British Homeopathic Journal (1999) 88, 49–57

http://www.stockton-press.co.uk/bhj

ORIGINAL PAPER

Homeopathy in HIV infection: a trial report of double-blind placebo controlled study

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Objective: This study was aimed to evaluate the immuno-modulator role of homeopathic remedies in Human Immunodeficiency Virus (HIV) infection.

Methodology: A randomised double blind clinical trial was conducted to compare the effect of homeopathic remedies with placebo, on $CD4^{+ve}$ T-lymphocytes in HIV infected individuals, conforming to Centres for Disease Control (CDC) stage II & III. 100 HIV^{+ve} individuals between 18–50 y (71% males) were included in the study. 50 cases conformed to CDC stage II — Asymptomatic HIV infection, and 50 cases to CDC stage III — Persistent Generalised Lymphadenopathy (PGL). Cases were stratified according to their clinical status and $CD4^{+ve}$ lymphocyte counts. The randomisation charts were prepared much before the start of the trial by randomly assigning placebo and verum codes to registration numbers from 1 to 50. A single individualised homeopathic remedy was prescribed in each case and was followed up at intervals of 15 d to one month. A six months study was performed for each registered case. Assessment of progress was made by evaluation of $CD4^{+ve}$ lymphocyte counts, which was the prospectively-defined main outcome measure of the study; the results were compared with the base line immune status.

Results: In PGL, a statistically significant difference was observed in $CD4^{+ve}$ T-lymphocyte counts between pre and post trial levels in verum group ($P < 0.01$). In the placebo group a similar comparison yielded non-significant results. ($P = 0.91$). Analysis of change in the pre and post trial counts of $CD4^{+ve}$ cells between groups was also statistically significant ($P = 0.04$).

In asymptomatic HIV infection, differences in absolute $CD4^{+ve}$ lymphocyte counts between pre and post trial levels were not significant. Analysis of changes in pre and post trial CD4 levels of placebo and verum groups for combined strata of asymptomatic and PGL groups was also not significant.

Conclusion: The study suggests a possible role of homeopathic treatment in HIV infection in symptomatic phase, as evidenced by a statistically significant elevation of base line immune status in persistent generalised lymphadenopathy.

Keywords: homeopathy; HIV; immunomodulator; CD4; India

Introduction

Double blind placebo controlled trials are uncommon in homeopathy due to inherent problems in the methodology of treatment, that is, individualisation procedure, treatment by multiple remedial agents for a single clinical diagnosis, etc. However, small group studies have been conducted on clinical problems like acute childhood diarrhoea,[1] influenza,[2] allergic rhinitis,[3] fibrositis,[4] and osteoarthritis.[5] These trials with the exception of the last have suggested a significant positive role of homeopathic treatment when compared to placebo. A meta-analysis of placebo controlled trials in homeopathy has been conducted.[6] The results of this analysis are not compatible with the

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hypothesis that clinical effects of homeopathy are completely due to placebo. However, the investigators could not find enough evidence of efficacy of homeopathy for any clinical condition.

Placebo controlled trials of therapy to inhibit progress of HIV associated disease have met considerable resistance, as patients have been reluctant to accept the risk of receiving a placebo. In this context, it is worthwhile to consider that in the face of HIV disease the smallest chance of benefit is perceived as better than no benefit. Additionally, enough measures have been included in out trial protocol, so that patients not benefited by the therapy could receive active therapeutic intervention in such an eventuality and not be allowed to deteriorate further. No placebo controlled trial with homeopathic medicines had been conducted in HIV infection, prior to our study. A preliminary report of our study is already published.[7] The present article deals with interpretation of the results of the study.

The primary target of HIV is the lymphocytes which express CD4 protein on their surface, the virus attaches to the lymphocyte using this protein. These $CD4^{+ve}$ T-lymphocytes are preferentially infected and killed as the infection progresses, depleting their numbers and enhancing the risk of opportunistic infections. Furthermore, it is known that extent of CD4 depletion is strongly associated with the risk of clinical progression and survival. Although any one individual may be an exception, for populations of HIV infected persons, studies have shown an unequivocal association between low levels of $CD4^{+ve}$ cells and AIDS defining phenomena and by extrapolation, predict survival. The absolute $CD4^{+ve}$ T-lymphocyte count is the best available cellular predictor of HIV progression, and is the most important factor of survival. Relatively small shifts in the numbers of $CD4^{+ve}$ cells can be very important if they bring an individual's cell count into a better prognostic category. A stable CD4 level indicates HIV non-progression and a halt in the decline in the number of $CD4^{+ve}$ cells is viewed as meaningful.[8] Therefore $CD4^{+ve}$ T-lymphocytes are often used as surrogate markers in clinical trials. Initial trials using CD4 cells as surrogate immunological markers would establish that a therapy is potentially effective.[9] This should then pave way for larger multi-parametric studies involving immunological and virological markers.

