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Short communication

# Inter-Company Collaboration for AIDS Drug Development: perspective on combination studies[1]

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## 1. Introduction

Therapy of HIV-infected patients involves an increasingly wide array of antiretroviral drugs. Physicians and patients are often in need of information and guidance as to the use of the various possible combinations from this plethora of alternatives. It is important that studies for the evaluation of combination therapies be designed to produce answers quickly, making optimal use of new techniques for measuring efficacy of such drugs. The Inter-Company Collaboration for AIDS Drug Development (ICC) established a Clinical Trial Subcommittee to coordinate and expedite the evaluation of combinations of drugs produced by the different member companies[1]. A master protocol was developed, after consultation with investigators, the FDA and the HIV community, which would provide a common framework for the comparative study of various triple combinations in patients with early stage HIV disease and with a history of no previous antiretroviral therapy. The rationale for this design will be discussed here.

## 2. Master protocol design

A key objective of the Master Protocol is to provide rapid comparative evaluation of different combinations. Laboratory data have indicated that triple drug combinations have greater potential for producing inhibition of HIV replication, possibly with a reduced emergence of resistance

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[1] Participating companies include: Aji Pharma USA, Astra, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Ciba-Geigy, Dupont Merck, Gilead Sciences, Glaxo Wellcome, Hoechst, Hoffmann-La Roche, Merck, Pfizer, Sigma-Tau, Smith Kline Beecham, Upjohn.


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than double or single drug use. The protocol design, therefore, is based on the addition of a third experimental drug to a combination of two (generally marketed) drugs for which there is a reasonable database indicating safety and efficacy with the combination. Ideally there should also be laboratory data suggesting that addition of the third drug to the double combination will produce additional antiviral activity without excessive toxicity. It was determined that the optimal patient population was one which had no previous antiretroviral treatment in that this would minimize the possible confounding of results because of pre-existing resistance mutations. Patients with $CD_4$ counts of 200–500 cells/mm$^3$ were selected for study in the ICC clinical trials which will be limited to 48 weeks duration after enrollment of the last subject. This combination of factors is expected to result in a low occurrence of clinical events in the study patients. The study design, therefore, targets changes in virus load as measured by RNA PCR and $CD_4$ counts with evaluation of the safety profile of the different combinations, rather than clinical endpoints.

## 3. Data review

An interim analysis will be conducted when the first 100 patients have completed 24 weeks of follow-up. The primary reason for this analysis is to review the safety experience and to drop any study arm with an unacceptable safety profile. Once a decision to continue the study, with or without modifications based on safety, has been made on the blinded data, the preliminary efficacy results will be reviewed on an unblinded basis by members of the ICC Clinical Trial Subcommittee to provide data for modification of future studies.

## 4. Viral load measurements

Measurement of virus load by quantification of viral RNA or DNA copy numbers by variations of PCR technology is proving to be a good marker of antiviral efficacy and may be predictive of clinical progression. The ICC Master Protocol utilizes the Roche RNA PCR assay as the primary means of determining which combinations produce the greatest and most sustained reduction in virus load. All laboratory assays are carried out in a central facility (Roche Biomedical Labs) to ensure uniformity. Samples will be assayed in batches as appropriate and in order to maintain the blinded nature of the study RNA PCR results will not be made available to investigators while the study is ongoing. Serum samples collected for viral load determinations in the first study are also being provided to Chiron Laboratories for parallel determinations of viral load by branched DNA techniques; comparison of the data from the Roche and Chiron assays will be a separate aspect of the initial study and will not be part of the primary study report.

## 5. Statistical plan

A great amount of effort has gone into development of the statistical analysis plan for the Master Protocol. The primary analysis will define antiviral efficacy of the different combinations as demonstrated by changes in viral load and $CD_4$ cell counts. Safety and tolerability are also key measurements in this analysis. Clinical disease progression and quality of life parameters will also be analyzed but it is not expected that significant numbers of clinical events will be obtained in this early disease population. The study size, with 75 patients in each of three arms, will provide reasonable power to differentiate $CD_4$ cell responses and a high level of power for comparison of viral RNA PCR changes. Both longitudinal NAUC measures of PCR and $CD_4$ changes will be analyzed as well as specific response criteria. The primary analyses will be based on an as-treated rather than an intent-to-treat analysis (secondary analysis), with specific criteria for evaluability based on total drug compliance. The lack of cross-over options in the Master Protocol will hopefully minimize some of the problems associated with intent-to-treat analysis of data from complex studies utilizing such cross-over procedures.

