate Aminotransferase (SGOT)							
<150	49.5	46.8	68.4	54.7	34.4	77.5	66.3
150-199	9.9	10.6	5.3	8.6	13.9	2.8	4.7
200-249	6.6	7.3	2.3	4.7	8.6	2.1	8.1
250-299	3.7	3.7	3.8	3.9	4.6	2.1	3.5
300+	30.3	31.6	20.3	28.1	38.6	15.5	17.4
(Unknown)	(736)	(696)	(20)	(20)	(120)	(611)	(5)
Admission Viremia							
0	2.0	2.0	-	-	1.4	4.1	66.7
3-19	14.1	14.1	-	-	7.2	32.9	0.0
20-39	53.4	53.4	-	-	60.4	34.2	33.3
40-59	29.2	29.2	-	-	30.2	26.0	0.0
60+	1.3	1.3	-	-	0.9	2.7	0.0
(Unknown)	(1856)	(1555)	(153)	(148)	(798)	(970)	(88)
Admission Hematocrit							
<20	3.3	2.7	7.3	4.2	3.2	3.4	3.6
20-29	13.7	11.6	27.0	18.9	14.9	11.6	10.7
30-39	45.1	45.9	40.1	42.7	43.6	48.6	44.0
40-49	32.5	33.6	24.1	30.8	31.8	32.6	39.3
50+	5.4	6.1	1.5	3.5	6.5	3.7	2.4
(Unknown)	(661)	(636)	(16)	(9)	(49)	(605)	(7)
Mean Admission SGOT ± SEM[2]	737.6±50.1	762.0±57.1	483.4±97.9	780.6±175.7	891.8±68.7	447.4±68.2	579.5±197.8
Minimum SGOT	2	4	13	2	10	4	2
Maximum SGOT	20,952	20,952	7,582	12,746	20,952	13,968	11,176
Mean Admission Viremia ± SEM[2]	30.6±0.8	30.6±0.8	-	-	26.2±2.2	32.1±0.8	24.3±8.3
Minimum Viremia	0	0	-	-	0	0	16
Maximum Viremia	70	70	-	-	70	66	41
Mean Admission HCT ± SEM[2]	36.9±0.2	37.5±0.2	33.3±0.8	35.154±0.8	37.0±0.3	36.6±0.4	36.6±1.0
Minimum HCT	3	5	11	3	9	5	3
maximum HCT	92	92	70	70	90	92	65

[1] Percentages are based only upon known values and may not sum to 100 due to rounding.

[1] Standard error of the mean.

EXHIBIT III-2

PERCENTAGE DISTRIBUTION[1] OF PATIENTS BY SELECTED CHARACTERISTICS AND BY TREATMENT GROUP

PATIENT CHARACTERISTICS	TREATMENT GROUP[2]											
	All Patients	I	II	III	IV	V	VI	VII	VIII	IX	X	Unknown
	(1,850)	(n=967)	(n=601)	(n=37)	(n=76)	(n=34)	(n=12)	(n=26)	(n=9)	(n=17)	(n=35)	(n=36)
Age (Years)												
<5	1.2	0.2	2.2	0.0	0.0	12.1	0.0	0.0	0.0	5.9	3.1	0.0
5-9	2.7	0.7	3.9	0.0	0.0	39.4	0.0	8.0	0.0	0.0	9.4	0.0
10-14	3.2	2.3	2.9	0.0	0.0	30.3	0.0	8.0	0.0	5.9	15.6	0.0
15-19	11.4	10.7	12.4	11.1	11.8	18.2	8.3	0.0	14.3	17.6	12.5	11.8
20-29	42.3	46.5	37.7	44.4	51.3	0.0	66.7	36.0	42.9	47.1	15.6	47.1
30-39	23.9	25.3	22.6	22.2	26.3	0.0	25.0	24.0	28.6	23.5	21.9	23.5
40+	15.4	14.2	18.3	22.2	10.5	0.0	0.0	24.0	14.3	0.0	21.9	17.6
(Unknown)	(51)	(11)	(12)	(1)	(0)	(1)	(0)	(1)	(2)	(0)	(3)	(19)
Gender												
Male	45.6	41.7	52.2	44.4	42.1	50.0	0.0	52.0	62.5	52.9	51.4	46.7
Female	54.4	58.3	47.8	55.6	57.9	50.0	100.0	48.0	37.5	47.1	48.6	53.3
(Unknown)	(14)	(0)	(5)	(1)	(0)	(0)	(0)	(1)	(1)	(0)	(0)	(6)
Body Weight (Kgs)												
<10	3.9	25.0	3.8	0.0	0.0	13.3	0.0	0.0	0.0	0.0	0.0	-
10-29	11.3	25.0	9.2	0.0	100.0	53.3	0.0	7.7	0.0	7.1	0.0	-
30-49	30.3	25.0	29.5	42.1	0.0	33.3	33.3	30.8	28.6	35.7	0.0	-
50-69	51.8	25.0	54.2	57.9	0.0	0.0	66.7	57.7	71.4	57.1	100.0	-
70+	2.7	0.0	3.3	0.0	0.0	0.0	0.0	3.8	0.0	0.0	0.0	-
(Unknown)	(1,368)	(963)	(232)	(18)	(75)	(4)	(3)	(0)	(2)	(3)	(32)	(36)
Pregnancy Status[3] (Females 15-44 yrs)												
Pregnant	10.0	3.8	12.8	17.6	35.7	0.0	83.3	14.3	0.0	33.3	40.0	33.3
Not Pregnant	90.0	96.2	87.2	82.4	64.3	100.0	16.7	85.7	100.0	66.7	60.0	66.7
(Unknown)	(4)	(0)	(1)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)

[1] Percentages are based only upon known values and may not sum to 100 due to rounding.

[2] Treated groups are as follows:
I--No treatment given.
II--Ribavirin only, minus doses 5,6,7,8,9,10 and prostacyclin
III--Ribavirin + plasma
IV--Plasma only
V--Ribavirin (dose 5).
VI--Ribavirin (dose 6).
VII--Ribavirin (dose 9).
VIII--Ribavirin (dose 10).
IX--Ribavirin + prostacyclin.
X--Drugs were not available.

[3] Based upon 990 observations for women aged 15 to 44 years of age.

EXHIBIT III-2

PERCENTAGE DISTRIBUTION[1] OF PATIENTS BY SELECTED CHARACTERISTICS AND BY TREATMENT GROUP

PATIENT CHARACTERISTICS	TREATMENT GROUP[2]											
	All Patients	I	II	III	IV	V	VI	VII	VIII	IX	X	Unknown
	(n=1,850)	(n=967)	(n=601)	(n=37)	(n=76)	(n=34)	(n=12)	(n=26)	(n=9)	(n=17)	(n=35)	(n=36)
Outcome												
Died	18.1	14.0	20.0	21.6	25.0	14.7	41.7	16.0	44.4	82.4	32.4	17.2
Survived	81.9	86.0	80.0	78.4	75.0	85.3	58.3	84.0	55.6	17.6	67.6	82.8
(Unknown)	(26)	(28)	(140)	(2)	(2)	(18)	(8)	(29)	(11)	(2)	(24)	(7)
Mean Age ± SEM[3]	28.3±0.2	28.8±0.2	28.6±0.5	27.8±0.8	9.6±0.7	25.3±1.7	30.2±2.3	30.4±3.2	22.3±1.8	22.3±1.8	26.4±2.5	29.6±2.2
Minimum Age	1	3	1	16	1	15	8	15	3	3	1	16
Maximum Age	99	99	90	48	16	36	49	40	33	33	55	50
Mean Body Weight ± SEM[3]	45.4±0.7	30.2±9.7	46.5±0.7	49.3±2.0	-	21.6±1.9	49.0±2.2	51.8±2.6	52.7±2.7	45.6±3.6	58.3±1.6	-
	3	4	3	35	-	3	35	19	42	10		-
Minimum Body Weight	76	50	76	60	-	42	56	73	60	60		-
Maximum Body Weight												

[1] Percentages are based only upon known values and may not sum to 100 due to rounding.

[2] Treatment groups are as follows:
I--No treatment given.
II--Ribavirin only, minus doses 5,6,7,8,9,10 and prostacyclin
III--Ribavirin + plasma
IV--Plasma only
V--Ribaviran (dose 5).
VI-Ribaviran (dose 6).
VII--Ribaviran (dose 9).
VIII--Ribaviran (dose 10).
IX--Ribaviran + prostacyclin.
X--Drugs were not available.

[3] Standard error of the mean.

EXHIBIT III-2

PERCENTAGE DISTRIBUTION[1] OF PATIENTS BY SELECTED CHARACTERISTICS AND BY TREATMENT GROUP

PATIENT CHARACTERISTICS	TREATMENT GROUP[2]											
	All Patients	I	II	III	IV	V	VI	VII	VIII	IX	X	Unknown
	(n=1,850)	(n=967)	(n=601)	(n=37)	(n=76)	(n=34)	(n=12)	(n=26)	(n=9)	(n=17)	(n=35)	(n=36)
Days between onset and admission												
0	1.2	1.8	0.7	0.0	0.0	2.9	0.0	0.0	0.0	0.0	0.0	0.0
1-4	33.8	40.8	24.9	24.3	53.9	14.7	16.7	15.4	0.0	35.3	8.8	26.9
5-9	43.1	39.2	48.0	43.2	32.9	58.8	75.0	53.8	88.9	41.2	50.0	30.8
10-14	16.1	12.5	20.5	24.3	10.5	17.6	8.3	19.2	0.0	0.0	38.2	34.6
15+	5.9	5.7	5.9	8.1	2.6	5.9	0.0	11.5	11.1	23.5	2.9	7.7
Unknown	(27)	(14)	(7)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(10)
Days between admission and treatment												
0	50.8	0.0	48.6	42.3	60.0	75.8	50.0	53.8	71.4	57.1	33.3	60.0
1	22.1	0.0	21.6	42.3	26.7	6.1	20.0	23.1	28.6	21.4	66.7	20.0
2	10.7	100.0	12.1	3.8	13.3	6.1	10.0	3.8	0.0	7.1	0.0	0.0
3	5.8	0.0	5.8	11.5	0.0	6.1	0.0	7.7	0.0	7.1	0.0	0.0
4+	10.6	0.0	11.9	0.0	0.0	6.1	20.0	11.5	0.0	7.1	0.0	20.0
Unknown	(1,247)	(966)	(138)	(11)	(61)	(1)	(2)	(0)	(2)	(3)	(32)	(31)
Days between onset and discharge												
<5	2.1	2.6	1.2	0.0	1.3	8.8	8.3	4.0	0.0	5.9	0.0	0.0
5-9	11.7	14.7	7.0	2.7	17.1	5.9	16.7	4.0	12.5	29.4	11.4	7.7
10-14	25.3	30.9	17.8	13.5	40.8	11.8	16.7	8.0	12.5	11.8	14.3	30.8
15-19	28.2	23.2	36.1	29.7	15.8	50.0	41.7	40.0	62.5	23.5	17.1	23.1
20-29	25.0	20.9	30.2	37.8	19.7	14.7	16.7	40.0	12.5	11.8	54.3	30.8
30+	7.7	7.6	7.7	16.2	5.3	8.8	0.0	4.0	0.0	17.6	2.9	7.7
Unknown	(33)	(16)	(5)	(0)	(0)	(0)	(0)	(1)	(1)	(0)	(0)	(10)

[1] Percentages are based only upon known values and may not sum to 100 due to rounding.

[2] Treatment groups are as follows:
I--No treatment given.
II--Ribavirin only, minus doses 5,6,7,8,9,10 and prostacyclin
III--Ribavirin + plasma
IV--Plasma only
V--Ribavirin (dose 5).
VI--Ribavirin (dose 6).
VII--Ribavirin (dose 9).
VIII--Ribavirin (dose 10).
IX--Ribavirin + prostacyclin.
X--Drugs were not available.

EXHIBIT III-2

PERCENTAGE DISTRIBUTION[1] OF PATIENTS BY SELECTED CHARACTERISTICS AND BY TREATMENT GROUP

PATIENT CHARACTERISTICS	TREATMENT GROUP[2]											
	All Patients	I	II	III	IV	V	VI	VII	VIII	IX	X	Unknown
	(n=1,850)	(n=967)	(n=601)	(n=37)	(n=78)	(n=34)	(n=12)	(n=26)	(n=9)	(n=17)	(n=35)	(n=36)
Maximum Immunofluorescent Antibody (IFA)												
<30	10.2	3.9	17.6	10.8	6.7	42.4	60.0	11.8	0.0	17.6	36.0	8.8
30-39	8.4	8.2	8.1	5.4	10.7	6.1	10.0	0.0	42.9	17.6	4.0	11.8
40-49	56.3	60.4	52.1	54.1	34.7	39.4	20.0	88.2	57.1	52.9	56.0	70.6
50-59	22.9	25.5	18.7	29.7	46.7	12.1	10.0	0.0	0.0	11.8	4.0	5.9
60+	2.3	2.0	3.5	0.0	1.3	0.0	0.0	0.0	0.0	0.0	0.0	2.9
(Unknown)	(136)	(26)	(83)	(0)	(1)	(1)	(2)	(9)	(2)	(0)	(10)	(2)
Admission Serum Aspartate Aminotransferase (SGOT)												
<150	46.8	84.3	28.5	11.4	51.0	32.3	41.7	23.1	0.0	29.4	23.5	58.8
150-199	10.6	2.2	15.7	5.7	9.8	12.9	8.3	26.9	55.6	0.0	8.8	2.9
200-249	7.3	2.0	9.9	11.4	0.0	22.6	16.7	7.7	11.1	5.9	5.9	11.8
250-299	3.7	1.1	5.7	2.9	7.8	0.0	0.0	3.8	0.0	0.0	2.9	2.9
300+	31.6	10.4	40.3	68.6	31.4	32.3	33.3	38.5	33.3	64.7	58.8	23.5
(Unknown)	(696)	(610)	(53)	(2)	(25)	(3)	(0)	(0)	(0)	(0)	(1)	(2)
Admission Viremia												
0	2.0	1.4	2.0	0.0	0.0	0.0	0.0	-	-	0.0	100.0	0.0
3-19	14.1	33.8	7.8	0.0	6.9	25.0	0.0	-	-	0.0	0.0	66.7
20-39	53.4	35.2	61.4	61.1	48.3	62.5	50.0	-	-	75.0	0.0	0.0
40-59	29.2	26.8	28.8	33.3	41.4	12.5	50.0	-	-	25.0	0.0	33.3
60+	1.3	2.8	0.0	5.6	3.4	0.0	0.0	-	-	0.0	0.0	0.0
(Unknown)	(1,555)	(914)	(581)	(21)	(49)	(44)	(18)	(54)	(20)	(7)	(56)	(33)
Admission Hematocrit												
<20	2.7	3.6	2.6	0.0	0.0	8.8	0.0	0.0	0.0	0.0	0.0	3.0
20-29	11.6	10.2	12.1	8.1	8.6	26.5	25.0	11.5	11.1	5.9	17.1	6.1
30-39	45.9	49.9	45.4	29.7	36.2	52.9	66.7	34.6	66.7	47.1	45.7	36.4
40-49	33.6	32.5	32.4	56.8	37.9	11.8	8.3	53.8	22.2	35.3	34.3	51.5
50+	6.1	3.9	7.5	5.4	17.2	0.0	0.0	0.0	0.0	11.8	2.9	3.0
(Unknown)	(640)	(604)	(15)	(0)	(18)	(0)	(0)	(0)	(0)	(0)	(0)	(3)

[1] Percentages are based only upon known values and may not sum to 100 due to rounding.