A few studies have suggested beneficial effect of homeopathic treatment in HIV infection.[10,11] The Central Council for Research in Homoeopathy has carried out open pilot studies and followed a number of HIV^{+ve} cases in different CDC stages and observed improvement both in terms of clinical manifestations and immunological status.[12–15] However, if a placebo controlled trial of homeopathic medicines showed to influence $CD4^{+ve}$ T-lymphocytes in a beneficial manner, it would confirm the observations made in earlier studies.

Methods and subjects

A randomised double blind placebo controlled clinical trial of homeopathic treatment in HIV infection was conducted by Central Council for Research in Homoeopathy at Regional Research Institute for Homoeopathy, Mumbai, India between 22nd July 1995 and 8th February 1997.

Subjects were divided into two different stratum. The first stratum, comprising of Asymptomatic HIV^{+ve} cases defined by absence of clinical signs and symptoms that correspond to symptomatic HIV disease, for example, chronic recurrent fever, chronic recurrent diarrhoea, progressive neurasthenia/weakness, weight loss, generalised lymphadenopathy, minor or major opportunistic infections, etc. and a $CD4^{+ve}$ count that otherwise classifies the case under symptomatic HIV disease/AIDS. The second stratum comprised of HIV^{+ve} cases that belonged to CDC stage III, Persistent Generalised Lymphadenopathy (PGL, defined as enlargement of lymph nodes having a size of >1 cm in diameter, in more than two extra inguinal sites and of $>$ three months duration), with good number of $CD4^{+ve}$ lymphocytes.

Fifty cases were registered in each stratum. Each stratum was treated separately by two co-investigators in patient interview, counselling, history taking, remedy selection, follow-up review and periodical analysis. The randomisation, blinding of the subjects and medicine dispensing was handled by a co-ordinator separately in absolute confidentiality. The randomisation charts were prepared before the start of the trial by randomly assigning placebo and verum codes to different registration numbers from 1 to 50. The cases were registered at different points of time during the study in the order they reported to the Institute and were assigned a registration code as per the pre-coded randomisation chart, thus randomly receiving either placebo or verum.

Subjects between 18–50 y of age (males = 71%) who had a positive antibody reaction to HIV-1 or HIV2 or both confirmed by repeat ELISA and/or Western blot were inducted into the trial (99% HIV-1 infection). Subjects having past history of convulsions or cardiac disease and currently requiring medication for control, those having taken AZT in the immediately preceding four weeks and pregnant and lactating women formed the exclusion criteria and were not considered for the trial. Any subject with poor compliance and follow-up less than three months, having taken any other therapy, or who developed any life threatening condition or adverse effects of the therapy which required active therapeutic intervention, and women who have conceived subsequent to registration were considered as lost to follow-up and were not considered for final analysis.

Every case was subjected to pre-entry investigations as below:

