55th NATIONAL CONFERENCE on Tuberculosis
Kolkata, India, Dec. 2000.

Efficacy Of An Indigenous Immunomodulator In Enhancing The Life Quality & Longevity In HIV Infected Immunocompromised Hosts With Respiratory Diseases

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Background:
In the early days of ARV in the mid 90's, when the maximum sensitivity of the available viral load assays was 400 copies/ml, it was thought that the then available ARV drugs were able to totally inhibit viral replication. Also at that point of time, only one type of CD4 cells with a half life of 1.2 days were known. It was therefore thought that 3 years of continuous therapy with a combination of 3 drugs i.e HAART comprising of 2 NRTIs + 1 PI would be sufficient to allow the already infected CD4 cells which had a half-life of 1.2 days to undergo apoptosis, and since it was then assumed that this therapy was totally suppressive, no new virus would be generated, therefore at the end of 3 years the host would be free of HIV.

However subsequently with the availability of ultra-sensitive viral load assays which could measure up to 20 copies/ml, it was soon realized that even a 8-drug mega-HAART could not totally suppress viral replication, with viral blips seen even in patients showing sustained suppression.

The subsequent discovery long-lived CD4 cells with a half-life in excess of 44 months and which function as latent reservoirs of HIV that are established very early in the course of the infection, have implicated life long therapy with currently available ARV drugs, since it would take in excess of 73 years for these long lived infected CD4 cells to auto-destruct. This has made eradication an unrealistic goal implicating life-long therapy with ARV.

However the use of ARV drugs has substantially improved the survival rates with reduction in morbidity & mortality. Thus the focus has shifted from “curable” to “treatable” chronic infectious disease. Increased experience in the use of ARV have brought to fore that the long-term success is determined by an complex interplay of number of factors. These include:

Patient's factors
- o Financial status
- o Educational status
- o Adherence & Compliance
- o Therapy interruption
- o Addiction

Clinician's Factors
- o Counseling for ARV
- o Determination of therapy goal
- o Choice of initial regimens
- o Drug regimen &dosages
- o Monitoring ARV-(baseline and follow up investigations)
- o Management of O.Is

Drug Factors
- o Availability
- o Accessibility
- o Cost
- o Adverse reactions (ADRs)
- o Development of resistance
- o Pill burden

As more insights have been gained in the HIV disease and more experience gained with available therapeutic options, consensus appears to be on deferring initiation of ARV in the asymptomatic patients. The increasing recognition of long-term antiretroviral toxicity has led us to question whether patients will be able to tolerate therapy for decades. Evidence from multiple cohorts demonstrates that the CD4+ cell count is a more important predictor of clinical progression, mortality, and benefit from antiretroviral therapy than is viral load, and that patients who defer

therapy (usually until the CD4+ cell count has fallen to between 200 and 350 cells/mm^3) do as well as those who start therapy at an earlier stage. There is considerable concern over the high rates of virologic failure in the clinical setting -- which have been as high as 50%-60% at 1 year of therapy in several cohorts -- and the poorer response to therapy observed in patients on second- or third-line regimens. Thus in the early 90's when a seropositive status was an indication to initiate ARV, by 1998 initiation of ARV was recommended only at CD4 values <500 cells/mm^3. By 2001 the initiation of ARV was recommended to be deferred to still lower CD4 values <350 to 200 cells/mm^3.

In the Indian context, where dual NRTIs form the mainstay of ARV therapy apart from the other factors, the durability of response is the major cause of concern, since duration of responce with dual NRTIs is reported to be 9 to 14 months. Lack of prescription surveillance further adds to the woes. This is further compounded by the limited success of salvage regimens. The restricted number of drugs available in India for salvage regimens and uncertainty of introduction of newer molecules in the subcontinent are further limitations.

In this backdrop alternative modalities that could restore the immune apparatus and impede disease progression need to be explored. This would facilitate further deferring initiating ARV and the related complications in the patients with CD4 counts >200. This would further increase the survival rates and reduce HIV related morbidity & mortality.

Various herbs have been shown to possess immunomodulatory activities. These herbs have been shown to differentially modulate the cytokine profile, inducing and amplifying the effects of certain cytokines while at the same time inhibiting others. Reimun is a herbomineral formulation comprising of such immunomodulating & immunopotentiating herbs.

Aims & Objective:
This study evaluates the efficacy of an indigenous herbomineral immunomodulator Reimun in enhancing the life quality & longevity in HIV infected immunocompromised hosts with respiratory diseases.