[2] Treated groups are as follows:
I--No treatment given.
II--Ribavirin only, minus doses 5,6,7,8,9,10 and prostacyclin
III--Ribavirin + plasma
IV--Plasma only
V--Ribavirin (dose 5).
VI--Ribavirin (dose 6).
VII--Ribavirin (dose 9).
VIII--Ribavirin (dose 10).
IX--Ribavirin + prostacyclin.
X--Drugs were not available.

EXHIBIT III-3

PERCENTAGE DISTRIBUTION[1] OF PATIENTS BY SELECTED CHARACTERISTICS AND BY SGOT STATUS

PATIENT CHARACTERISTICS	SGOT Status			
	All Patients	<150	150+	Unknown
	(n=2,154)	(n=702)	(n=718)	(n=734)
Age (Years)				
<5	1.5	1.5	2.9	0.1
5-9	3.2	3.5	5.5	0.7
10-14	3.5	3.8	4.1	2.5
15-19	11.4	9.8	11.5	12.8
20-29	41.8	42.8	37.1	45.3
30-39	23.2	20.6	21.9	26.6
40+	15.5	17.8	17.0	12.0
(Unknown)	(133)	(52)	(65)	(16)
Gender				
Male	46.0	44.6	51.1	42.5
Female	54.0	55.4	48.9	57.5
(Unknown)	(32)	(12)	(20)	(0)
Body Weight (Kgs)				
<10	4.7	5.7	4.1	4.5
10-29	12.2	13.0	12.7	4.5
30-49	30.3	36.8	26.9	31.8
50-69	49.6	41.5	53.6	50.0
70+	3.2	3.1	2.6	9.1
(Unknown)	(1,531)	(509)	(332)	(690)
Pregnancy Status[2]				
Pregnant	11.3	11.1	21.8	4.5
Not Pregnant	88.7	88.9	78.2	95.5
(Unknown)	(4)	(1)	(3)	(0)
Diagnosis				
Lassa Fever	92.4	85.6	93.5	97.3
Not Lassa Fever	7.6	14.4	6.5	2.7
(Unknown)	(148)	(70)	(58)	(20)
Outcome				
Died	18.0	8.3	31.9	16.9
Survived	82.0	91.7	68.1	83.1
(Unknown)	(31)	(16)	(12)	(3)
Mean Age ± SEM[3]	28.1 ±0.26	28.4 ±0.49	27.6 ±0.50	28.3 ±0.38
Minimum Age	1	1	1	1
Maximum Age	99	65	90	99
Mean Body Weight ± SEM[3]	44.9 ±0.66	42.9 ±1.21	45.4 ±0.83	48.7 ±2.41
Minimum Body Weight	3	3	3	6
Maximum Body Weight	86	76	75	86

[1] Percentages are based only upon known values and may not sum to 100 due to rounding.

[2] Based upon 926 observations for women aged 15 to 44 years of age.

[3] Standard error of the mean.

EXHIBIT III-3

PERCENTAGE DISTRIBUTION[1] OF PATIENTS BY SELECTED CHARACTERISTICS AND BY SGOT STATUS

Page 2 of 3

PATIENT CHARACTERISTICS	SGOT STATUS			
	All Patients (n=2,154)	<150 (n=702)	150+ (n=715)	Unknown (n=737)
Days between onset and admission				
0	1.0	1.0	0.4	1.9
1-4	33.6	33.6	21.0	45.1
5-9	43.5	43.9	49.9	37.4
10-14	16.0	14.3	21.6	12.4
15+	6.1	7.1	7.0	3.3
(Unknown)	(51)	(26)	(16)	(9)
Days between admission and treatment				
0	49.3	27.1	60.2	46.3
1	21.8	19.7	22.4	25.9
2	12.1	21.4	7.7	13.0
3	6.4	12.7	3.5	5.6
4+	10.3	19.2	6.2	9.3
(Unknown)	(1,388)	(473)	(232)	(683)
Days between onset and discharge				
<5	2.1	0.9	2.9	2.9
5-9	11.9	8.2	15.2	15.2
10-14	25.0	27.8	27.7	27.7
15-19	28.9	28.6	26.3	26.3
20-29	24.6	26.1	20.5	20.5
30+	7.5	8.4	7.3	7.3
(Unknown)	(54)	(23)	(16)	(15)
Mean Onset-to-Admission ± SEM[2]	7.1± 0.13	7.4± 0.27	8.2± 0.21	6.0±0.21
Minimum Onset-to-Admission	0	0	0	0
Maximum Onset-to-Admission	79	77	61	79
Mean Admission-to-Treatment ± SEM[2]	1.5± 0.10	2.5± 0.23	1.0± 0.12	1.2±0.21
Minimum Admission-to-Treatment	0	0	0	0
Maximum Admission-to-Treatment	32	32	31	7
Mean Admission-to-Discharge ± SEM[2]	17.8± 0.21	18.4± 0.38	18.1±0.39	16.8±0.33
Minimum Admission-to-Discharge	1	3	1	1
Maximum Admission-to-Discharge	135	135	134	91

[1] Percentages are based only upon known values and may not sum to 100 due to rounding.

[2] Standard error of the mean.

EXHIBIT III-3

PERCENTAGE DISTRIBUTION[1] OF PATIENTS BY SELECTED CHARACTERISTICS AND BY SGOT STATUS

Page 3 of 3

PATIENT CHARACTERISTICS	SGOT STATUS			
	All Patients	<150	150+	Unknown
	(n=2,154)	(n=702)	(n=718)	(n=734)
Maximum Immunofluorescent Antibody (IFA)				
<30	17.0	16.9	27.7	8.1
30-39	7.6	6.3	6.2	9.9
40-49	52.5	54.1	46.1	56.3
50-59	20.9	21.0	17.4	23.7
60+	2.0	1.6	2.5	2.0
(Unknown)	(209)	(70)	(122)	(127)
Admission Viremia				
0	2.0	2.6	1.7	2.1
3-19	14.1	19.5	4.6	40.4
20-39	53.4	67.5	53.4	29.8
40-59	29.2	10.4	38.5	25.5
60+	1.3	0.0	1.7	2.1
(Unknown)	(1,856)	(625)	(544)	(687)
Admission Hematocrit				
<20	3.3	4.1	3.0	0.7
20-29	13.7	12.8	14.8	12.8
30-39	45.1	49.8	42.2	37.2
40-49	32.5	30.6	33.4	36.5
50+	5.4	2.6	6.5	12.8
(Unknown)	(661)	(46)	(29)	(586)
Mean Admission Viremia ± SEM[2]	30.6±0.80	25.5±1.21	34.3±0.91	25.0±2.81
Minimum Viremia	0	0	0	3
Maximum Viremia	70	51	66	70
Mean Admission HCT ± SEM[2]	36.9±0.24	36.0±0.33	37.0±0.36	39.7±0.91
Minimum HCT	3	5	3	12
maximum HCT	92	92	90	75

1 Percentages are based only upon known values and may not sum to 100 due to rounding.

2 Standard error of the mean.

EXHIBIT III-4

CASE FATALITY RATE BY RECRUITMENT YEAR

TREATMENT STATUS[1]	NUMBER RECRUITED AND CASE FATALITY RATE	YEAR RECRUITED INTO THE STUDY														
		1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
TOTAL	NUMBER RECRUITED	197	227	142	158	92	60	82	131	135	112	190	234	121	93	35
	CASE FATALITY RATE	16.8	17.1	18.3	17.7	16.0	16.7	11.0	10.4	13.9	32.1	22.1	19.2	21.1	32.3	37.1
TREATED	NUMBER RECRUITED	0	1	62	75	34	21	36	63	63	103	168	219	79	52	34
	CASE FATALITY RATE	0.0	0.0	14.5	17.3	23.5	38.1	13.9	15.9	25.4	32.0	19.6	20.1	31.6	30.8	38.2
NOT TREATED	NUMBER RECRUITED	197	226	80	113	58	39	46	68	72	9	22	15	42	41	1
	CASE FATALITY RATE	16.8	17.3	21.3	13.3	10.3	5.1	8.7	4.4	2.8	33.3	40.9	6.7	11.9	34.1	0.0

[1]Patients where treatment status was known.

EXHIBIT III-5

CORRELATION MATRIX FOR SELECTED VARIABLES

VARIABLE	GENDER	PATIENT AGE	PATIENT WEIGHT	ADMISSION[1] ONSET	ADMISSION[2] TREATMENT	ADMISSION[3] DISCHARGE	PREGNANCY STATUS	ADMISSION SGOT	ADMISSION HEMATOCRIT	ADMISSION VIREMIA	OUTCOME	DATE OF ADMISSION
GENDER	1.000	-.1929**	-.0591	-.0172	-.0438	-.0191	-	-.0100	-.2741**	-.0746	.0351	-.0306
PATIENT AGE	-.1929**	1.000	.5770**	.0238	-.0327	.0157	.0246	.0340	.2041**	.0515	-.0368	-.0876**
PATIENT WEIGHT	-.0591	.5770**	1.0000	.0537	-.0757	-.0717	-.1463	.1078*	.3283**	-.0116	-.1263**	.0355
ADMISSION ONSET[1]	-.0172	.0238	.0537	1.0000	-.0257	.8452**	.0184	.0489	-.0568	.0321	-.0041	.0773**
ADMISSION TREATMENT[2]	-.0438	-.0327	-.0757	-.0257	1.0000	.0064	.0200	-.0245	-.0475	-.0060	.0284	.0305
ADMISSION DISCHARGE[3]	-.0191	.0157	-.0717	.8452**	.0064	1.0000	.0241	.0721*	.0737*	-.1196	.1455**	.0433
PREGNANCY STATUS	-	.0246	-.1463	.0184	.0200	.0241	1.0000	-.0682	.0600	-.2057*	.1719**	-.2052**
ADMISSION SGOT	-.0100	.0340	.1078**	.0489	-.0245	-.0721*	-.0682	1.0000	.1373**	.1860*	-.3642**	.0714*
ADMISSION HEMATOCRIT	-.2741**	.2041**	.3283**	-.0568	-.0475	-.0737*	.0600	.1373**	1.0000	.1376	-.0069	-.2081**
ADMISSION VIREMIA	-.0746	.0515	-.0116	.0321	-.0060	-.1196	-.2057*	.1860*	.1376	1.0000	-.2483**	-.0647
OUTCOME	.0351	-.0368	-.1263**	-.0041	.0284	.1455**	.1719**	-.3642**	-.0069	-.2483**	1.0000	-.0845**
DATE OF ADMISSION	-.0306	-.0876**	.0355	.0773**	.0305	.0433	-.2052**	.0714*	-.2081**	-.0647	-.0845**	1.0000

1 Days between onset and admission.

2 Days between admission and treatment.

3 Days between admission and discharge.

* One-tailed significance at 0.01 level.
** One-tailed significance at 0.001 level.

EXHIBIT III-6

CASE FATALITY RATE BY PREGNANCY STATUS

PREGNANCY STATUS		TREATMENT GROUP									
		I	II	III	IV	V	VI	VII	VIII	IX	X
PREGNANT	Number	19	30	3	15	0	10	1	0	2	2
	Case Fatality Rate	21.1	36.7	33.3	46.7	-	40.0	0.0	-	100.0	50.0
NOT PREGNANT	Number	482	200	14	27	3	2	5	2	4	3
	Case Fatality Rate	12.9	13.0	14.3	18.5	0.0	50.0	20.0	0.0	75.0	33.3

SURVIVORSHIP AMONG TREATMENT GROUPS

STATUS/ SIGNIFICANCE	TREATMENT GROUP								
	CONTROL[1]	II	III	IV	V	VI	VII	VIII	IX
SURVIVED	846(85.4)	475(80.0)	29(78.4)	57(75.0)	29(85.3)	7(58.3)	21(84.0)	5(55.6)	3(17.6)
DIED	145	119	8	19	5	5	4	4	14
TOTAL	991	594	37	76	34	12	25	9	17
X^2 (Corrected)[2]		7.4	0.9	5.1	NC	NC	NC	NC	NC
P-VALUE		.0064	.3484	.0244	NC	NC	NC	NC	NC

[1] Includes treatment groups I and X.

[2] NC represents value not computed since cells with expected frequencies of < 5 exceeded 20 percent.

EXHIBIT III-8

CASE FATALITY BY TREATMENT GROUP AND ADMISSION SGOT[1]

TREATMENT[2] GROUP	TOTAL		SGOT LEVEL			
			<150 SGOT		>= 150 SGOT	
	N	PERCENT DIED	N	PERCENT DIED	N	PERCENT DIED
I	352	10.5	296	4.1	56	44.6
II	542	20.5	154	9.1*	388	25.0**
III	35	22.9	4	25.0*	31	22.6*
IV	51	29.4	26	15.4**	25	44.0
V	31	12.9	10	0.0	21	19.0*
VI	12	41.7	5	20.0	7	57.1
VII	25	16.0	5	0.0	20	20.0*
VIII	9	44.4	0	0.0	9	44.4
IX	17	82.4	5	100.0**	12	75.0
X	34	32.4	8	12.5	26	38.5
TOTAL TREATED[3]	722	22.9	209	12.0**	513	27.3**
TOTAL NOT TREATED[4]	386	12.4	304	4.3	82	42.7

1 Cases included are those where admission SGOTs were known.

2 Treated groups are as follows:
I--No treatment given.
II--Ribavirin only, minus doses 5,6,7,8,9,10 and prostacyclin
III--Ribavirin + plasma
IV--Plasma only
V--Ribavirin (dose 5).
VI--Ribavirin (dose 6).
VII--Ribavirin (dose 9).
VIII--Ribavirin (dose 10).
IX--Ribavirin + prostacyclin.
X--Drugs were not available.

3 Treated are groups II-IX.

4 Not treated are groups I & X.

* Significant at 0.05 level (Chi-Square).
** Significant at 0.01 level (Chi-Square).

EXHIBIT III-9

LOGISTIC REGRESSION RESULTS

FACTOR	NUMERICAL VALUE	LOGISTIC COEFFICIENT	SIGNIFICANCE	RELATIVE RISK
INDEPENDENT VARIABLES Age	Age in Years	-0.0111	0.2934	0.989
Gender	Male=1 Female=0	-0.2212	0.4435	0.802
Interval Onset to Admission	Time in Days	-0.3232	0.0000	0.724
Interval Admission to Treatment	Time in Days	-0.0686	0.0918	0.934
Length of Stay	Time in Days	0.3214	0.0000	1.379
Log(SGOT)	Base 10 Log of SGOT	-0.9379	0.0001	0.391
Treatment	Treated=1 Untreated=0	0.1289	0.0015	1.138
DEPENDENT VARIABLE Survival	Died=0 Survived=1	Constant=1.4235	0.0815	

EXHIBIT III-10

EFFECTS OF TREATMENT[1]

FACTORS	TOTAL[2]		DISEASED		NON-DISEASED	
	Percent	No.	Percent	No.	Percent	No.
TOTAL	18.0	1,980	18.1	1,831	16.8	149
TREATMENT						
Yes	19.4	794	19.6	693	17.8	101
No	14.4	1,014	14.6	992	4.5	22
SEVERITY						
Low	7.3	618	7.4	529	6.7	89
High	30.5	656	29.6	615	43.9	41

---

1 "Yes" represents treatment groups II, III, V, and VII while "no" represents treatment groups I and X.

2 These totals do not conform to prior tabulations of patients by disease status due to the excluded treatment groups noted in the prior footnote.