- ELISA for HIV antibodies was performed by:
  1. ImmunoComb®, HIV 1 & 2 Bispot, PBS Orgenics, France—A qualitative and differential detection of HIV-1 &HIV2 IgG antibodies by Solid phase Enzyme Immunoassay (EIA). (Sensitivity: 100%; Specificity: 98.4%); Batch #: 950027 (Exp 27/08/1996); 960205 (Exp 25/01/1997);
  2. HIV-SPOT, Diagnostic Biotechnology, Singapore—A rapid qualitative test for the detection of HIV 1 & 2 Antibodies. (Sensitivity: 98.8%; Specificity: 100%); Batch #: 5LD105 (Exp 2/11/1996), 6HG104 (Exp 19/7/1997);
  3. The institute did not posses facilities for Western blot testing, but the result of a subject who undertook this test in any private laboratory was noted.
- Vacutainer® brand (Becton-Dickinson, USA) Blood collection tubes were used throughout the study for collection of blood samples, sera, and whole blood, etc. The sera were preserved for possible future analysis.
- Routine Haematological investigations were performed using QBCII Centrifugal Haematology System (Becton-Dickinson, USA) and QBC Venous and Capillary Blood Tubes (Becton-Dickinson, USA).
- ESR was tested using Monovette® (Starstedt, Germany) brand of blood collection system.
- VDRL was tested using TrepoStat® (Ranbaxy Diagnostics, India)—Reagen Protein Reaction (RPR) method.
- A Delayed hypersensitivity reaction was obtained by Montoux skin test which was performed with Tuberculin PPD Solution (10 TU), Span Diagnostics, India.
- Immunocytometry tests (CD4/CD8/CD3) were conducted with FACSCount™ System (Becton-Dickinson, USA) and FACSCount™ system reagents and controls. The instrument employs direct two-colour immunofluorescence for enumerating absolute lymphocytes ($CD3^+$ cells) and its subsets T-helper lymphocytes ($CD3^+CD4^+$) and T-suppressor lymphocytes ($CD3^+CD8^+$). The system is fully automated, run by a FACSCount system software and requires no user intervention while running the samples. The enumeration of absolute lymphocytes is direct method and does not require an external haematology instrument. Reagent Lot Batch # 50012121 (Exp 13/10/1995); 50042121 (Exp 5/2/1996); 60012121 (Exp 15/4/1997); Control Lot Batch #: 49071721 (Exp 13/11/ 1995); 59011721 (Exp 5/2/1996); 59051721 (Exp 20/6/1997).
- Fluctuations are known to occur in total lymphocyte counts with diurnal cycles.[16] This has been avoided by consistently collecting the haematological samples during the morning 0900h–1100h, throughout the study period. All samples were processed on the same day of collection to avoid sample instability which may affect the results.
- A routine ECG and chest X-ray was also taken to rule out any underlying cardiac or chest disease.

Subjects fulfilling the inclusion criteria were inducted into the trial after obtaining an informed consent. Appropriate counselling was provided by the medico-social worker and the treating co-investigator as well. A thorough homeopathic case was taken and the details were entered in a standard data recording proforma. Processing and analysis of symptoms were done using a computerised homeopathic software–HOMPATH©(Jawahar Shah, India). Kent, Boenninghausen and Synthetic Repertories were consulted for analysis of symptoms and arriving at the homeopathic remedy. A range of homeopathic potencies were used from 6x to LM scale, as per the requirement and analysis by the co-investigator.

After initiation of the treatment, the routine haematological investigations were carried out at intervals of one month and immunological and serological investigations at three months.

During every follow-up visit a pre-defined check list was used to assess the clinical status and response to the treatment. The observations were entered in the standard data recording proforma. The checklist was prepared so as to ensure that the co-investigator inquires into the subject's normal biological functioning like appetite, stool, urine and sleep and appearance of any clinical event attributable to HIV infection. Body weight was recorded on every visit using a standard personal weighing scale. The indicated homeopathic remedy was prescribed during each follow-up by the co-investigator, which is either continuation of previous remedy in the same potency or higher scale. Any acute complaint arising during the follow-up was prescribed the indicated remedy as the prevailing symptomatology suggested. However, the subjects under control group received placebo and those under active group received the prescribed homeopathic remedy. After completion of six months study all investigations were repeated and the final assessment was done in relation to clinical status, haematological and immunological status.

Statistical procedures were performed using SPSS ver 3.0 and Microsoft® Excel 7.0 Analysis toolpack. The analysis was independently done at Institute of Research in Reproduction, Parel, (ICMR) Bombay and also at the institute where the trial was conducted, and the results were cross checked and confirmed. Comparison of mean difference at the beginning and end of the trial between placebo and verum groups was made by two-tailed unpaired *t*-test (parametric), Mann-Whitney-U (non-parametric) was considered, to obtain the *P* value, due to non-normal distribution of haematological and immunological test values.

The outcome measures were assessed by observing the mean differences in pre and post trial levels of haematological and immunological status, within

placebo and verum groups separately. Exact means were arrived by paired *t*-test (parametric) and Wilcoxon matched pairs signed rank test (non-parametric) was used to test significance level. Though the $CD4^+$ and $CD8^+$ T-lymphocyte counts were considered as the main outcome measure, other quantifiable haematological parameters were also subjected for the analysis and presented in the tables.