Methods:
Design: Open labeled sequential study

Participants:	160 HIV positive patients
Inclusion criteria:	HIV positive adult patients of either sex not affording ARV, Age 18-60 years, Karnofsky Performance Score 60 and Above, Hb > 7 gm%,
Exclusion criteria:	Pregnant and lactating mothers, Patients on antiretroviral therapy, Patients with significant cardiac, hepatic, renal and neurological disorders or malignancies.
Study duration:	18 months
Baseline investigations:	Clinical examination, Blood chemistry, Liver & renal chemistry
Assessment Parameters:	The monthly/quarterly clinical record included, Physical examination, X-ray chest, Blood chemistry, Hemocrit, SputumAFB Karnofsky performance score. The adverse drug reactions were recorded in patients as and when they occurred.

Study Groups

Group I: Conventional Therapy + Reimun (n=60)
- Group IA: Pulmonary T.B. (n=46)
- Group IB: P.C.P. (N=9)
- Group IC: Other respiratory infections (n=5)

Group II: Conventional Therapy (n=100)
- Group IIA: Pulmonary T.B. (N=79)
- Group IIB: P.C.P. (N=16)
- Group IIC: Other respiratory infections (n=5)

Outcome measures: Survival rates, Incidence of newer opportunistic infections, Response to specific anti-infective therapy, Frequency of hospitalization, Effect on Karnofsky Performance Score, Impact on clinical status of the patients

Treatment Regimens

Pulmonary T.B.		
	Newly diagnosed	2 E H R Z + 4 H R
	Retreated cases	2/3 C H E R Et K/Cly + 9 C H E
PCP		TMP/SMX

Reimun is a combipack comprising Reimun-A Tablets & Reimun-B Tablets, which contain processed extracts of Astralagus membranacaus, Asparagus racemosus, Allium sativum, Trichosanthes spp, Angelica galuca, Achyranthes bidentata, Picrorhiza kurroa, Prunella vulgaris, Tinospora cordifolia, Glycerrhiza glabra, Zinziber officinale, Curcuma longa, Taraxum officinale, Withania somnifera, Camphor & Mautik bhasma (oxide of pearl), Loha bhasma (oxide of iron), Yasad bhasma (oxide of zinc), Abhrak bhasma (calyx of mica & silicates)

3 Reimun-A Tablets to be taken early morning on empty stomach with 200 ml milk once a day followed by 3 Reimun-B Tablets to be taken thrice a day with 200 ml milk, 2 hours after food-intake

Before starting the regimen, patients were counseled to help them modify their risk behavior. Patients were counseled regarding HIV disease, available ARV therapy & Reimun. Therapeutic counseling sessions continued throughout study course to ensure adherence and compliance.

Results:

Baseline Characteristics of the Treatment Groups

Characteristics	Group I (n=60) Grp IA (Pul. TB; n=46)	Grp IB (PCP;n=9)	Grp IC (Other;n=5)
Age, y Mean	34	33	37
Range	(18-60)	(20-45)	(23-48)
Sex (No.)			
Male	32	4	4
Female	14	5	1
KarnofskyScore (Mean)	63	62	66
Hb gm%	8.3	7.9	9.7
Body weight	47.4	46	44
	Group II (n=100)		
	GrpIIA (Pul. TB; n=79)	**GrpIIB (PCP; n=16)**	**Grp IIC (Other; n=5)**
Age, y Mean	35	36	38
Range	(18-60)	(26-45)	(21-58)
Sex (No.)			
Male	52	10	4
Female	27	6	1
Karnofsky Score (Mean)	65	61	64
Hb gm %	7.3	7.9	9.2
Body weight	49	43	46

In the patients receiving Reimun

No deaths occurred

- Improvement in appetite
- Mean weight gain of 6.3 kgs in the first 3 months
- Mean Karnofsky Pperformance Score increased from mean baseline value of 78 to 89 at the end of one year
- Patients did not develop other opportunistic infections
- Significant improvement in the clinical status of patients
- 2 patients with Pulmonary T.B. however needed a subsequent brief spell of hospitalization
- In the patients with PCP & other respiratory infections, there was 100% cure rate with x-ray clearing observed within a mean of 25.5 days
- In the tubercular patients:
    - The sputum conversion rate at 3 months was 96% and 76% in the newly diagnosed and retreated patients respectively
    - Excellent radiological improvement in 31% of the patients and moderate improvement in 32% of the patients while 18% had very little improvement and these were retreatment

In the patients receiving only conventional drugs

- 25 deaths: 10 due to respiratory diseases and rest due to other causes including hepatic failure.
- The sputum conversion rate at 3 months was 69% and 51% in the newly diagnosed and retreated tubercular patients respectively cases

Conclusions:

With use of the herbomineral immunomodulator (Reimun) resulted in

- Higher weight gain
- Relapse did not occur
- Clinical well being was better
- Patient went back to normal active life
- No deaths occurred.