CHAPTER IV

CONCLUSIONS

CHAPTER IV

CONCLUSIONS

Aside from the presentation of descriptive statistics on the demographic and clinical attributes of the study population, as noted in the introduction, the analysis sought to resolve five key questions. Based on the results, answers to these questions are as follows:

- **Is the drug correlated with a beneficial outcome?**--The data are somewhat ambiguous but suggest that ribavirin has a modest impact on improving patient survival. This effect is only true for patients with SGOTs of 150 or more. For patients with lower SGOTs, treatment appears to be associated with a higher risk of dying.

- **Has the drug non-beneficial effects on non-disease conditions?**--The data on potentially adverse effects are ambiguous. Part of this ambiguity arises due to the uncertainty regarding just what non-diseased patients represent. Non-diseased patients who are treated have a case fatality rate that is approximately four times greater than their untreated peers. Non-diseased patients who are severely ill in terms of their admission SGOT exhibit a case fatality rate that is greater than that experienced by diseased patients in this category. It is possible that non-diseased patients could represent actual Lassa cases who die or are discharged before a definitive diagnosis can be made.

- **Are there any other relevant statistics to strengthen the case of the drug application?**--The data on admission SGOT suggest that treatment is only effective among patients with SGOTs greater than 150.

- **Are there differences within/between the nine different treatments?**--Further definitional clarifications yielded eight treatment groups and two control groups. Only treatment group II (ribavirin alone) produced a significantly lower case fatality rate.

- **Are there any correlations of the drug with concomitantly used drugs?**--The data were of too poor quality and there were insufficient observations to resolve this question.

In summary, the evidence supporting the clinical efficacy of ribavirin is not strong. Ribavirin's therapeutic effects are relatively weak while safety issues regarding the potential adverse effects of treatment on non-Lassa patients or with disease of lesser severity remain unresolved. Although this extended trial yielded a large amount of data, a large percentage of missing values for some variables such as protocol compliance raises data quality issues. Further, bias associated with the selection of patients for drug treatment weakens the study findings. Finally, changes over time in the treatment protocol were not carefully documented.

Thus, while provocative, the results remain inconclusive. The ultimate resolution of these issues is pending the institution of a carefully documented and methodologically rigorous clinical trial.

APPENDIX A

DATA DICTIONARY

DATA DICTIONARIES

RECEIVED FROM DR. JOHN HUGGINS, 6/91

2 DATA DICTIONARIES: VERIFY
VERIFY2

DATA DICTIONARY: VERIFY

CODED DATA	CODE	MEANING
:IFYCD	-9	Missing value
	-8	Verify not attempted
	0	None found
	1	Patient chart
	2	Laboratory log [Bible]
	3	Primary CDC Data forms, not coded data
	4	Primary CDC Data form, coded data
	5	Doctors notes, not part of Pt chart
	6	Nursing notes, not part of chart
	7	Research notes, Investigators
	8	Hospital patient administration records
	9	Other Hospital records
	10	Old CDC computer printouts of data
	11	CDC databases (no known conflicts)
	12	Conflicting CDC databases
	20	Conflict among sources, Most reliable source used, (see audit
	30	Conflict among sources, CDC database used as source (see
SEXCD	-9	Missing value
	-1	Uknown, no record exists
	1	Male
	2	Female
PATIENTCD	-9	Missing value
	-8	Error
	-1	Unknown, no record exists
	1	Adult
	2	Pregnant
	3	Pediatric (<15Y)
DIAGCD	-9	Missing Value
	-8	Error
	-1	Unknown, no record exists
	0	Non-Lassa
	1	Lassa
	2	Unknown [diagnosis not established]
OUTCD	-9	Missing value
	-1	Unknown, no record exists
	0	Died
	1	Survived
	2	DCH AMA Morbund, high probability died

CODED DATA	CODE	MEANING
~~MACD	-9	Missing value
	1	Unknown, no record exists
	2	DCH AMA, resolving, expect live
	3	DCH AMA, Morbund
IFACD	20	Neg;undiluted
TREATCD	-9	Missing value
	-8	Error
	-1	Unknown, no record exists
	0	None
	1	Ribaviran
	2	Riba + Plasma
	3	Plasma
ROUTECD	-9	Missing value
	-8	Error
	-1	Unknown, no record exists
	0	None
	1	IV
	2	Oral
ECD	-9	Missing value
	-8	Error
	-1	Unknown, no record exists
	0	None
	1	Full
	2	Half
	3	1 U
	4	2 U
	5	L 25-30 mg/kg
	6	M 34 mg/kg
RANDOMCD	-9	Missing value
	-8	Error
	-1	Unknown, no record exists
	0	Open Rx Protocol, No randomization
	1	Randomization Protocol, Randomized
	2	Randomization Protocol, Not Randomized
	3	Randomization requirement not known, Not randomized

CODED DATA	CODE	MEANING
CORDCD	-9	Missing value
	-1	Unknown, no record exists
	1	CDC Form 11(Dose Admin Form)
	2	Patient Chart stated Rx
	3	Lab Log [BIBLE] stated Rx
	4	CDC Coding Form coded as part of DIAG code
PROTOCD	-9	Missing value
	-1	Missing value
	0	No protocol
	1	No violations
INFORMCD	-8	Verify not attempted
PROTOCD	2	Minor violations (see log)
	3	Major violations (see log)
INFORMCD	-9	Missing value
	-1	Unknown, no record exists
	0	Not obtained
	1	Written, Record found
	2	Written, Record not found
	3	Oral, Documented
	4	Oral, Not Documented
	5	Physician waved, DOC
	6	Physician waved, Not DOC
INFORMED	40	Conflict in records; not resolved;preaudit DB value used
IFACD	21	NEG;1:2
	22	NEG;1:4
	23	NEG;1:8
	24	NEG:1:16
	25	NEG;1:32
	26	NEG;1:64
	30	POS;UNDIL
	31	POS;>=1:2
	32	POS;>=1:4
	33	POS;>=1:8

CODED DATA	CODE	MEANING
	34	POS;>=1:16
	35	POS;>=1:32
	36	POS;>=1:64
	37	POS;>=1:128
	38	POS;>=1:256
	39	POS;>=1:512
	40	POS;>=1:1024
	41	POS;>=1:2048
	42	POS;>=1:4096
	50	POS;=UNDIL
	51	POS;=1:2
	52	POS;=1:4
	53	POS;=1:8
	54	POS;=1:16
	55	POS;=1:32
	56	POS;=1:64
	57	POS;=1:128
	58	POS;=1:256
	59	POS;=1:512
	60	POS;=1:1024
	61	POS;=1:2048
	62	POS;=1:4096
VERIFYCD	15	RECORD IN ALTANTA
IACD	0	NORMAL DISCHARGE
	4	DCH AMA, UNKNOWN OUTCOME
RECORDCD	5	Form 11 in ATL

DATA DICTIONARY : VERIFY2

DATA CODED	CODE	MEANING
MACD	-1	Unknown, no record exists
	-9	Missing value
	2	DCH AMA, resolving, expect live
	3	DCH AMA, Morbund
DIAGCD	-1	Unknown, no record exists
	-8	Error
	-9	Missing Value
	0	Non-Lassa
	1	Lassa
	2	Unknown [diagnosis not established]
DOSECD	-1	Unknown, no record exists
	-8	Error
	-9	Missing value
	0	None
	1	Full
	2	Half
	3	1 U
	4	2 U
	5	L 25-30 mg/kg
	6	M 34 mg/kg
ICD	20	Neg;undiluted
INFORMCD	-1	Unknown, no record exists
	-8	Verify not attempted
	-9	Missing value
	0	Not obtained
	1	Written, Record found
	2	Written, Record not found
	3	Oral, Documented
	4	Oral, Not Documented
	5	Physician waved, DOC
	6	Physician waved, Not DOC
OUTCD	-1	Unknown, no record exists
	-9	Missing value
	0	Died
	1	Survived

DATA CODED	CODE	MEANING
	2	DCH AMA Morbund, high probability died
PATIENTCD	-1	Unknown, no record exists
	-8	Error
	-9	Missing value
	1	Adult
	2	Pregnant
	3	Pediatric (<15Y)
PROTOCD	-1	Missing value
	-9	Missing value
	0	No protocol
	1	No violations
	2	Minor violations (see log)
	3	Major violations (see log)
RANDOMCD	-1	Unknown, no record exists
	-8	Error
	-9	Missing value
	0	Open Rx Protocol, No randomization
	1	Randomization Protocol, Randomized
	2	Randomization Protocol, Not Randomized
	3	Randomization requirement not known, Not randomized
RECORDCD	-1	Unknown, no record exists
	-9	Missing value
	1	CDC Form 10(Dose Admin Form)
	2	Patient Chart stated Rx
	3	Lab Log [BIBLE] stated Rx
	4	CDC Coding Form coded as part of DIAG code
ROUTECD	-1	Unknown, no record exists
	-8	Error
	-9	Missing value
	0	None
	1	IV
	2	Oral
SEXCD	-1	Uknown, no record exists
	-9	Missing value

DATA CODED	CODE	MEANING
	0	Male
	1	Female
TREATCD	-1	Unknown, no record exists
	-8	Error
	-9	Missing value
	0	None
	1	Ribaviran
	2	Riba + Plasma
	3	Plasma
VERIFYCD	-8	Verify not attempted
	-9	Missing value
	0	None found
	1	Patient chart
	10	Old CDC computer printouts of data
	11	CDC databases (no known conflicts)
	12	Conflicting CDC databases
	2	Laboratory lag [Bible]
	20	Conflict among sources, Most reliable source used, (see audi
	3	Primary CDC Data forms, not coded data
	30	Conflict among sources, CDC database used as source (see aud
	4	Primary CDC Data form, coded data
	40	
	5	Doctors notes, not part of Pt chart
	6	Nursing notes, not part of chart
	7	Research notes, Investigators
	8	Hospital patient administration records
	9	Other Hospital records

APPENDIX B

LISTING OF ADDITIONAL DATA ELEMENTS

ORIGINAL DATABASE STRUCTURE

RECEIVED FROM DR. JOHN HUGGINS 6/91

5 DATABASES: CDC_1.DBF
CDC_2.DBF
CDC_3.DBF
CDC_4.DBF
CDC_5.DBF

Structure for database: B:\CDC_1.DBF
Number of data records: 828
:e of last update : 10/15/91

eld	Field Name	Type	Width	Dec
1	EERDIAG	Character	1	
2	AGE	Character	4	
3	RX_PCL	Character	5	
4	NAME	Character	20	
5	CDC_CD	Character	78	
6	RX_CPL_TX	Character	80	
7	MN_HGB_D	Date	8	
8	MN_HCT_D	Date	8	
9	MX_VIR_D	Date	8	
10	MX_SGO_D	Date	8	
11	A_HGB_D	Date	8	
12	A_HCT_D	Date	8	
13	ONSET	Date	8	
14	A_VIR_D	Date	8	
15	ADMISS	Date	8	
16	A_SGOT_D	Date	8	
17	D_DCH	Date	8	
18	D_HGB_D	Date	8	
19	D_VIR_D	Date	8	
20	D_RX	Date	8	
21	D_HCT_D	Date	8	
22	D_SGOT_D	Date	8	
23	PROB_PT	Logical	1	
24	DS_RED	Logical	1	
25	LOG	Memo	10	
26	OC	Numeric	2	
27	MAX_IFA	Numeric	2	
28	V_DX	Numeric	2	
29	V_D_RX	Numeric	2	
30	V_D_HGB	Numeric	2	
31	V_T_RX	Numeric	2	
32	RX	Numeric	2	
33	V_RX	Numeric	2	
34	RT	Numeric	2	
35	V_RT	Numeric	2	
36	DS	Numeric	2	
37	V_DS	Numeric	2	
38	V_D_HCT	Numeric	2	
39	DX	Numeric	2	
40	V_RX_PCL	Numeric	2	
41	PT_RDM	Numeric	2	
42	V_PT_RDM	Numeric	2	
43	R_RX_CPL	Numeric	2	
44	V_DAMA	Numeric	2	
45	V_DS_RED	Numeric	2	
46	DSCPLMD	Numeric	2	
47	V_DSCPLMD	Numeric	2	
48	DSCPLMMD	Numeric	2	
49	V_DSCPLMMD	Numeric	2	
50	V_D_DCH	Numeric	2	
51	PCL_CPL	Numeric	2	
52	INF_CT	Numeric	2	
53	V_INF_CT	Numeric	2	
54	DAMA	Numeric	2	
55	V_OC	Numeric	2	

56	V_ADMISS	Numeric	2	
57	V_A_SGOT	Numeric	2	
58	V_D_VIR	Numeric	2	
59	V_ONSET	Numeric	2	
60	V_A_VIR	Numeric	2	
61	V_NAME	Numeric	2	
62	W_PREG	Numeric	2	
63	V_A_HCT	Numeric	2	
64	V_D_SGOT	Numeric	2	
65	V_PT	Numeric	2	
66	V_A_HGB	Numeric	2	
67	V_AGE	Numeric	2	
68	PT	Numeric	2	
69	V_MX_SGOT	Numeric	2	
70	V_MN_HGB	Numeric	2	
71	V_PT_WT	Numeric	2	
72	V_MX_VIR	Numeric	2	
73	SEX	Numeric	2	
74	V_MN_HCT	Numeric	2	
75	DIAG	Numeric	3	
76	T_RX	Numeric	4	
77	TOTAL_DS	Numeric	4	1
78	PT_WT	Numeric	5	1
79	MX_VIR	Numeric	6	
80	D_SGOT	Numeric	6	
81	MX_SGOT	Numeric	6	
82	A_HGB	Numeric	6	
83	D_VIR	Numeric	6	
84	A_HCT	Numeric	6	
85	A_VIR	Numeric	6	
86	D_HCT	Numeric	6	
87	A_SGOT	Numeric	6	
88	MN_HGB	Numeric	6	
89	D_HGB	Numeric	6	
90	MN_HCT	Numeric	6	
91	ACCESSNO	Numeric	8	
** Total **			523	

Structure for database: B:\CDC_2.DBF
Number of data records: 369
Date of last update : 03/19/91

Fld	Field Name	Type	Width	Dec
1	EERDIAG	Character	1	
2	AGE	Character	4	
3	RX_PCL	Character	5	
4	NAME	Character	20	
5	CDC_CD	Character	78	
6	RX_CPL_TX	Character	80	
7	MN_HGB_D	Date	8	
8	MN_HCT_D	Date	8	
9	MX_VIR_D	Date	8	
10	MX_SGO_D	Date	8	
11	A_HGB_D	Date	8	
12	A_HCT_D	Date	8	
13	ONSET	Date	8	
14	A_VIR_D	Date	8	
15	ADMISS	Date	8	
16	A_SGOT_D	Date	8	
17	D_DCH	Date	8	
18	D_HGB_D	Date	8	
19	D_VIR_D	Date	8	
20	D_RX	Date	8	
21	D_HCT_D	Date	8	
22	D_SGOT_D	Date	8	
23	PROB_PT	Logical	1	
24	DS_RED	Logical	1	
25	LOG	Memo	10	
26	OC	Numeric	2	
27	MAX_IFA	Numeric	2	
28	V_DX	Numeric	2	
29	V_D_RX	Numeric	2	
30	V_D_HGB	Numeric	2	
31	V_T_RX	Numeric	2	
32	RX	Numeric	2	
33	V_RX	Numeric	2	
34	RT	Numeric	2	
35	V_RT	Numeric	2	
36	DS	Numeric	2	
37	V_DS	Numeric	2	
38	V_D_HCT	Numeric	2	
39	DX	Numeric	2	
40	V_RX_PCL	Numeric	2	
41	PT_RDM	Numeric	2	
42	V_PT_RDM	Numeric	2	
43	R_RX_CPL	Numeric	2	
44	V_DAMA	Numeric	2	
45	V_DS_RED	Numeric	2	
46	DSCPLMD	Numeric	2	
47	V_DSCPLMD	Numeric	2	
48	DSCPLMMD	Numeric	2	
49	V_DSCPLMMD	Numeric	2	
50	V_D_DCH	Numeric	2	
51	PCL_CPL	Numeric	2	
52	INF_CT	Numeric	2	
53	V_INF_CT	Numeric	2	
54	DAMA	Numeric	2	
55	V_OC	Numeric	2	