Results

In each stratum twenty-five cases were assigned to placebo group and an equal number to the verum group. In asymptomatic stratum, two cases under placebo group left the treatment. Under the verum group one woman who was detected as pregnant subsequent to the registration was withdrawn from the study. Five other cases, with poor follow-up compliance were also withdrawn and not considered for analysis. A total eight out of the fifty cases (16%) were withdrawn in asymptomatic strata (Placebo group 2, Verum group 6 cases).

Similarly, in the PGL stratum placebo group, one subject was withdrawn owing to the progression of disease which required active therapeutic intervention. The unblinding of the subject was done at the conclusion of trial period. Six other cases were also withdrawn due to poor follow-up and failing to complete the study protocol. In the verum group one woman who conceived during the follow-up period was dropped from the study. Two cases underwent other therapy during the follow-up and hence were not considered for analysis. Two subjects were treated as lost to follow-up due to poor compliance. Twelve of fifty (24%) cases were withdrawn from PGL strata. (Placebo group 7, Verum group 5 cases). All withdrawn cases were marked out before final analysis and unblinding the codes. The details of withdrawn cases is given in Table 3.

The comparison of the base line characteristics on entry to the study are presented in the Table 1.1 and 2.1. All the subjects had contracted HIV through heterosexual transmission. 21% were spouses of sexually promiscuous husbands. There was no significant difference in the placebo and verum groups, in either

Table 1.1 Descriptive characteristics at the beginning of study—asymptomatic strata

Parameter	*Placebo† (n=25)*	*Verum† (n=25)*	*P value**
Age (y)	27.96 (5.51)	27.37 (6.01)	0.74
Body weight (kg)	53.67 (10.11)	55.04 (14.19)	0.70
$CD4^{+ve}$ T-lymphocytes	648.48 (230.87)	638.48 (237.49)	0.85
$CD8^{+ve}$ T-lymphocytes	1245.16 (403.17)	1198.04 (456.21)	0.52
Haemaglobin	13.19 (1.61)	13.18 (1.88)	0.96
Haematocrit	40.72 (5.02)	40.88 (5.29)	0.82
White blood corpuscles (WBC)	7768 (3408.77)	7120 (1750.23)	0.80
Granulocytes	4992 (3008.44)	4416 (1507.11)	0.77
Agranulocytes	2776 (598.11)	2704 (570.44)	0.71
Platlets	2.54 (0.75)	2.36 (0.63)	0.25
Erythrocyte sedimentation rate (ESR)	18.40 (14.5)	17.67 (14.39)	0.90

†Means with s.d.
**P* value obtained by Mann Whitney U-test.

Table 1.2 Comparison of outcome measure in *Placebo* group—asymptomatic strata

	Placebo group (n=23)		
Parameter	*Before trial†*	*After trial†*	*P value**
Body weight (kg)	54.17 (10.02)	55.48 (11.51)	0.28
$CD4^{+ve}$ T-lymphocytes	645.13 (240.31)	622.61 (246.50)	0.52
$CD8^{+ve}$ T-lymphocytes	1250.30 (420.64)	1269.30 (459.92)	0.68
Haemoglobin	13.31 (1.54)	13.08 (1.59)	0.27
Haematocrit	41.04 (4.91)	40.51 (4.81)	0.16
White blood corpuscles (WBC)	7869.56 (3533.15)	6834.78 (1630.28)	0.34
Granulocytes	5056.52 (3125.38)	4260.87 (1283.01)	0.67
Agranulocytes	2813.04 (609.99)	2573.91 (587.15)	0.22
Platelets	2.51 (0.77)	2.45 (1.00)	0.55
Erythrocyte sedimentation rate (ESR)	18.04 (15.03)	19.56 (16.29)	0.32

†Means with s.d.
**P* value obtained by Wilcoxon matched-pairs Signed Rank test.

Table 1.3 Comparison of outcome measures in *Verum* group—asymptomatic strata

	Verum group (n=19)		
Parameter	*Before trial†*	*After trial†*	*P value**
Body weight (kg)	55.63 (15.33)	56.79 (16.03)	0.32
$CD4^{+ve}$ T-lymphocytes	611.63 (256.12)	580.21 (243.90)	0.57
$CD8^{+ve}$ T-lymphocytes	1087.26 (409.71)	1129.95 (431.97)	0.24
Haemoglobin	12.96 (1.75)	13.28 (1.78)	0.50
Haematocrit	40.29 (5.06)	40.74 (5.55)	0.76
White blood corpuscles (WBC)	7236.84 (1983.60)	7242.10 (1473.21)	0.82
Granulocytes	4589.47 (1682.23)	4605.26 (1343.08)	0.82
Agranulocytes	2647.37 (628.37)	2636.84 (480.98)	0.93
Platelets	2.27 (0.51)	2.24 (0.82)	0.53
Erythrocyte sedimentation rate (ESR)	16.58 (7.77)	24.68 (3.42)	0.01

†Means with s.d.
**P* value obtained by Wilcoxon matched-pairs Signed Rank test.