Table 1
ICC studies in progress

| Study | Arm | | | Status |
|---|---|---|---|---|
| | 1 | 2 | 3 | |
| 001 | ZDV<br>ddC<br>Placebo[a] | ZDV<br>ddC<br>saq | ZDV<br>ddC<br>NVP | Initiated Feb. 95, enrollment completed June 1995, 22 sites, 200 subjects enrolled |
| 002 | ZDV<br>ddI<br>Placebo[b] | ZDV<br>ddI<br>NVP | ZDV<br>ddI<br>3TC | Initiation summer 1995 |

[a]NVP placebo for 50% subjects in Arm 1 and all subjects in Arm 2, saquinavir placebo for 50% subjects in Arm 1 and all subjects in Arm 3.
[6] 3TC placebo for 50% subjects in Arm 1 and all subjects in Arm 2, NVP placebo for 50% subjects in Arm 1 and all subjects in Arm 3.
Drug doses and regimens:
ZDV (zidovudine) 200 mg q 8 h
ddC (zalcitabine) 0.75 mg q 8 h
NVP (nevirapine) 200 mg qd 2 weeks then 200 mg q 12 h
saq (saquinavir) 600 mg q 8 h
ddI (didanosine) 200 mg q 12 h (125 mg q 12 h for subjects $<60$ kg)
3TC (lamivudine) 150 mg q 12 h

## 6. Study logistics

The logistics of initiating and executing clinical trials with multiple corporate sponsors are great. Individual companies have accepted that this collaboration can only work if consensus agreements are reached and flexibility in the approach to study management is demonstrated. Parexel, a contract research organization (CRO), was chosen to handle the administration of the initial ICC clinical trials. Its responsibilities include coordinating discussions on the protocol design, preparation of protocol documents and case report forms, selection and enrollment of investigators, distribution of drug supplies and monitoring study sites. It is also responsible for data collection, clean-up and analysis and preparation of study reports. Each sponsor in each ICC protocol has a separate contract agreement with Parexel. While Parexel and its medical monitor are the primary contact for reporting of adverse events, the IND for each study is held by one of the sponsor companies which has an experimental, non-approved, drug in the clinical trial. Review of serious adverse events is a joint effort involving the Parexel and sponsoring companies' medical reviewers. This is a potentially difficult area involving blinded study treatments in which causality may not be readily apparent.

The design of the ICC Master Protocol and the drugs to be examined in the first two studies are reviewed below and in Table 1.

## 7. Master protocol

This is a multi-center, randomized, modified double-blind, placebo controlled parallel group study. After a 30-day pre-entry period, eligible patients may receive treatment for a minimum of 48 weeks. Male or female patients 13 years of age or older with HIV infection documented by licensed ELISA confirmed by Western Blot, positive HIV culture or positive HIV antigen, and with a $CD_4$ count $\geq 200$ and $\leq 500$ cells/mm$^3$ within 30 days prior to entry may participate. Eligible participants will be patients with no prior antiretroviral therapy. The primary objective of the study is to evaluate the tolerance and immunologic and virologic effects of multi-drug

combinations of antiretrovirals. A total of 225 patients will be enrolled with a ratio of 1:1:1 in each of three study regimens. Patients who discontinue prematurely will not be replaced. The primary study endpoints are:• prolonged decrease in viral load in plasma as measured by quantitative polymerase chain reaction (PCR)• prolonged increase in immunologic function as measured by $CD_4$ cell count• development of $\geq$ Grade 3 clinical adverse experiences or laboratory test abnormalities.

The secondary study endpoints are:• development of viral resistance to any of the antiretroviral agents used in the study• effect of triple drug therapy in preventing disease progression as evidenced by development of AIDS-defining indicated diseases and survival• effect of triple drug therapy on secondary measures of clinical status including quality of life measures and development of secondary infections.

Patients will be monitored throughout the study for changes in physical and neurological examination results, vital signs, weight, and peripheral neuropathy and quality of life scores. Patients will also be monitored for the occurrence of AIDS-defining indication diseases and secondary infections and the development of drug toxicities and clinical adverse experiences.

Interim analysis is planned after all data through week 24 have been collected for the first 100 enrolled patients. The final analysis will include all data collected through 48 weeks of dosing. Two analyses of efficacy will be performed on the final data. In the primary analysis, patients who are still receiving all three study treatments at any of the last three study visits (at weeks 40, 44 or 48) will be included. The secondary, intent-to-treat analysis, will include all patients randomized into the study who had at least one post-baseline visit, unless documentation confirms that the patient did not receive any study treatments. The safety analysis will include all intent-to-treat patients. Patients will be grouped according to the study treatment they received.

Characterization of virus susceptibility to the study drugs may be conducted by any of the sponsors of the study; analyses of such data will be separate from the primary study report.

## 8. Future studies

The design and combinations to be used in future studies are under extensive discussion. The possibility of adding an additional arm to examine four-drug combinations is being considered. To increase the rate at which drug combinations can be evaluated, the option of utilizing a shorter study period has been discussed. The objective of the ICC Clinical Trial Subcommittee remains to identify combinations which provide the greatest reduction in viral load and increase in $CD_4$ cell counts and which may provide a significant improvement in clinical benefits over the monotherapy and limited combination therapies presently in use. Because of the limited scale of the ICC studies, it is expected that individual sponsors will need to take responsibility for further expanded studies of combinations shown to have promise in the ICC studies.

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