56	V_ADMISS	Numeric	2	
57	V_A_SGOT	Numeric	2	
58	V_D_VIR	Numeric	2	
59	V_ONSET	Numeric	2	
60	V_A_VIR	Numeric	2	
61	V_NAME	Numeric	2	
62	W_PREG	Numeric	2	
63	V_A_HCT	Numeric	2	
64	V_D_SGOT	Numeric	2	
65	V_PT	Numeric	2	
66	V_A_HGB	Numeric	2	
67	V_AGE	Numeric	2	
68	PT	Numeric	2	
69	V_MX_SGOT	Numeric	2	
70	V_MN_HGB	Numeric	2	
71	V_PT_WT	Numeric	2	
72	V_MX_VIR	Numeric	2	
73	SEX	Numeric	2	
74	V_MN_HCT	Numeric	2	
75	DIAG	Numeric	3	
76	T_RX	Numeric	4	
77	TOTAL_DS	Numeric	4	1
78	PT_WT	Numeric	5	1
79	MX_VIR	Numeric	6	
80	D_SGOT	Numeric	6	
81	MX_SGOT	Numeric	6	
82	A_HGB	Numeric	6	
83	D_VIR	Numeric	6	
84	A_HCT	Numeric	6	
85	A_VIR	Numeric	6	
86	D_HCT	Numeric	6	
87	A_SGOT	Numeric	6	
88	MN_HGB	Numeric	6	
89	D_HGB	Numeric	6	
90	MN_HCT	Numeric	6	
91	ACCESSNO	Numeric	8	
** Total **			523	

Structure for database: B:\CDC_3.DBF
Number of data records: 466
Date of last update : 03/20/91

Id	Field Name	Type	Width	Dec
1	EERDIAG	Character	1	
2	AGE	Character	4	
3	RX_PCL	Character	5	
4	NAME	Character	20	
5	CDC_CD	Character	78	
6	RX_CPL_TX	Character	80	
7	MN_HGB_D	Date	8	
8	MN_HCT_D	Date	8	
9	MX_VIR_D	Date	8	
10	MX_SGO_D	Date	8	
11	A_HGB_D	Date	8	
12	A_HCT_D	Date	8	
13	ONSET	Date	8	
14	A_VIR_D	Date	8	
15	ADMISS	Date	8	
16	A_SGOT_D	Date	8	
17	D_DCH	Date	8	
18	D_HGB_D	Date	8	
19	D_VIR_D	Date	8	
20	D_RX	Date	8	
21	D_HCT_D	Date	8	
22	D_SGOT_D	Date	8	
23	PROB_PT	Logical	1	
24	DS_RED	Logical	1	
25	LOG	Memo	10	
26	OC	Numeric	2	
27	MAX_IFA	Numeric	2	
28	V_DX	Numeric	2	
29	V_D_RX	Numeric	2	
30	V_D_HGB	Numeric	2	
31	V_T_RX	Numeric	2	
32	RX	Numeric	2	
33	V_RX	Numeric	2	
34	RT	Numeric	2	
35	V_RT	Numeric	2	
36	DS	Numeric	2	
37	V_DS	Numeric	2	
38	V_D_HCT	Numeric	2	
39	DX	Numeric	2	
40	V_RX_PCL	Numeric	2	
41	PT_RDM	Numeric	2	
42	V_PT_RDM	Numeric	2	
43	R_RX_CPL	Numeric	2	
44	V_DAMA	Numeric	2	
45	V_DS_RED	Numeric	2	
46	DSCPLMD	Numeric	2	
47	V_DSCPLMD	Numeric	2	
48	DSCPLMMD	Numeric	2	
49	V_DSCPLMMD	Numeric	2	
50	V_D_DCH	Numeric	2	
1	PCL_CPL	Numeric	2	
52	INF_CT	Numeric	2	
53	V_INF_CT	Numeric	2	
54	DAMA	Numeric	2	
55	V_OC	Numeric	2	

56	V_ADMISS	Numeric	2	
57	V_A_SGOT	Numeric	2	
58	V_D_VIR	Numeric	2	
59	V_ONSET	Numeric	2	
60	V_A_VIR	Numeric	2	
61	V_NAME	Numeric	2	
62	W_PREG	Numeric	2	
63	V_A_HCT	Numeric	2	
64	V_D_SGOT	Numeric	2	
65	V_PT	Numeric	2	
66	V_A_HGB	Numeric	2	
67	V_AGE	Numeric	2	
68	PT	Numeric	2	
69	V_MX_SGOT	Numeric	2	
70	V_MN_HGB	Numeric	2	
71	V_PT_WT	Numeric	2	
72	V_MX_VIR	Numeric	2	
73	SEX	Numeric	2	
74	V_MN_HCT	Numeric	2	
75	DIAG	Numeric	3	
76	T_RX	Numeric	4	
77	TOTAL_DS	Numeric	4	1
78	PT_WT	Numeric	5	1
79	MX_VIR	Numeric	6	
80	D_SGOT	Numeric	6	
81	MX_SGOT	Numeric	6	
82	A_HGB	Numeric	6	
83	D_VIR	Numeric	6	
84	A_HCT	Numeric	6	
85	A_VIR	Numeric	6	
6	D_HCT	Numeric	6	
87	A_SGOT	Numeric	6	
88	MN_HGB	Numeric	6	
89	D_HGB	Numeric	6	
90	MN_HCT	Numeric	6	
91	ACCESSNO	Numeric	8	
** Total **			523	

Structure for database: B:\CDC_4.DBF
Number of data records: 167
Date of last update : 03/20/91

Fld	Field Name	Type	Width	Dec
1	EERDIAG	Character	1	
2	AGE	Character	4	
3	RX_PCL	Character	5	
4	NAME	Character	20	
5	CDC_CD	Character	78	
6	RX_CPL_TX	Character	80	
7	MN_HGB_D	Date	8	
8	MN_HCT_D	Date	8	
9	MX_VIR_D	Date	8	
10	MX_SGO_D	Date	8	
11	A_HGB_D	Date	8	
12	A_HCT_D	Date	8	
13	ONSET	Date	8	
14	A_VIR_D	Date	8	
15	ADMISS	Date	8	
16	A_SGOT_D	Date	8	
17	D_DCH	Date	8	
18	D_HGB_D	Date	8	
19	D_VIR_D	Date	8	
20	D_RX	Date	8	
21	D_HCT_D	Date	8	
22	D_SGOT_D	Date	8	
23	PROB_PT	Logical	1	
24	DS_RED	Logical	1	
25	LOG	Memo	10	
26	OC	Numeric	2	
27	MAX_IFA	Numeric	2	
28	V_DX	Numeric	2	
29	V_D_RX	Numeric	2	
30	V_D_HGB	Numeric	2	
31	V_T_RX	Numeric	2	
32	RX	Numeric	2	
33	V_RX	Numeric	2	
34	RT	Numeric	2	
35	V_RT	Numeric	2	
36	DS	Numeric	2	
37	V_DS	Numeric	2	
38	V_D_HCT	Numeric	2	
39	DX	Numeric	2	
40	V_RX_PCL	Numeric	2	
41	PT_RDM	Numeric	2	
42	V_PT_RDM	Numeric	2	
43	R_RX_CPL	Numeric	2	
44	V_DAMA	Numeric	2	
45	V_DS_RED	Numeric	2	
46	DSCPLMD	Numeric	2	
47	V_DSCPLMD	Numeric	2	
48	DSCPLMMD	Numeric	2	
49	V_DSCPLMMD	Numeric	2	
50	V_D_DCH	Numeric	2	
51	PCL_CPL	Numeric	2	
52	INF_CT	Numeric	2	
53	V_INF_CT	Numeric	2	
54	DAMA	Numeric	2	
55	V_OC	Numeric	2	

56	V_ADMISS	Numeric	2	
57	V_A_SGOT	Numeric	2	
58	V_D_VIR	Numeric	2	
59	V_ONSET	Numeric	2	
60	V_A_VIR	Numeric	2	
61	V_NAME	Numeric	2	
62	W_PREG	Numeric	2	
63	V_A_HCT	Numeric	2	
64	V_D_SGOT	Numeric	2	
65	V_PT	Numeric	2	
66	V_A_HGB	Numeric	2	
67	V_AGE	Numeric	2	
68	PT	Numeric	2	
69	V_MX_SGOT	Numeric	2	
70	V_MN_HGB	Numeric	2	
71	V_PT_WT	Numeric	2	
72	V_MX_VIR	Numeric	2	
73	SEX	Numeric	2	
74	V_MN_HCT	Numeric	2	
75	DIAG	Numeric	3	
76	T_RX	Numeric	4	
77	TOTAL_DS	Numeric	4	1
78	PT_WT	Numeric	5	1
79	MX_VIR	Numeric	6	
80	D_SGOT	Numeric	6	
81	MX_SGOT	Numeric	6	
82	A_HGB	Numeric	6	
83	D_VIR	Numeric	6	
84	A_HCT	Numeric	6	
85	A_VIR	Numeric	6	
86	D_HCT	Numeric	6	
87	A_SGOT	Numeric	6	
88	MN_HGB	Numeric	6	
89	D_HGB	Numeric	6	
90	MN_HCT	Numeric	6	
91	ACCESSNO	Numeric	8	
** Total **			523	

Structure for database: B:\CDC_5.DBF
Number of data records: 3
Date of last update : 03/20/91

Id	Field Name	Type	Width	Dec
1	EERDIAG	Character	1	
2	AGE	Character	4	
3	RX_PCL	Character	5	
4	NAME	Character	20	
5	CDC_CD	Character	78	
6	RX_CPL_TX	Character	80	
7	MN_HGB_D	Date	8	
8	MN_HCT_D	Date	8	
9	MX_VIR_D	Date	8	
10	MX_SGO_D	Date	8	
11	A_HGB_D	Date	8	
12	A_HCT_D	Date	8	
13	ONSET	Date	8	
14	A_VIR_D	Date	8	
15	ADMISS	Date	8	
16	A_SGOT_D	Date	8	
17	D_DCH	Date	8	
18	D_HGB_D	Date	8	
19	D_VIR_D	Date	8	
20	D_RX	Date	8	
21	D_HCT_D	Date	8	
22	D_SGOT_D	Date	8	
23	PROB_PT	Logical	1	
24	DS_RED	Logical	1	
25	LOG	Memo	10	
26	OC	Numeric	2	
27	MAX_IFA	Numeric	2	
28	V_DX	Numeric	2	
29	V_D_RX	Numeric	2	
30	V_D_HGB	Numeric	2	
31	V_T_RX	Numeric	2	
32	RX	Numeric	2	
33	V_RX	Numeric	2	
34	RT	Numeric	2	
35	V_RT	Numeric	2	
36	DS	Numeric	2	
37	V_DS	Numeric	2	
38	V_D_HCT	Numeric	2	
39	DX	Numeric	2	
40	V_RX_PCL	Numeric	2	
41	PT_RDM	Numeric	2	
42	V_PT_RDM	Numeric	2	
43	R_RX_CPL	Numeric	2	
44	V_DAMA	Numeric	2	
45	V_DS_RED	Numeric	2	
46	DSCPLMD	Numeric	2	
47	V_DSCPLMD	Numeric	2	
48	DSCPLMMD	Numeric	2	
49	V_DSCPLMMD	Numeric	2	
50	V_D_DCH	Numeric	2	
1	PCL_CPL	Numeric	2	
52	INF_CT	Numeric	2	
53	V_INF_CT	Numeric	2	
54	DAMA	Numeric	2	
55	V_OC	Numeric	2	

56	V_ADMISS	Numeric	2	
57	V_A_SGOT	Numeric	2	
58	V_D_VIR	Numeric	2	
59	V_ONSET	Numeric	2	
60	V_A_VIR	Numeric	2	
61	V_NAME	Numeric	2	
62	W_PREG	Numeric	2	
63	V_A_HCT	Numeric	2	
64	V_D_SGOT	Numeric	2	
65	V_PT	Numeric	2	
66	V_A_HGB	Numeric	2	
67	V_AGE	Numeric	2	
68	PT	Numeric	2	
69	V_MX_SGOT	Numeric	2	
70	V_MN_HGB	Numeric	2	
71	V_PT_WT	Numeric	2	
72	V_MX_VIR	Numeric	2	
73	SEX	Numeric	2	
74	V_MN_HCT	Numeric	2	
75	DIAG	Numeric	3	
76	T_RX	Numeric	4	
77	TOTAL_DS	Numeric	4	1
78	PT_WT	Numeric	5	1
79	MX_VIR	Numeric	6	
80	D_SGOT	Numeric	6	
81	MX_SGOT	Numeric	6	
82	A_HGB	Numeric	6	
83	D_VIR	Numeric	6	
84	A_HCT	Numeric	6	
85	A_VIR	Numeric	6	
86	D_HCT	Numeric	6	
87	A_SGOT	Numeric	6	
88	MN_HGB	Numeric	6	
89	D_HGB	Numeric	6	
90	MN_HCT	Numeric	6	
91	ACCESSNO	Numeric	8	
** Total **			523	

DATABASE

DEVELOPED BY SHERIKON, INC., 6/91

FOR COMBINED DATA AND VERIFICATION

1 DATABASE: NEW4CDC.DBF

Structure for database: C:\FOXPRO\RIBAV\NEW4CDC.DBF
Number of data records: 2154
Date of last update : 01/03/92

Field	Field Name	Type	Width	Dec
1	ACCESSNO	Numeric	8	
2	PROB_PT	Logical	1	
3	NAME	Character	20	
4	V_NAME	Numeric	2	
5	AGE	Character	4	
6	V_AGE	Numeric	2	
7	AGECALC	Numeric	2	
8	PT_WT	Numeric	5	1
9	V_PT_WT	Numeric	2	
10	SEX	Numeric	2	
11	PT	Numeric	2	
12	V_PT	Numeric	2	
13	W_PREG	Numeric	2	
14	ONSET	Date	8	
15	V_ONSET	Numeric	2	
16	ADMISS	Date	8	
17	V_ADMISS	Numeric	2	
18	D_DCH	Date	8	
19	V_D_DCH	Numeric	2	
20	PREADMIS	Numeric	4	
21	DX	Numeric	2	
22	PRETREAT	Numeric	4	
23	V_DX	Numeric	2	
24	DIAG	Numeric	3	
25	TOTTIME	Numeric	4	
26	MAX_IFA	Numeric	2	
27	OC	Numeric	2	
28	V_OC	Numeric	2	
29	DAMA	Numeric	2	
30	V_DAMA	Numeric	2	
31	CDC_CD	Character	78	
32	D_RX	Date	8	
33	V_D_RX	Numeric	2	
34	T_RX	Numeric	4	
35	V_T_RX	Numeric	2	
36	RX	Numeric	2	
37	V_RX	Numeric	2	
38	RT	Numeric	2	
39	V_RT	Numeric	2	
40	DS	Numeric	2	
41	V_DS	Numeric	2	
42	TOTAL_DS	Numeric	6	1
43	PT_RDM	Numeric	2	
44	V_PT_RDM	Numeric	2	
45	RX_PCL	Character	5	
46	R_RX_CPL	Numeric	2	
47	V_RX_PCL	Numeric	2	
48	DS_RED	Logical	1	
49	V_DS_RED	Numeric	2	
50	DSCPLMD	Numeric	2	
51	V_DSCPLMD	Numeric	2	
52	DSCPLMMD	Numeric	2	
53	V_DSCPLMMD	Numeric	2	
54	PCL_CPL	Numeric	2	
55	INF_CT	Numeric	2	