Table 1.4 Descriptive characteristics at the end of study—asymptomatic strata

Parameter	*Placebo†* *(n=23)*	*Verum†* *(n=19)*	*P value**
Body weight (kg)	55.47 (11.61)	56.79 (16.03)	0.88
$CD4^{+ve}$ T-lymphocytes	622.61 (246.50)	580.21 (243.90)	0.53
$CD8^{+ve}$ T-lymphocytes	1269.30 (459.91)	1129.95 (431.97)	0.22
Haemoglobin	13.09 (1.59)	13.28 (1.78)	0.91
Haematocrit	40.52 (4.81)	40.75 (5.55)	0.82
White blood corpuscles (WBC)	6834.78 (1630.28)	7242.10 (1473.21)	0.48
Granulocytes	4260.87 (1283.01)	4605.26 (1343.08)	0.50
Agranulocytes	2573.91 (587.15)	2636.84 (480.96)	0.78
Platelets	2.45 (1.00)	2.24 (0.82)	0.30
Erythrocyte sedimentation rate (ESR)	19.57 (16.29)	24.68 (14.91)	0.16

†Means with s.d.
**P* value obtained by Mann Whitney U-test.

strata, in relation to age distribution, body weight, immune status, or the routine haematological values.

There was wide variation in absolute $CD4^{+ve}$ and $CD8^{+ve}$ T-lymphocyte counts. However, this was not considered abnormal given the wide difference in normal ranges for white blood cell counts and CD4 cell population. The normal ranges of CD4 lymphocytes in Indian healthy adults has not been established but multicentric studies[17] in three geographically distinct sites showed the normal counts for healthy adults to be in the range of $355/mm^3$–$1213/mm^3$ for CD4 lymphocytes. For CD8 lymphocytes this was in the range of $208/mm^3$–$796/mm^3$. In our study, it was noted that for the same clinical status, the CD4 counts showed wide variations among individuals. Asymptomatic cases were registered with counts as low as 263 cells/mm^3 and as high as 1049 cells/mm^3 in PGL.

In the PGL strata, the comparison of outcome measures *within* the placebo group at entry and conclusion of trial showed no statistical significance in $CD4^+$ and $CD8^+$ T-lymphocytes (Table 2.2). Similar results were also observed in body weight and haematological profiles. Within the verum group (Table 2.3), $CD4^+$ T-lymphocytes exhibited a significant increase from the pre-trial levels ($P < 0.01$). Significant elevation in $CD8^+$ T-lymphocytes ($P < 0.05$) was also observed. Other changes in the haematological parameters and body weight were not significant. A comparison was also made between the control and the active groups (Table 2.4). Though a clear difference between the means of CD4 (placebo = 452, verum = 534) and CD8 (placebo = 1298.50, verum = 1327.25) was observed, the *P*-value (0.52 for CD4 and 0.98 for CD8) was not significant.

In the asymptomatic strata, the outcome measures either *within* placebo group (Table 1.2) or *within* the verum group (Table 1.3) were not significant. A comparison *between* the groups also was not significant (Table 1.4). Neither the results establish marked difference in pre and post study immunological and haematological values, which shifted within the normal ranges for a specific parameter.

Table 2.1 Descriptive characteristics at the beginning of study—PGL strata

Parameter	*Placebo†* *(n=25)*	*Verum†* *(n=25)*	*P value**
Age (y)	30.11 (7.68)	27.65 (6.05)	0.28
Body weight (kg)	53.88 (9.53)	52.56 (11.20)	0.65
$CD4^{+ve}$ T-lymphocytes	432.08 (146.66)	490.84 (229.26)	0.60
$CD8^{+ve}$ T-lymphocytes	1225.60 (458.85)	1205.56 (506.60)	0.88
Haemoglobin	13.03 (1.67)	12.95 (2.01)	0.81
Haematocrit	40.35 (4.83)	40.41 (5.71)	0.43
White blood corpuscles (WBC)	7400 (2048.48)	6792 (2149.98)	0.10
Granulocytes	4648.00 (1567.41)	4116.00 (1770.99)	0.07
Agranulocytes	2752.91 (630.55)	2676.84 (696.59)	0.62
Platelets	2.22 (0.74)	2.48 (0.68)	0.21
Erythrocyte sedimentation rate (ESR)	31.64 (22.80)	25.00 (17.75)	0.43

†Means with s.d.
**P* value obtained by Mann Whitney U-test.