56	V_INF_CT	Numeric	2
57	EERDIAG	Character	1
58	A_SGOT	Numeric	6
59	A_SGOT_D	Date	8
60	V_A_SGOT	Numeric	2
61	A_VIR	Numeric	6
62	A_VIR_D	Date	8
63	V_A_VIR	Numeric	2
64	A_HCT	Numeric	6
65	A_HCT_D	Date	8
66	V_A_HCT	Numeric	2
67	A_HGB	Numeric	6
68	A_HGB_D	Date	8
69	V_A_HGB	Numeric	2
70	MX_SGOT	Numeric	6
71	MX_SGO_D	Date	8
72	V_MX_SGOT	Numeric	2
73	MX_VIR	Numeric	6
74	MX_VIR_D	Date	8
75	V_MX_VIR	Numeric	2
76	MN_HCT	Numeric	6
77	MN_HCT_D	Date	8
78	V_MN_HCT	Numeric	2
79	MN_HGB	Numeric	6
80	MN_HGB_D	Date	8
81	V_MN_HGB	Numeric	2
82	D_SGOT	Numeric	6
83	D_SGOT_D	Date	8
84	V_D_SGOT	Numeric	2
95	D_VIR	Numeric	6
86	D_VIR_D	Date	8
87	V_D_VIR	Numeric	2
88	D_HCT	Numeric	6
89	D_HCT_D	Date	8
90	V_D_HCT	Numeric	2
91	D_HGB	Numeric	6
92	D_HGB_D	Date	8
93	V_D_HGB	Numeric	2
94	RX_CPL_TX	Character	80
95	LOG	Memo	10
96	RECUSED	Logical	1
97	XTRA_DRUGS	Logical	1
** Total **			541

RELATIONAL DATABASES

DEVELOPED BY SHERIKON, INC., 10/91

2 DATABASES: NEW4TREAT.DBF
NEW4DIAG.DBF

Structure for database: C:\FOXPRO\RIBAV\NEW4DIAG.DBF
Number of data records: 2154
Date of last update : 01/02/92

Id	Field Name	Type	Width	Dec
1	ACCESSNO	Numeric	8	
2	NAME	Character	20	
3	V_ONSET	Numeric	2	
4	V_ADMISS	Numeric	2	
5	V_D_DCH	Numeric	2	
6	PREADMIS	Numeric	4	
7	DX	Numeric	2	
8	PRETREAT	Numeric	4	
9	V_DX	Numeric	2	
10	MAX_IFA	Numeric	2	
11	A_SGOT	Numeric	6	
12	V_A_SGOT	Numeric	2	
13	A_VIR	Numeric	6	
14	V_A_VIR	Numeric	2	
15	A_HCT	Numeric	6	
16	V_A_HCT	Numeric	2	
17	A_HGB	Numeric	6	
18	V_A_HGB	Numeric	2	
19	SHEET	Logical	1	
20	WRITTEN	Logical	1	
21	QUESTNABLE	Logical	1	
22	OLD_LASSA	Logical	1	
23	VI	Character	10	
24	RE	Character	2	
25	LTP	Character	10	
26	RE_	Character	2	
27	NEED_VERIF	Logical	1	
28	IGM	Character	10	
29	IGG	Character	10	
30	SPECL_ATTN	Logical	1	
31	IFA_DATA	Character	12	
** Total **			143	

Structure for database: C:\FOXPRO\RIBAV\NEW4TREA.DBF
Number of data records: 2154
Date of last update : 11/05/91

Fld	Field Name	Type	Width	Dec
1	ACCESSNO	Numeric	8	
2	DS_MIXED	Logical	1	
3	IR_OR	Character	10	
4	TR_DUR_RX	Character	2	
5	TR_PRE_RX	Character	2	
6	XTRA_TR_QS	Character	2	
7	RX_DISCONT	Logical	1	
8	REASON	Character	30	
9	ABORT_PRE	Character	8	
10	ABORT_DUR	Character	8	
11	ABORT_AFTR	Character	8	
12	PREG_OTHER	Character	20	
13	DOSE_CODE	Character	10	
14	NEED_VERIF	Logical	1	
15	SPEC_HANDL	Logical	1	
16	NOTES	Character	20	
17	NAME	Character	20	
18	AGECALC	Numeric	2	
19	SEX	Numeric	2	
20	PT	Numeric	2	
21	W_PREG	Numeric	2	
22	ADMISS	Date	8	
23	PRETREAT	Numeric	4	
24	OC	Numeric	2	
25	V_OC	Numeric	2	
26	D_RX	Date	8	
27	V_D_RX	Numeric	2	
28	T_RX	Numeric	4	
29	V_T_RX	Numeric	2	
30	RX	Numeric	2	
31	V_RX	Numeric	2	
32	RT	Numeric	2	
33	V_RT	Numeric	2	
34	DS	Numeric	2	
35	V_DS	Numeric	2	
36	TOTAL_DS	Numeric	6	
37	RX_PCL	Character	5	
38	XTRA_DRUGS	Logical	1	
39	RX_CPL_TX	Character	80	
** Total **			297	

INTENT TO TREAT

APPENDIX C

ANALYSIS PLAN

PLAN FOR THE ANALYSIS OF DATA FROM A CLINICAL TRIAL OF THE SAFETY AND EFFICACY OF RIBAVIRIN IN INCREASING THE SURVIVAL OF HOSPITALIZED PATIENTS WITH LASSA FEVER

Lassa fever represents a severe and often fatal viral disease that is endemic to West Africa. The disease is caused by an arenavirus and is characterized by a high fever and is accompanied by headache and significant myalgia and malaise. Up until the past five years, the prognosis of Lassa patients was grim, with a reported 16 percent case fatality rate in hospitalized febrile patients[1]. Lassa-convalescent plasma, although the efficacy is unknown, has been the only vehicle with which to treat the disease other than symptomatically. Ribaviran, a nucleoside that has been shown to inhibit viral replication, represents a potentially promising treatment alternative. The following data are based upon a clinical trial of Ribavirin in a West African patient population.

1. INTRODUCTION

The fundamental objective of this analysis is to determine which subgroups of hospitalized patients with SGOT greater than 150 benefit the most from Ribavirin treatment, i.e., which subgroups of patients treated with Ribavirin have the best outcome (survival rate). This document describes the analysis plan for accomplishing this task. It is confined to the interpretation and analysis of the statistical data derived from the clinical trial and does not addresses the methodology used. However, it does addresses the safety and effectiveness of Ribaviran in treating hospitalized Lassa fever patients.

The analysis plan is organized into four sections as follows: (1) analytical issues, (2) effectiveness, (3) safety, and (4) task statement. The analytical issues section considers definitional and other issues that will affect the conduct of the analysis. The next two sections conform to FDA Guidelines for the Format and Content of the Clinical and Statistical Sections of New Drug Applications. The final section considers the technical approach pertinent to specific requirements of the statement of work.

2. ANALYTICAL ISSUES

Several issues were identified that could affect the design and execution of the analysis. These issues include the:

- Identification of cases
- Identification of treatments
- Identification of outcomes
- Changes in the disease over time

Each of these issues is discussed separately below. In addition, a discussion of general analytical issues concludes this section.

2.1 IDENTIFICATION OF CASES

An examination of the literature suggests that cases typically consist of hospitalized individuals with febrile illness (oral or axillary temperature greater than or equal to 38° Centigrade) and:

- Virus isolated from serum or other body fluids/organs

- Seroconversion from titers < 1:4 to >= 1:16 by immunofluorescent antibody (IFA)
- Titer of Lassa-specific antibody >= 1:256 with Lassa-specific IgM antibody titer >= 1:16 on admission

For this trial, the definition of the diagnosis of Lassa fever is based on an initial IFA reading of 30 or any of the following:

- A positive VI or viremia
- A positive PCR (DNA test)

The Lassa status of patients who died can be confirmed by a positive liver touch prep if an autopsy was conducted.

Another important issue is that some of the deaths occurred among non-IFA positive subjects. It could take up to 14 days for patients to develop antibodies to the Lassa virus and since deaths frequently occurred within 7 to 8 days, some patients will have died before their true status is known. This effect would tend to make the presumed control group sicker and thus bias the results in favor of treatment.

2.2 IDENTIFICATION OF TREATMENT

A total of nine treatment groups and a group that received no treatment were identified in the statement of work:

- No treatment
- IV Ribavirin followed by oral dose
- Ribavirin + plasma
- Plasma alone
- Ribavirin + prostacyclin
- Serum aspartate aminotransferase (AST) > 150: IV Ribavirin, high dose/low dose
- AST < 150: Oral Ribavirin, high dose/low dose
- Initial dose 25-30mg Ribavirin, followed by 1/2 dose, 1/4 dose
- Initial dose of 34mg Ribavirin, followed by 1/2 dose, 1/4 dose
- Ribavirin high dose, followed by 1/4 dose
- Ribavirin low dose, followed by 1/8 dose

Some of these treatments were started and not completed because the drug was not available or, the patient did not complete the treatment for other reasons. Patients who completed partial treatment regimens will be examined separately from those who completed the full treatment regimen.

In some instances, the treatment was administered to an insufficient number of patients to achieve acceptable levels of statistical robustness. These instances will be noted in the final analytical report.

2.3 IDENTIFICATION OF OUTCOMES

The assessment of outcome will focus strictly on survival, i.e., discharged alive or dead. The research database also includes a "discharged against medical advice" field which will be analyzed separately to determine if it has any effect on trial results. These patients were discharged to reduce hospital expenses or due to cultural practices.

2.4 CHANGES IN THE DISEASE OVER TIME

Since the study was conducted over a period of more than 10 years, it is possible that it became more or less virulent during this period of time. The results of this would be that the treatment affect could be mis-represented. This is particularly true since patients were not randomly assigned to all treatments throughout the study. The effect of time on outcome will be assessed.

2.5 OTHER ISSUES

The quality of the available data is a key concern. The trial was conducted under less than optimal conditions and preliminary examination of the data suggests that missing and outlier data may pose problems. It will be important to conduct an exhaustive exploratory analysis of the data to establish the level of missing data problems. The variables that are primary to this study and need to be expunged of outliers are:

- Treatment
- SGOT
- Compliance
- Outcome
- Patient type

A separate verification step was incorporated within the trial and the verified data will be used to adjust the results.

Noncompliance also poses an important complicating factor. Noncompliance reflects the inability of staff to correctly follow the prescribed treatment regimen and the patient's failure to adhere to this regimen. Other forms of noncompliance include patient withdrawals and incomplete evaluations. Given the low level of side-effects associated with Ribavirin (rigor), most cessations of therapy are likely due to discharges against medical advice and to the inability to obtain medication.

The effect of aborting fetuses during pregnancy by Lassa fever subjects is also thought to affect outcome by increasing the survival of the mother. To adequately determine the affect of this, it will be controlled for when comparing treatment and control groups.

The analysis will include all eligible patients as long as it is possible to determine that they received some treatment and that their discharge status is known. New treatment categories will be created to reflect the nature of these early withdrawals or will be controlled for in the analysis.

3. EFFECTIVENESS ANALYSIS

The effectiveness analysis considers how well Ribavirin performs in increasing patient survival. Ideally the assessment of performance includes some indication of the dose-response relationship as well as control groups treated with alternative or no therapies. While total dose is recorded in the patient record, it remains to be seen whether this variable is accurate and reliable. However, every effort will be made to verify as many of the total dose levels as possible. Total dose level groups might also be combined to reduce the error inherent in trying to specify the levels so precisely.

To determine effectiveness of the treatment, control groups where no treatment was given, or, where smaller doses and other treatment variations were used will be compared to determine differential effects. Characteristics of the patients will be controlled for, to remove biasing effects. In some instances, groups that appear to be comparable cannot be used because of small sample sizes. Given the long duration of the study, temporal changes in efficacy will also need to be assessed.

The ensuing discussion is organized into five sections as follows:

- Demographic and baseline features of patients
- Effectiveness measures
- Statistical issues
- Examination of subgroups
- Statistical methods

These topic areas relate to content areas suggested in the FDA Guidelines for the Format and Content of the Clinical and Statistical Sections of New Drug Applications.

3.1 DEMOGRAPHIC AND BASELINE FEATURES OF PATIENTS

The FDA guidelines suggest that both group and individual patient characteristics will need to be considered. Each of these areas will be discussed separately below.

3.1.1 Group (Aggregate) Characteristics

The initial analytical steps will entail extensive exploratory analysis of all pertinent variables through simple frequencies, box-plots, measurement of central tendency (where appropriate), and crosstabulations of these variables by key descriptors that include:

- Age
- Sex
- Weight
- Pregnancy
- Abortion status
- Diagnosis

- SGOT
- Viremia
- Other lab values
- Interval between the onset of symptoms and admission
- Interval between onset of symptoms and discharge
- Interval between admission and treatment
- Discharge status

Some of these variables are continuous and may require recoding into categories to support crosstabulation. In establishing categories, we will be guided by accepted standards (National Center for Health Statistics) and the literature.

Extreme values will be identified, flagged and noted in all presentations. A determination will be made as to whether the extreme values should be included in the analysis, replaced with an imputed value or declared unknown.

In addition to conducting these analyses across the totality of patients, the following subgroups will also be examined:

- Diseased versus nondiseased patients
- Treated versus nontreated patients
- Pregnant patients aborting versus those not aborting
- Patients in various lab value ranges for SGOT, viremia, hematocrit, and hemoglobin
- Patients not treated because of Ribavirin unavailability
- Treated compliant versus noncompliant patients
- Patients in different treatment groups

These data presentations will be useful in establishing the statistical properties of the study variables. The primary concern is with missing data but also extends to the data's distributional properties, apparent natural groupings for subsequent analysis, and potential outliers or unusual values. Neither missing values nor outliers can be safely ignored as they could have a significant impact on hypothesis testing. In terms of missings, it is important to identify those patient groups where missings predominate to determine whether the potential for bias exists. Thus, while there are no plans to impute data where missing, the potential impact of missing data on the results will be assessed. Outliers, if found to represent true values, affect the choice of analytical techniques since they may have a strong effect on classical statistics that rely on the normal distribution.

Particular attention must be paid to the accuracy and validity of the dependent variable, mortality. As noted earlier, it is difficult to establish Lassa cases within the first 14 days from the appearance of symptoms. Since patients often died before diagnostic evidence of Lassa, they may confound the

results. The characteristics of patients who expired before a definitive diagnosis need to be carefully considered and, if possible, their status should be reclassified via autopsy or other pertinent data that are available from the CDC.

Ultimately, of course, these variables are of use in further clarifying treatment effects that are likely to be heterogeneous across all groups.

A set of tabular presentations, including all of those listed in the Statement of Work, will be produced and included in the final report.

3.1.2 Individual Characteristics

The FDA requests that listings be made available of individual patient characteristics. We propose to append listings that include the following types of data, with individuals designated by their unique identifier number:

- Demographic (age, sex, weight, pregnancy)
- Diagnostic
- Therapeutic (treatment group, compliance status, initiation and duration of therapy)
- Admission and discharge characteristics (duration of illness, duration of hospitalization, discharge status)
- Laboratory values (IFA titer, SGOT, viremia, hematocrit, hemoglobin)

3.2 EFFECTIVENESS MEASURES

As noted above, the effects of treatment (or nontreatment) will be assessed by whether or not the patient survived their period of hospitalization. Basic survival data will be supplemented by indications of discharges against medical advice where the patient is moribund and likely to die.