Table 2.2 Comparison of outcome measures in *Placebo* group—PGL strata

	Placebo group (n=18)		
Parameter	*Before trial†*	*After trial†*	*P value**
Body weight (kg)	53.39 (8.81)	53.61 (9.44)	0.59
$CD4^{+ve}$ T-lymphocytes	443.61 (152.48)	452.00 (158.67)	0.91
$CD8^{+ve}$ T-lymphocytes	1256.89 (488.23)	1298.50 (293.97	0.41
Haemoglobin	12.77 (1.87)	12.73 (1.39)	0.38
Haematocrit	39.58 (5.39)	39.38 (4.15)	0.43
White blood corpuscles (WBC)	7222.22 (2052.42)	6744.44 (1513.17)	0.41
Granulocytes	4577.78 (1625.00)	4288.89 (1253.18)	0.68
Agranulocytes	2644.44 (557.54)	2455.55 (434.16)	0.74
Platelets	1.99 (0.65)	2.15 (0.71)	0.13
Erythrocyte sedimentation rate (ESR)	35.05 (22.16)	40.17 (22.10)	0.21

†Means with s.d.
**P* value obtained by Wilcoxon matched-pairs Signed Rank test.

The response of the placebo and verum groups to the treatment was further assessed by analysing the *change* in the $CD4^+/CD8^+$ T-lymphocytes from pre-trial levels. This exclusive analysis for immunological

Table 2.3 Comparison of outcome measures in *Verum* group—PGL strata

Parameter	Verum group (n = 20)		
	Before trial†	After trial†	P value*
Body weight (kg)	52.95 (11.52)	53.30 (11.63)	0.60
$CD4^{+ve}$ T-lymphocytes	433.30 (195.19)	534.35 (278.23)	0.008
$CD8^{+ve}$ T-lymphocytes	1234.20 (539.77)	1327.25 (534.68	0.04
Haemoglobin	12.89 (1.69)	12.49 (2.25)	0.16
Haematocrit	40.20 (4.92)	38.60 (6.67)	0.08
White blood corpuscles (WBC)	6550 (1416.26)	6410 (1372.68)	0.74
Granulocytes	3915.00 (965.88)	3780.00 (1089.95)	0.63
Agranulocytes	2635.00 (658.77)	2630.00 (656.22)	0.95
Platelets	2.36 (0.66)	2.26 (0.82)	0.41
Erythrocyte sedimentation rate (ESR)	28.16 (18.22)	31.42 (21.10)	0.20

†Means with s.d.
*P value obtained by Wilcoxon matched-pairs Signed Rank test.

Table 2.4 Descriptive characteristics at the end of the study—PGL strata

Parameter	Placebo† (n = 18)	Verum† (n = 20)	P value*
Body weight (kg)	53.61 (9.44)	53.30 (11.63)	0.74
$CD4^{+ve}$ T-lymphocytes	452.00 (158.67)	534.35 (278.23)	0.52
$CD8^{+ve}$ T-lymphocytes	1298.50 (393.97)	1327.25 (534.68)	0.98
Haemoglobin	12.73 (1.39)	12.40 (2.25)	0.96
Haematocrit	39.38 (4.15)	38.59 (6.67)	0.83
White blood corpuscles (WBC)	6744.44 (1513.17)	6410.00 (1372.63)	0.66
Granulocytes	4288.89 (1253.18)	3780.00 (1089.95)	0.36
Agranulocytes	2455.55 (434.16)	2630.00 (656.22)	0.34
Platelets	2.15 (0.70)	2.26 (0.80)	0.81
Erythrocyte sedimentation rate (ESR)	40.17 (21.10)	37.55 (30.33)	0.36

†Means with s.d.
*P value obtained by Mann Whitney U-test.