3.3 STATISTICAL ISSUES

A subset of patient records were verified and, thus, it is possible to compute error rates for specific variables and to, potentially, adjust the study results based upon these findings. Practically, it is usually undesirable to adjust the data since it complicates the analysis and the interpretation of findings. Thus, we plan to avoid adjustment unless large scale systematic errors are identified with respect to key study variables. In this case, we can weight the data to reflect the probable distribution of this variable based upon the verification study. Separate weights will have to be developed for each variable of interest.

3.4 EXAMINATION OF SUBGROUPS

The main study concern is with the effectiveness of treatment groups in the overall study population. However, from a therapeutic perspective, it is important to know about variations in effectiveness between different subgroups. Depending on the number of these subgroups, there may not be sufficient observations to meet commonly accepted standards for Type I and Type II error.

Treatment outcome will be assessed with respect to the following subgroups:

- Age
- Sex
- Weight
- Pregnancy
- Diagnosis
- IFA titer
- Other laboratory values (i.e., SGOT and viremia)
- Interval between symptoms and admission
- Interval between symptoms and discharge
- Interval between admission and treatment

3.5 STATISTICAL METHODS

The choice of a dichotomous variable as an outcome measure affects the choice of statistical tests. Much of the significance testing will be based upon variations of the chi square. For testing the significance of the differences between the proportion surviving among m treatment groups, the appropriate value of chi square would be computed as follows[2]

$$X^2 = \sum_{i=1}^{m} \sum_{j=1}^{2} \frac{(n_{ij} - n_{i.} n_{.j} / n_{..})^2}{n_{i.} n_{.j} / n_{..}}$$

where the j's are used to designate survival, the i's designate specific treatment groups, and the n's represent observation counts. The chi square has m-1 degrees of freedom. The results can be partitioned to identify the treatments that contributed to the significant difference.

The Mantel-Haenszel chi square will be used to test the homogeneity of treatment effects among subgroups. This test will assess the significance but not the magnitude of treatment differences. A key advantage of the Mantel-Haenszel is in its simplicity and ease of interpretation. More complex multiple logistic models will be applied to this problem to further explicate the relation between treatment and outcome as well as to establish a magnitude dimension for treatment effectiveness.

5. DETAILED TASK PLAN

Some of the issues, analytical principles, and processes required to complete the statement of work have been elucidated in the prior discussion. The ensuing discussion considers these elements with respect to the conduct of specific analytical tasks referenced in the statement of work. The overall timeline for completing these tasks is depicted in Exhibit I.

TASK 1--PREPARE TABULAR LISTINGS ON SELECTED CHARACTERISTICS OF THE PATIENT POPULATION

This activity was discussed in section 3.1. The associated task activities are exploratory and provide an opportunity to understand the statistical properties of specific variables and to assess their potential limitations. A key focus of this effort will be on identifying extreme values (outliers) and values that are outside of the apparent coding protocol. Close liaison will be maintained with the prime contractor to rectify any potential keying errors.

Careful attention will also be paid to the effects of missing values on subsequent analyses. Where missings are determined to represent a major problem, crosstabulations will be prepared by subset variables to identify any patterns that could introduce systematic biases. If potential biases are identified, they will be documented in the final analytical report.

TASK 2--DETERMINE THE HOMOGENEITY OF SUBSET VARIABLES

For the findings to be valid, it is important that no significant differences exist between the various treatment/control groups with respect to any of the important subgroup variables. This analysis needs to extend to the validity of controls in terms of their verified disease status. Further, there should be no systematic differences in terms of compliance, disease status, and other factors that could interfere with the therapeutic efficacy of Ribavirin. The types of subgroups are listed in Section 3.4. A suggested table shell for supporting such analyses is provided as Exhibit II.

The statement of work also stipulates "correlation to eliminate artifactual variables and to highlight real variables." There are numerous opportunities for variables to distort the observed relationship between treatment and outcomes. For example, if the treatment was not effective in adults aged 40 or more years yet only patients in this age group received treatment, then the null hypothesis of no treatment effect could not be rejected. The types of analyses planned for this task, entailing extensive crosstabulations, will be able to identify differences between the various patient groups that could confound the observed relationship between treatment and outcome. However, without a firm grounding in theory based upon medical guidance and an exhaustive review of the literature, it will be difficult to distinguish between artifactual and real variables and effects that have occurred strictly by chance. This limitation will in not diminish the ability to test for treatment effects.

TASK 3--DETERMINE THE BASELINE ERROR RATE FOR EACH SUBSET VARIABLE

As noted in Section 3.3, verification efforts were undertaken for a subset of patients. The implication of this verification effort is that the data could be adjusted to reflect the "true" distribution of particular study variables. Such adjustments will only be undertaken with reluctance since they introduce analytical complexity. Adjustments may be warranted where error rates are high. At a minimum, these adjustments should be undertaken to assess the sensitivity of our assessment of treatment effects.

A proportional weighting scheme will be employed that is based upon the distributions of the verified variables. A separate weight will be developed for each verified variable.

TASK 4--ADJUST THE RESULTS OF THE ANALYSIS BASED UPON VERIFIED DATA

As noted above, proportional weights will be applied in those circumstances where high error rates introduce a high potential for bias. Thus if, for example, a dichotomous variable is observed to have a proportional distribution of .2 and .8 and its verified distribution is .4 and .6, then the value of each observation for those in the first group would receive a weight of 2 while those in the second group

would receive a weight of .75. The effective distribution would, thus, be the same as in the verified population.

TASK 5--ESTABLISH TREATMENT EFFECTS

In establishing treatment effects, both the significance of effects as well as their magnitude are of interest. Given the nature of the data, the most straightforward assessment of beneficial effect is via application of the chi square (see Section 3.5). This approach is also effective in establishing significance effects within the different treatment groups as well as within specific subgroups.

From a clinical perspective, it will also be useful to establish the magnitude of the treatment effect within particular treatments and patient subgroups. Multiple logistic models will be applied to establish these effects.

Nonbeneficial effects will be established with respect to both disease and nondisease groups using the techniques described above. The types of nonbeneficial effects that will be considered are discussed in Section 4. Concomitant medications represent a key subgroup for this analysis.

Ideally, the effectiveness of the treatment will be further supported by the demonstration of a dose-response relationship. Dose is reported in the data file but its completeness has not yet been assessed. There are many pitfalls to the interpretation of dose-response relationships that will require attention. For example, patients who have died soon after hospitalization will have not received a high drug dose. Further, higher doses may cause more adverse outcomes.

TASK 6--DESCRIBE STATISTICAL TESTS USED IN THE ANALYSIS

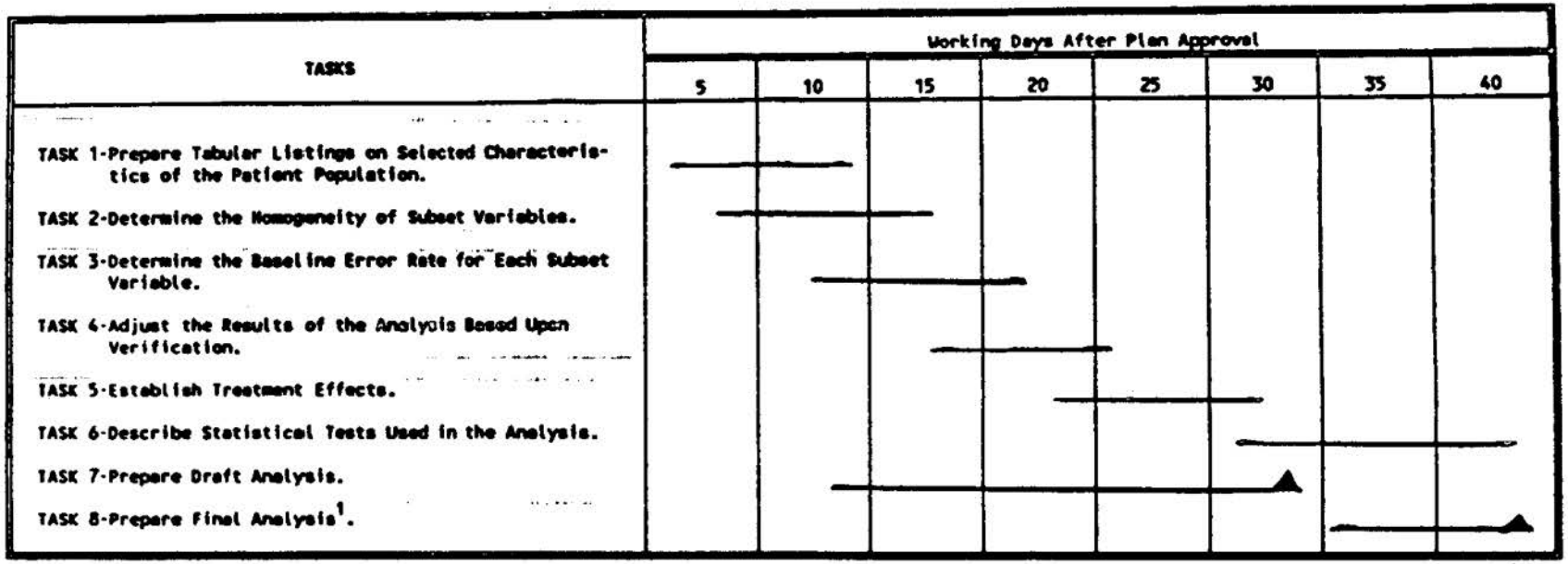
The types of statistical tests to be employed in this analysis have been discussed in Section 3.5. At this stage, we anticipate that most tests will be variants of the chi square given the nature of the data. Other parametric and nonparametric tests will be considered given their appropriateness to the specific data.

1. Joseph B. McCormick, et. al., "A Case-Control Study Of The Clinical Diagnosis And Course Of Lassa Fever," The Journal Of Infectious Diseases, 155(3):445,1987.

2. Joseph L. Fleiss. Statistical Methods for Rates and Proportions. New York: Wiley & Sons, 1981, p. 139.

EXHIBIT I

TASKS SCHEDULES AND DELIVERABLES



[1]Ten (10) working days after draft approval.

▲ --Deliverables.

EXHIBIT II

Table A. Characteristics of patients participating in the lassa fever clinical trials study

PATIENT CHARACTERISTICS	TYPE PATIENT						
	All Patients (n=2160) (%)	Diseased (n=1605) (%)	Non-Diseased (n=215) (%)	Treated (n=1018) (%)	Not Treated (n=1055) (%)	Compliant (n=xxxx) (%)	Non-Compliant (n=xxxx) (%)
Age(Years)							
<5							
5-9							
10-14							
15-19							
20-29							
30-39							
40+							
Unknown							
Gender							
Male							
Female							
Unknown							
Body Weight(Kgs)							
<50							
50-60							
61-70							
71-80							
80+							
Unknown							
Pregnancy Status(Females)							
Pregnant							
Not Pregnant							
Unknown							
Diagnosis							
Lassa Fever							
Not Lassa Fever							
Unknown							
Outcome							
Died							
Survived							
Unknown							
Time:Onset to Admission (Appropriate categories)							
Time:Admission to Treatment (Appropriate categories)							
Time:Onset to Discharge (Appropriate categories)							
Mean Age ± SEM							
Mean Body Weight ± SEM							
Mean Time ± SEM: Onset to Admission							
Mean Time ± SEM: Admission to Treatment							
Mean Time ± SEM: Onset to Discharge							

EXHIBIT II (Continued)

Table B. Characteristics of patients participating in the lassa fever clinical trials study

	TREATMENT GROUP[1]								
	I	II	III	IV	V	VI	VII	VIII	IX
TIENTS CHARACTERISTICS	(n=XX) (%)	(n=XX) (%)	(n=XX) (%)	(n=XX) (%)	(n=XX) (%)	(n=XX) (%)	(n=XX) (%)	(n=XX) (%)	(n=XX) (%)
Age (Years)									
<5									
5-9									
10-14									
15-19									
20-29									
30-39									
40+									
Unknown									
Gender									
Male									
Female									
Unknown									
Body Weight(Kgs)									
<50									
50-60									
61-70									
71-80									
80+									
Unknown									
Pregnancy Status (Females)									
Pregnant									
Not Pregnant									
Unknown									
gnosis									
ssa Fever									
ot Lassa Fever									
Unknown									
Outcome									
Died									
Survived									
Unknown									
Time: Onset to Admission (Appropriate categories)									
Time: Admission to Treatment (Appropriate categories)									
Time: Onset to Discharge (Appropriate categories)									
Mean Age ± SEM									
Mean Body Weight ± SEM									
Mean Time ± SEM: Onset to Admission									
Mean Time ± SEM: Admission to Treatment									
Mean Time ± SEM: Onset to Discharge									

T- ment groups are as follows:
- IV Ribavirin followed by oral dose.
- Ribavirin + prostacyclin.
- AST <150 : Oral Ribavirin, high dose/low dose.
- Initial dose of 34 mg Ribavirin, followed by 1/2 dose 1/4 dose.

IX--Ribavirin low dose, followed by 1/8 dose.

II--Ribavirin, Ribavirin + Plasma, Plasma.
IV--AST>150 : IV Ribavirin, high dose/low dose.
VI--Initial dose 25-30 mg Ribavirin, followed by 1/2 dose, 1/4 dose.
VIII--Ribavirin high dose, followed by 1/4 dose.