parameters was separately carried out for asymptomatic and PGL strata and a third for a pooled strata of the two. In the PGL strata, the verum group showed significant difference in absolute CD4 cell numbers from pre trial levels ($P = 0.04$), while the same significance was not observed for CD8 cell numbers ($P = 0.75$). In asymptomatic and combined strata no significance for $CD4^+/CD8^+$ T-lymphocytes was observed (Table 4)

Twenty-five different homeopathic remedies were prescribed based on the totality of symptoms obtained through patient interviews and after consulting repertorial analysis. Homeopathic potencies used were 6x, 30C, 200C, LM3, LM5. The frequency of repetition of centesimal scale potency ranged between once every day to 3 times a day. High centesimal potencies were not prescribed by the co-investigators because of dose repetition problem. LM potencies were prescribed in water doses 3 to 4 times a day. The control group received placebo looking exactly similar to the medication received by the verum group. The most commonly prescribed remedies are represented in Table 5.1. Due to randomisation, equal representation of a given remedy in placebo and verum group could not be achieved. The symptom totality for these cases was represented as mental, physical generals and particular symptoms for each remedy in Table 5.2. Expressions more frequently observed were italicised.

Discussion

It was not within the scope and objective of this study to ascertain the molecular basis for the immunomodulatory action of homeopathic medicines or offer an explanation for mechanism of action. The study was limited to observe changes in base line immune level by the variation in absolute numbers of $CD4^{+ve}$ and $CD8^{+ve}$ T-lymphocytes. Other immunological predictors like β-2 Microglobulin, Neopterin, and virologic marker of quantification of HIV—RNA by PCR are also equally important in the prognosis of an HIV infected individual. At the time of this study, these facilities were not readily available to us and could not be included in the study design.

Further, the objective of the study was to evaluate the role of the system of homeopathic therapy rather than to evaluate or suggest any single homeopathic remedy for the HIV disease. Larger trials in future may suggest a sub group of remedies that are more often indicated in HIV infection.

Though there exists no clear difference between asymptomatic and PGL stages, either clinically or epidemiologically, we have chosen to conduct the study in two separate strata by following the CDC classification system.

In the normal course of HIV disease, the CD4 T-lymphocytes tend to remain stable for prolonged periods during asymptomatic phase,[18] while the individual maintains normal health status, free from clinical problems. The decline in the $CD4^+$ cell numbers is a gradual phenomenon.[19] Little variation may be seen in their numbers over a short period of time. This perhaps explains the non-significance of the results in asymptomatic cases; the study period being only 190 d. Longitudinal studies are required to address these questions. Prolonged studies on placebo are unethical and compounded with the problems of long term patient compliance.

Additionally, the problem with the asymptomatic cases is a lack of precise prescribing totality which

Table 3 Withdrawn cases

Strata	Treatment	No. of dropouts	Reasons for dropout#
Asymptomatic	Placebo	2	Subjects withdrew themselves from the study
	Verum	1	Detected as pregnant during study*
		5	Failed to follow-up for minimum required duration/investigations for the conduct of analysis
PGL	Placebo	1	Needed active therapeutic intervention for non responding febrile illness, during the course of trial
	Placebo	6	Failed to follow-up for minimum required duration/investigations for the conduct of analysis
	Verum	2	Developed hepatitis during the course of study. Subjects attended for other treatment in the middle of study
	Verum	2	Failed to follow-up for minimum required duration/investigations for the conduct of analysis
	Verum	1	Detected as pregnant during study*

Total no. of dropouts: 20 Asymptomatic; 8 (Placebo 2, Verum 6); PGL 12 (Placebo 7, Verum 5).*Protocol guidelines stipulate exclusion of study on pregnant/lactating women.
#Details of dropout criteria in the study mentioned in the text.

Table 4 Difference in pre and post trial levels of immunological parameters

Parameter	Placebo† (n=23)	Verum† (n=19)	P value*
Asymptomatic strata			
$CD4^{+ve}$ T-lymphocytes	22.52 (216.63)	31.42 (201.44)	0.92
$CD8^{+ve}$ T-lymphocytes	− 19.0 (429.43)	− 42.68 (272.13)	0.22
PGL strata			
	Placebo† (n=18)	Verum† (n=20)	P value*
$CD4^{+ve}$ T-lymphocytes	− 8.39 (106.90)	− 101.05 (160.11)	0.04
$CD8^{+ve}$ T-lymphocytes	− 41.93 (338.56)	− 93.05 (218.35)	0.75
Combined strata			
	Placebo† (n=41)	Verum† (n=39)	P value*
$CD4^{+ve}$ T-lymphocytes	8.95 (175.81)	− 36.51 (190.95)	0.20
$CD8^{+ve}$ T-lymphocytes	− 28.93 (387.64)	− 68.51 (244.06)	0.26