EXHIBIT II (Continued)

Table C. Laboratory results of patients participating in the lassa fever clinical trials study

LABORATORY RESULTS	TYPE PATIENT						
	All Patients	Diseased	Non-Diseased	Treated	Not Treated	Compliant	Non-Compliant
	(n=2160) (%)	(n=1605) (%)	(n=215) (%)	(n=1018) (%)	(n=1055) (%)	(n=xxxx) (%)	(n=xxxx) (%)
SGOT (Appropriate categories)							
Hematocrit (Appropriate categories)							
Hemoglobin (Appropriate categories)							
Viremia (Appropriate categories)							
Mean SGOT ± SEM Mean Hematocrit ± SEM Mean Hemoglobin ± SEM Mean Viremia ± SEM							

EXHIBIT II (Continued)

Table D. Laboratory results of patients participating in the lassa fever clinical trials study

LABORATORY RESULTS	TREATMENT GROUP								
	I	II	III	IV	V	VI	VII	VIII	IX
	(n=xx) (%)	(n=xx) (%)	(n=xx) (%)	(n=xx) (%)	(n=xx) (%)	(n=xx) (%)	(n=xx) (%)	(n=xx) (%)	(n=xx) (%)
SGOT (Appropriate categories)									
Hematocrit (Appropriate categories)									
Hemoglobin (Appropriate categories)									
Viremia (Appropriate categories)									
Mean SGOT ± SEM Mean Hematocrit ± SEM Mean Hemoglobin ± SEM Mean Viremia ± SEM									

LEGEND TO TABLES

1. Cases with an asterisks are those who discontinued treatment.
2. Minus nine (-9) represents missing data.
3. Age is in years.
4. For pregnancy, one (1) indicates pregnancy and two (2) not pregnant. Pregnancy status is given fol all females.
5. Onset to Admission, Admission to Treatment, and Onset to Discharge are in days.
6. Diagnosis: One (1)=Non-Lassa Two (2)=Lassa.
7. Gender: One (1)=Male Two (2)=Female.
8. Treatment Groups:

Code Treatment Description
0-Control Group (no treatment)
1-Ribavirin only, minus doses 5,6,7,8,9,10 and prostacyclin
2-Ribavirin + plasma
3-Plasma only
5-Ribavirin (dose 5)
6-Ribavirin (dose 6)
7-Ribavirin (dose 7)
8-Ribavirin (dose 8)
9-Ribavirin (dose 9)
10-Ribavirin (dose 10)
11-Ribavirin (dose 11)
12-Ribavirin + prostacyclin
13-Assigned to ribavirin treatment group but drug was not available

APPENDIX D

LISTING OF DECEASED PATIENTS

PATIENTS WHO DIED BY SELECTED CHARACTERISTICS

Patient ID	Age (YEARS)	Pregnant	Maximum IFA	Admission SGOT	Admission Viremia	Onset to Admission	Admission to Treatment	Onset to Discharge	Diagnosis	Treatment	Gender
79127799	-9	-9	30	1187	-9	3	-9	3	1	-9	-9
83087534	-9	-9	22	40	-9	-9	0	-9	-9	1	-9
83087623*	30	-9	22	7682	-9	4	-9	5	-9	-9	-9
83087625	37	-9	40	11176	-9	16	-9	17	-9	-9	-9
83087654	-9	-9	24	314	-9	2	-9	2	-9	-9	-9
79127998	-9	-9	-9	1187	-9	3	-9	3	2	1	-9
83087183	39	-9	40	4540	-9	12	0	12	-9	1	-9
83087686*	14	-9	56	349	-9	14	-9	14	-9	1	-9
87048093	32	-9	-9	2081	-9	10	0	10	2	1	-9
79127351	22	-9	40	3754	-9	10	3	24	2	2	-9
83087856*	-9	-9	-9	168	-9	9	0	18	-9	5	-9
83087861*	-9	-9	-9	17	-9	3	9	13	-9	5	-9
87048327	-9	-9	24	5323	-9	12	0	3	2	9	-9
87048351*	39	-9	30	1963	-9	6	1	8	2	10	-9
79127165*	46	-9	22	349	-9	3	1	5	2	-9	1
79127271*	26	-9	22	3422	-9	13	0	13	2	-9	1
83087202	-9	-9	40	91	-9	12	-9	30	-9	-9	1
83087631	-9	-9	22	167	-9	3	-9	5	-9	-9	1
83087689	50	-9	22	4190	-9	13	-9	14	-9	-9	1
87048282	-9	-9	40	68	-9	11	-9	14	2	-9	1
76087168	32	-9	53	-9	-9	6	-9	15	2	0	1
76087169	15	-9	38	-9	41	6	-9	13	2	0	1
76087187	16	-9	58	-9	-9	4	-9	9	2	0	1
76087238	22	-9	37	-9	-9	2	-9	5	2	0	1
76087241	27	-9	40	-9	-9	12	-9	27	2	0	1
76087249	29	-9	64	-9	70	3	-9	3	2	0	1
76087279	26	-9	40	-9	-9	3	-9	4	2	0	1
76087332	28	-9	22	-9	55	9	-9	10	2	0	1
76087345	55	-9	22	-9	40	5	-9	6	2	0	1
76087570	15	-9	38	-9	-9	2	-9	10	2	0	1
76091082	-9	-9	58	-9	-9	4	-9	7	2	0	1
76091110	29	-9	40	-9	-9	3	-9	6	2	0	1
76091137	55	-9	56	-9	-9	5	-9	9	2	0	1
76091176	37	-9	40	-9	3	21	-9	21	2	0	1
76091193	22	-9	56	-9	56	13	-9	16	2	0	1
76091223	27	-9	22	-9	-9	6	-9	8	2	0	1
76091251	17	-9	40	110	4	3	-9	6	2	0	1
76091272	15	-9	40	-9	-9	5	-9	16	2	0	1
76091320	25	-9	60	-9	-9	9	-9	14	2	0	1
76091384	46	-9	22	-9	3	3	-9	7	2	0	1
76091511	42	-9	40	-9	-9	6	-9	13	2	0	1
76091552	39	-9	41	-9	-9	5	-9	16	2	0	1
76091627	27	-9	40	-9	-9	5	-9	11	2	0	1
76091648	30	-9	55	934	50	9	-9	11	2	0	1
76091691	30	-9	54	32	23	6	-9	13	2	0	1
76091735	27	-9	54	83	36	3	-9	8	2	0	1
76093014	22	-9	-9	-9	6	11	-9	13	2	0	1
76093091	35	-9	58	150	30	5	-9	14	2	0	1
76093150	26	-9	58	-9	-9	6	-9	10	2	0	1
76093159	27	-9	22	-9	-9	6	-9	7	2	0	1
76093166	45	-9	22	-9	-9	4	-9	12	2	0	1
76093264	38	-9	-9	-9	-9	3	-9	14	2	0	1
76093273	22	-9	-9	-9	6	10	-9	11	2	0	1
76093298	15	-9	40	-9	1	4	-9	11	2	0	1
76093304	35	-9	52	2386	45	13	-9	15	2	0	1
76093372	25	-9	22	470	60	13	-9	14	2	0	1
76093586	35	-9	58	-9	1	11	-9	13	2	0	1
76093640	35	-9	40	-9	-9	9	-9	13	2	0	1

PATIENTS WHO DIED BY SELECTED CHARACTERISTICS

Patient ID	Age (YEARS)	Pregnant	Maximum IFA	Admission SGOT	Admission Viremia	Onset to Admission	Admission to Treatment	Onset to Discharge	Diagnosis	Treatment	Gender
76095428	25	-9	40	1627	40	4	-9	6	2	0	1
76095468	25	-9	55	-9	-9	7	-9	11	2	0	1
76095517	22	-9	22	110	35	2	-9	8	2	0	1
76098018	27	-9	40	1723	-9	2	-9	2	2	0	1
76098065	30	-9	40	-9	-9	1	-9	13	2	0	1
76098076	28	-9	40	-9	-9	8	-9	11	2	0	1
76098106	28	-9	58	834	56	6	-9	10	2	0	1
76098133	32	-9	58	3571	51	6	-9	7	2	0	1
76098311	33	-9	22	-9	41	4	-9	7	2	0	1
76098312	25	-9	54	-9	46	6	-9	9	2	0	1
76098500	6	-9	38	-9	-9	12	-9	14	2	0	1
76098522	5	-9	38	-9	-9	3	-9	3	2	0	1
79127018	17	-9	22	-9	-9	12	-9	15	2	0	1
79127093	26	-9	22	-9	2	5	-9	7	2	0	1
79127296	36	-9	61	51	-9	6	-9	21	2	0	1
79127400	26	-9	40	84	-9	4	-9	13	2	0	1
79127429	26	-9	55	3213	-9	10	-9	11	2	0	1
79127504	32	-9	58	13409	-9	12	-9	13	2	0	1
79127569	40	-9	40	5413	-9	6	-9	9	2	0	1
79127819	35	-9	-9	-9	-9	8	-9	8	2	0	1
83087082	30	-9	56	37	1	3	-9	4	2	0	1
83087485	50	-9	54	6111	-9	11	-9	13	2	0	1
87048068	7	-9	-9	76	-9	14	-9	18	2	0	1
76087130	22	-9	56	159	41	0	-9	6	2	1	1
76087138	32	-9	22	605	41	6	-9	11	2	1	1
76087505	22	-9	40	-9	-9	13	-9	21	2	1	1
76087712	47	-9	40	1711	50	6	-9	22	2	1	1
76087822	56	-9	53	-9	-9	20	-9	31	2	1	1
76098267	25	-9	34	-9	1	6	-9	7	2	1	1
76098391	28	-9	40	45	21	6	-9	16	2	1	1
79127175	43	-9	55	173	1	9	1	11	2	1	1
79127211	43	-9	22	520	-9	4	2	8	2	1	1
79127369	38	-9	22	9638	1	6	1	8	2	1	1
79127451	29	-9	22	309	2	8	1	10	2	1	1
79127639	70	-9	56	1606	-9	3	4	9	2	1	1
79127649	32	-9	40	314	21	6	0	20	2	1	1
79127664	16	-9	58	-9	-9	5	1	15	2	1	1
79127695	26	-9	22	9079	46	8	0	10	2	1	1
79127733	25	-9	34	960	1	14	4	43	2	1	1
79127762	25	-9	32	120	26	4	2	14	2	1	1
79127784	22	-9	22	820	-9	6	1	12	2	1	1
79127816	30	-9	54	1536	51	7	0	8	2	1	1
79127845	50	-9	59	323	51	23	-9	31	2	1	1
79127865	30	-9	54	3929	51	11	-9	13	2	1	1
79127868	45	-9	58	5902	-9	8	-9	13	2	1	1
79127874	24	-9	60	1851	46	7	-9	16	2	1	1
79127980	60	-9	22	2305	-9	6	-9	7	1	1	1
83087086	-9	-9	2	279	-9	-9	-9	-9	2	1	1
83087093	42	-9	40	68	21	2	-9	11	2	1	1
83087094	64	-9	40	49	1	6	2	24	2	1	1
83087185	-9	-9	40	2392	-9	7	0	21	-9	1	1
83087190	-9	-9	40	1676	-9	7	0	24	-9	1	1
83087203	-9	-9	40	1746	-9	14	1	15	-9	1	1
83087215	-9	-9	40	12746	-9	4	0	24	-9	1	1
83087224	-9	-9	24	39809	-9	2	0	4	2	1	1
83087275	-9	-9	56	629	-9	6	0	11	2	1	1
83087388	42	-9	40	2794	26	12	0	15	2	1	1
83087408	6	-9	34	140	-9	6	4	16	2	1	1
83087447	65	-9	52	91	-9	4	3	8	2	1	1

PATIENTS WHO DIED BY SELECTED CHARACTERISTICS

Patient ID	Age (YEARS)	Pregnant	Maximum IFA	Admission SGOT	Admission Viremia	Onset to Admission	Admission to Treatment	Onset to Discharge	Diagnosis	Treatment	Gender
83087458	60	-9	40	140	46	3	1	12	2	1	1
83087587	42	-9	34	161	1	6	-9	7	2	1	1
83087603	38	-9	40	419	-9	5	1	12	2	1	1
83087615	7	-9	22	279	2	14	0	17	2	1	1
83087618	27	-9	34	279	-9	2	2	12	2	1	1
83087642	18	-9	56	279	1	4	0	16	2	1	1
83087644*	45	-9	56	16412	41	6	0	7	2	1	1
83087660	18	-9	60	210	-9	6	2	10	2	1	1
83087673	48	-9	22	17460	-9	1	2	4	2	1	1
83087693	56	-9	22	210	-9	6	-9	9	2	1	1
83087703	25	-9	40	20952	31	13	0	14	2	1	1
83087708*	22	-9	22	182	16	6	0	11	2	1	1
83087711	46	-9	22	384	1	13	0	24	2	1	1
83087768*	39	-9	22	-9	1	7	0	9	-9	1	1
83087776	25	-9	40	96	-9	16	-9	31	2	1	1
83087778*	30	-9	40	1005	46	9	0	10	2	1	1
83087793	30	-9	40	-9	-9	7	2	13	2	1	1
83087803*	35	-9	56	-9	1	6	-9	6	2	1	1
83087811	23	-9	54	747	51	10	0	10	2	1	1
83087884	25	-9	24	1388	31	7	0	8	2	1	1
83087892	36	-9	22	40	1	7	-9	8	-9	1	1
83087918	32	-9	22	423	1	7	1	8	2	1	1
83087960	32	-9	34	1736	-9	6	1	8	2	1	1
83087961	18	-9	56	1823	-9	11	-9	36	2	1	1
83087989	26	-9	-9	206	-9	5	1	9	2	1	1
83087992	39	-9	24	4285	-9	3	0	3	2	1	1
83087996	30	-9	24	194	-9	7	0	10	2	1	1
83087999	32	-9	24	589	-9	6	0	2	2	1	1
87048003	60	-9	-9	283	-9	9	0	17	2	1	1
87048005	22	-9	-9	1691	-9	14	0	16	2	1	1
87048020	60	-9	-9	333	-9	6	0	13	2	1	1
87048030	35	-9	-9	587	-9	22	0	22	2	1	1
87048035	22	-9	-9	5287	-9	11	0	11	2	1	1
87048053	22	-9	-9	44	-9	12	7	24	2	1	1
87048056*	38	-9	-9	337	-9	5	0	7	2	1	1
87048064*	27	-9	-9	7105	-9	7	0	8	2	1	1
87048066	26	-9	-9	413	-9	7	0	15	2	1	1
87048071*	23	-9	-9	10387	-9	3	0	3	2	1	1
87048083	2	-9	-9	68	-9	1	92	11	1	1	1
87048084	30	-9	-9	5430	-9	12	0	15	2	1	1
87048088	-9	-9	-9	-9	-9	-9	-9	-9	1	1	1
87048089	45	-9	-9	551	-9	129	0	134	2	1	1
87048115	25	-9	-9	4637	-9	6	-9	7	2	1	1
87048126	30	-9	-9	278	-9	7	0	17	2	1	1
87048244	26	-9	24	231	0	6	2	11	2	1	1
76087939	26	-9	57	206	41	7	0	16	2	2	1
76087296	40	-9	40	488	45	6	-9	8	2	3	1
76087329	18	-9	57	112	1	3	-9	5	2	3	1
76087503	20	-9	38	1329	51	3	-9	5	2	3	1
76098269	38	-9	55	14	1	19	-9	20	2	3	1
76098332	32	-9	54	351	61	6	-9	7	2	3	1
76098352	48	-9	56	-9	36	10	-9	14	2	3	1
83087743	1	-9	-9	-9	-9	14	2	27	-9	5	1
83087779	14	-9	55	-9	-9	10	7	32	2	5	1
83087841*	14	-9	22	597	-9	7	1	8	2	5	1
83087857	-9	-9	22	1009	1	2	0	2	2	5	1
83087876	4	-9	24	68	-9	6	13	13	-9	5	1
83087905	15	-9	22	1380	31	3	0	3	2	5	1
83087908	13	-9	22	53	1	13	0	16	-9	5	1

PATIENTS WHO DIED BY SELECTED CHARACTERISTICS

Patient ID	Age (YEARS)	Pregnant	Maximum IFA	Admission SGOT	Admission Viremia	Onset to Admission	Admission to Treatment	Onset to Discharge	Diagnosis	Treatment	Gender
83087286	38	-9	40	786	-9	2	0	95	2	7	1
87048261	25	-9	24	286	-9	4	0	10	1	9	1
87048268	3	-9	-9	897	-9	12	0	-9	1	9	1
87048271	50	-9	-9	4072	-9	10	0	12	1	9	1
87048273	45	-9	40	1360	-9	11	0	14	1	9	1
87048279	26	-9	0	1731	-9	7	0	9	1	9	1
87048304	30	-9	-9	2159	-9	20	0	20	1	9	1
87048305	36	-9	-9	405	-9	4	2	12	1	9	1
87048308	29	-9	-9	6397	-9	15	0	17	1	9	1
87048318*	55	-9	24	128	-9	6	2	9	1	9	1
87048323*	40	-9	24	7582	-9	12	2	7	1	9	1
87048330*	-9	-9	24	1518	-9	4	10	16	1	9	1
87048341	37	-9	40	3295	-9	15	0	19	2	9	1
87048353	29	-9	-9	839	-9	7	0	-9	2	10	1
87048355	28	-9	0	2657	-9	8	0	9	1	10	1
87048360	-9	-9	0	911	-9	8	0	10	1	10	1
87048365	17	-9	24	1044	-9	11	0	11	1	10	1
87048378	-9	-9	40	193	-9	8	-9	12	2	10	1
83087102	33	-9	22	77	2	2	5	7	2	12	1
83087419	18	-9	34	140	21	3	-9	15	2	12	1
83087454	30	-9	40	47	31	2	-9	54	2	12	1
83087516	25	-9	40	349	31	9	1	17	2	12	1
83087583	25	-9	34	238	41	6	2	14	2	12	1
83087772*	30	-9	22	105	31	7	0	8	2	12	1
83087812	27	-9	59	12222	21	2	0	2	2	12	1
87048133	33	-9	-9	953	-9	14	-9	15	2	13	1
87048135	30	-9	-9	6653	-9	13	-9	13	2	13	1
87048138	47	-9	-9	3733	-9	22	1	24	2	13	1
87048155	55	-9	24	1756	-9	14	-9	16	2	13	1
87048158	8	-9	14	2316	-9	14	-9	14	2	13	1
87048194	17	-9	40	736	-9	11	-9	13	-9	13	1
87048205	-9	-9	24	110	-9	5	-9	11	-9	13	1
76087644	-9	2	-9	-9	-9	10	-9	14	-9	-9	2
79127017	40	-9	22	2	-9	4	-9	-9	-9	-9	2
79127638	16	2	22	37	-9	6	-9	9	-9	-9	2
83087283	20	2	54	351	-9	3	-9	7	-9	-9	2
83087632	-9	2	40	84	-9	-9	-9	-9	-9	-9	2
83087662	25	2	56	9778	-9	9	-9	9	-9	-9	2
87048055	-9	1	40	967	-9	-9	-9	-9	2	-9	2
87048061	25	2	-9	318	-9	14	-9	16	2	-9	2
87048074	30	2	-9	113	-9	8	-9	9	1	-9	2
76087017	25	2	56	-9	-9	2	-9	2	2	0	2
76087088	22	1	40	-9	-9	1	-9	13	2	0	2
76087175	32	2	38	-9	-9	3	-9	19	2	0	2
76087194	15	2	40	-9	-9	2	-9	12	2	0	2
76087205	22	2	56	-9	-9	14	-9	21	2	0	2
76087226	35	2	41	-9	-9	5	-9	24	2	0	2
76087234	45	2	58	-9	-9	6	-9	27	2	0	2
76087263	22	2	54	-9	-9	0	-9	9	2	0	2
76087284	22	2	22	-9	-9	3	-9	9	2	0	2
76087334	38	2	22	-9	-9	4	-9	11	2	0	2
76087418	35	1	22	-9	51	6	-9	9	2	0	2
76087423	30	2	37	-9	-9	5	-9	7	2	0	2
76087428	28	2	38	-9	-9	13	-9	18	2	0	2
76087487	21	1	59	-9	-9	0	-9	6	2	0	2
76087535	18	2	22	-9	-9	1	-9	3	2	0	2
76087636	30	2	36	-9	-9	4	-9	22	2	0	2
76087780	26	2	40	54	-9	5	-9	23	2	0	2
76087791	32	1	40	-9	-9	3	-9	15	2	0	2

PATIENTS WHO DIED BY SELECTED CHARACTERISTICS

Patient ID	Age (YEARS)	Pregnant	Maximum IFA	Admission SGOT	Admission Viremia	Onset to Admission	Admission to Treatment	Onset to Discharge	Diagnosis	Treatment	Gender
76087792	20	2	22	-9	-9	8	-9	26	2	0	2
76091072	15	2	40	-9	-9	6	-9	8	2	0	2
76091127	27	2	40	-9	-9	3	-9	9	2	0	2
76091245	32	2	40	-9	-9	13	-9	16	2	0	2
76091252	32	2	55	-9	-9	3	-9	13	2	0	2
76091310	22	2	57	-9	-9	6	-9	9	2	0	2
76091363	22	2	22	-9	4	6	-9	11	2	0	2
76091377	45	2	40	-9	-9	5	-9	19	2	0	2
76091395	17	2	62	-9	-9	6	-9	9	2	0	2
76091609	27	2	40	-9	-9	13	-9	14	2	0	2
76091626	17	2	22	-9	4	10	-9	16	2	0	2
76091651	45	2	53	-9	55	2	-9	4	2	0	2
76091653	25	2	32	-9	10	5	-9	5	2	0	2
76091677	60	2	56	-9	1	2	-9	3	2	0	2
76091687	20	2	40	1852	-9	4	-9	7	2	0	2
76091688	32	2	56	-9	51	4	-9	6	2	0	2
76091692	30	2	22	-9	-9	6	-9	12	2	0	2
76091693	29	2	-9	-9	-9	6	-9	15	2	0	2
76091764	32	2	40	-9	-9	1	-9	7	2	0	2
76091782	33	2	22	-9	-9	6	-9	12	2	0	2
76093018	18	2	40	-9	-9	9	-9	21	2	0	2
76093032	17	2	55	-9	-9	14	-9	15	2	0	2
76093036	35	2	-9	-9	6	1	-9	3	2	0	2
76093040	27	2	25	228	45	4	-9	6	2	0	2
76093057	17	2	40	-9	-9	3	-9	47	2	0	2
76093069	17	2	56	-9	-9	3	-9	6	2	0	2
76093223	21	2	58	-9	-9	6	-9	15	2	0	2
76093373	25	2	58	-9	1	13	-9	14	2	0	2
76093380	25	2	58	-9	-9	2	-9	6	2	0	2
76093664	29	2	59	-9	25	3	-9	12	2	0	2
76093668	17	2	58	1498	45	13	-9	17	2	0	2
76095403	25	2	22	-9	-9	4	-9	8	2	0	2
76095459	25	2	57	-9	-9	3	-9	7	2	0	2
76095467	27	2	40	-9	-9	7	-9	9	2	0	2
76095568	27	2	58	-9	-9	2	-9	22	2	0	2
76095571	17	2	40	-9	-9	5	-9	13	2	0	2
76098108	18	2	58	-9	-9	12	-9	19	2	0	2
76098239	30	2	58	-9	-9	2	-9	4	2	0	2
76098315	22	2	36	-9	-9	9	-9	9	2	0	2
76098465	28	2	59	-9	-9	5	-9	11	2	0	2
79127326	24	2	22	19	-9	5	-9	7	1	0	2
79127644	14	2	56	-9	-9	4	-9	8	2	0	2
79127682	20	2	32	2654	41	7	-9	8	2	0	2
79127983	26	2	56	30	1	6	-9	14	2	0	2
83087343	32	2	54	1885	-9	2	-9	2	2	0	2
83087356	23	2	52	1873	-9	6	-9	9	2	0	2
83087416	32	2	22	11873	-9	13	-9	13	2	0	2
83087420	32	2	22	13968	-9	378	-9	14	2	0	2
83087505	14	2	54	2270	-9	8	-9	9	2	0	2
83087521	58	2	22	91	16	3	-9	4	2	0	2
83087560	40	2	56	1396	51	5	-9	5	2	0	2
83087582	27	2	54	8381	-9	6	-9	6	2	0	2
83087589	32	2	54	56	21	2	-9	3	2	0	2
83087590	28	2	34	-9	-9	2	-9	4	2	0	2
83087651	40	2	40	3492	-9	9	-9	9	2	0	2
83087748	30	2	54	3492	31	14	-9	14	2	0	2
76087879	42	2	22	1328	-9	6	-9	8	2	1	2
76087919	36	2	55	47	-9	3	11	16	2	1	2
76098342	28	2	55	-9	-9	6	-9	11	2	1	2

PATIENTS WHO DIED BY SELECTED CHARACTERISTICS

Patient ID	Age (YEARS)	Pregnant	Maximum IFA	Admission SGOT	Admission Viremia	Onset to Admission	Admission to Treatment	Onset to Discharge	Diagnosis	Treatment	Gender
76098348	35	2	38	-9	31	7	-9	8	2	1	2
76098371	18	2	22	-9	1	1	-9	1	-9	1	2
79127418	40	2	40	2462	51	13	0	16	2	1	2
79127727	24	2	32	14	1	13	0	20	2	1	2
79127862	49	2	60	56	46	4	-9	10	2	1	2
79127864	15	2	22	821	51	4	-9	7	2	1	2
79127920	30	2	58	166	21	7	-9	18	2	1	2
83087005	28	1	52	4400	-9	3	10	14	2	1	2
83087084	35	2	2	309	-9	-9	2	-9	-9	1	2
83087178	20	2	40	3492	41	7	0	10	2	1	2
83087209	-9	2	24	161	-9	8	2	11	-9	1	2
83087210	-9	-9	56	391	-9	7	1	8	-9	1	2
83087261*	-9	1	22	93	-9	2	2	4	-9	1	2
83087272	15	2	-9	265	-9	13	1	15	2	1	2
83087274	-9	2	-9	21	-9	6	2	12	2	1	2
83087290	-9	2	-9	161	-9	8	2	11	-9	1	2
83087326*	26	2	40	13968	-9	9	3	15	2	1	2
83087359*	18	2	40	18158	-9	8	5	13	2	1	2
83087367	55	2	40	168	21	6	1	22	2	1	2
83087405	22	2	60	2095	21	6	-9	19	2	1	2
83087437	34	2	56	2794	46	6	-9	10	2	1	2
83087445	28	1	22	13270	-9	6	2	8	2	1	2
83087448	34	1	22	2095	21	2	1	5	2	1	2
83087515	30	2	40	342	21	13	0	24	2	1	2
83087584*	50	2	60	300	-9	6	2	8	2	1	2
83087591	29	1	34	314	-9	2	0	8	2	1	2
83087613	28	2	53	253	36	11	-9	22	2	1	2
83087653	40	2	34	1117	31	4	0	6	2	1	2
83087657	25	2	60	1729	51	15	0	16	2	1	2
83087661	6	2	22	227	-9	2	2	14	2	1	2
83087665	30	1	22	908	26	9	0	13	2	1	2
83087668	26	1	34	182	-9	20	0	24	2	1	2
83087671	24	1	22	237	41	6	1	8	2	1	2
83087679*	16	2	40	349	31	6	0	10	2	1	2
83087731	30	2	22	-9	-9	5	-9	6	-9	1	2
83087745*	30	1	22	-9	1	7	0	8	-9	1	2
83087809	25	2	22	-9	-9	4	4	9	-9	1	2
83087825	28	2	24	112	-9	4	3	15	-9	1	2
83087847	32	2	22	-9	-9	14	3	22	-9	1	2
83087951	25	2	24	773	-9	6	-9	6	2	1	2
83087963	32	1	22	-9	-9	11	0	12	-9	1	2
83087966	40	2	22	1178	-9	13	-9	14	2	1	2
83087991	28	2	24	236	-9	8	2	11	2	1	2
87048022	29	1	-9	1907	-9	14	0	15	2	1	2
87048062*	19	1	-9	1101	-9	8	0	9	2	1	2
87048078	15	2	-9	24	-9	7	3	20	1	1	2
87048087	34	1	-9	757	-9	7	0	9	2	1	2
87048110	28	2	-9	149	-9	7	3	22	2	1	2
87048111	15	2	-9	5131	-9	6	1	8	2	1	2
87048112	18	2	-9	2277	-9	7	0	8	2	1	2
87048122	35	2	-9	8859	-9	7	0	10	2	1	2
87048123	20	-9	-9	459	-9	8	2	10	2	1	2
87048238*	41	2	24	295	-9	7	0	7	1	1	2
87048245	10	2	24	3243	-9	6	0	7	1	1	2
87048252	6	2	40	1376	-9	7	2	14	2	1	2
87048254	26	1	40	169	-9	7	1	-9	2	1	2
87048255	22	2	24	106	-9	4	6	-9	1	1	2
76087654	30	2	22	6494	66	7	-9	8	2	2	2
76087845	55	2	57	960	51	6	-9	10	2	2	2

PATIENTS WHO DIED BY SELECTED CHARACTERISTICS

Patient ID	Age (YEARS)	Pregnant	Maximum IFA	Admission SGOT	Admission Viremia	Onset to Admission	Admission to Treatment	Onset to Discharge	Diagnosis	Treatment	Gender
79127001	36	2	59	4680	-9	13	1	16	2	2	2
79127016	56	2	57	3702	45	7	0	18	2	2	2
79127399	-9	2	40	8311	31	8	0	11	2	2	2
79127999	22	1	26	12	-9	2	-9	61	2	2	2
76087086	46	1	56	352	7	3	-9	6	2	3	2
76087118	22	2	58	296	51	5	-9	8	2	3	2
76087144	18	1	40	-9	-9	9	-9	12	2	3	2
76087734	30	1	55	573	-9	5	-9	10	2	3	2
76098271	17	2	38	-9	51	4	-9	7	2	3	2
76098347	25	2	40	-9	-9	9	-9	26	2	3	2
79127052	24	1	22	7892	-9	6	0	8	2	3	2
79127185	20	1	22	3771	46	1	0	2	2	3	2
79127192	36	1	59	38	26	10	0	12	2	3	2
79127238	18	2	22	2217	46	6	-9	8	2	3	2
79127355	34	1	40	1065	31	6	0	10	2	3	2
79127414	24	2	22	126	2	9	1	11	2	3	2
79127459	30	1	57	1938	-9	2	1	5	2	3	2
83087700	11	2	22	224	1	6	0	8	2	5	2
83087400	26	1	22	9778	-9	9	-9	10	2	6	2
83087714	36	1	22	6884	-9	6	0	7	2	6	2
83087735	27	1	-9	-9	-9	6	0	6	-9	6	2
83087752*	35	1	22	838	-9	3	0	3	2	6	2
83087756*	20	1	22	127	1	6	0	7	-9	6	2
83087759	40	1	22	-9	-9	6	0	15	-9	6	2
83087860*	15	2	22	203	1	6	0	7	2	6	2
83087879	22	1	40	21	41	6	1	16	2	6	2
83087917	20	1	-9	987	-9	4	1	11	-9	6	2
83087248	-9	2	20	168	-9	14	1	32	2	8	2
83087297	12	2	38	2794	-9	5	0	17	2	8	2
87048291	49	2	-9	564	-9	3	0	5	2	9	2
87048298	33	2	-9	3527	-9	7	1	-9	2	9	2
87048358	32	2	0	37362	-9	7	0	8	1	10	2
87048372	-9	-9	38	621	-9	20	-9	16	2	10	2
79128000	20	1	58	8171	-9	15	-9	16	2	12	2
83087207	-9	1	22	3841	-9	7	0	8	-9	12	2
83087338	22	2	40	1174	41	7	0	20	2	12	2
83087509*	17	1	40	2549	51	4	0	8	2	12	2
83087551*	17	2	22	13968	21	6	0	6	2	12	2
83087579	3	2	40	489	1	20	1	26	2	12	2
83087595	14	2	34	9079	-9	3	1	6	2	12	2
83087611*	22	2	40	112	-9	5	3	10	2	12	2
87048130	30	1	-9	3927	-9	8	-9	9	2	13	2
87048146	55	2	24	3363	-9	6	-9	7	2	13	2
87048147	8	2	56	3833	-9	6	-9	7	2	13	2
87048156	6	2	24	59	-9	4	-9	6	2	13	2
87048161	22	2	24	3551	-9	14	-9	17	2	13	2
87048181	-9	2	24	269	-9	3	-9	7	-9	13	2
87048188	-9	-9	40	60703	0	13	-9	14	2	13	2
87048199	-9	-9	24	5618	-9	7	-9	7	-9	13	2
87048219	-9	-9	56	3935	-9	4	-9	4	-9	13	2
87048223	-9	-9	56	1027	-9	2	-9	9	-9	13	2
87048227	-9	-9	40	287	-9	6	-9	15	-9	13	2