Negative values indicate a positive difference in absoute CD4/CD8 T-lymphocytes from pre-trial level. (Number of cells at the start of trial−Number of cells at the end of trial).
†Means with s.d.
*P value obtained by Mann Whitney U-test.

includes characteristic/key note symptoms. The physician must heavily rely on constitutional attributes, generalities and previous and family history of the patient. These too, on many an occasion may not indicate a clear choice of a specific homeopathic remedy and the distinction between many polychrest remedies that come upon repertorisation become difficult. Prescription in such an instance becomes presumptive rather than a certainty, and success or failure of the selected remedy is indicated only on serial repetition of CD4 counts, in the absence of demonstrable aberration in health.

The statistically significant positive influence on $CD4^+$ cell numbers of homeopathic medicines in the PGL stage does indicate beneficial role in symptomatic phase. Corresponding significant elevation in $CD8^+$ cell numbers with the treatment, as evident within the group analysis, also is a noteworthy observation. While the $CD4^+$ cell numbers are unequivocally associated with survival, it is now clear that $CD8^+$ T-lymphocytes are key components of body's response against HIV, complementing antibody production. These cells also control the infection *in vitro*.[20]

This institute in the past has conducted open trials on HIV disease in various stages. The results of these cases could not be compared with the trial cases for want of sufficient number of cases, comparable in terms in clinical stage, base line factors and repeat $CD4^+$ counts at specified intervals. This happened because of differences in the study designs which depended on availability of facilities for investigations at the corresponding periods of study. Therefore, consistency or otherwise of the outcome measures in this placebo controlled trial with other open studies could not be established.

In the light of the observations made in this study it is felt that future trials in this area should involve a larger sample size, in order to overcome the problem of high individual variations in immunological and haematological profiles. Other cellular, serological and virological predictors also must be included in the study design to establish the relationship of various predictors and their response to the treatment. Perhaps, no other study deserves such serious ethical considerations as required in the placebo controlled trials in HIV infection. Nevertheless, larger, carefully designed longitudinal and multi-centric studies with pre-determined end points, in various stages of the infection are needed to prove the efficacy of the therapy.

Acknowledgements

We are grateful to Dr HS Juneza, Director, Institute of Research in Reproduction, Mumbai for his permission to evaluate our results at the institute. We are pro-

Table 5.1 Medicines prescribed in the study

		Asymptomatic *n*		*PGL* *n*	
Name of medicine	*Potency*	*Placebo*	*Verum*	*Placebo*	*Verum*
Sep.	30c,200c	0	1	0	1
Ign.	30c,200c	1	0	0	1
Lach.	30c,200c	1	0	1	0
Rhus t.	30c	1	0	1	0
Sil.	30c	1	0	1	0
Calc.	30c,200c	0	3	1	0
Nux.v.	30c200c	1	2	0	2
Ars.	30c,200c LM1,3,5	1	3	x	x
Nat-m.	30c,200c	2	1	x	x
Lyc.	30c,200c,1M LM1,3,5	2	1	5	5
Sulph.	30c,200c, LM1,3,5	2	2	0	1
Puls.	30c,200c	4	2	4	4
Phos.	30c,200c	5	4	4	5

Other medicines prescribed in PGL strata: (Verum): *Ferr., Gels., Nit-ac., Ign.,* (1 case each); (Placebo): *Graph. Lach.* (1 case each).
In asymptomatic strata: (Verum): *Aur., Kali-c., Staph., Arg-n.* (1 case each); (Placebo): *Calc-s, Chin., Op., Zinc.* (1 case each).

foundly thankful to Shri Donta Balaiah, Assistant Director (Statistics), for his guidance and help in the statistical evaluation of the results. We would also like to thank the following individuals for their sincere co-operation in the study; Dr Janardhan Nair, ARO(H), Kottayam, Mrs Uma Clerk, Laboratory technician, RRI, Mumbai and Mr Nagesh Gosavi, Medico Social Worker, RRI, Mumbai.

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Table 5.2 Constitutional features/Rubrics/Indications on basis of which some of the medicines were prescribed

Medicine	*Indications*
Calc.	• Obesity, industrious; *desires company* of intimate friends; weeping tearful mood, sentimental, dreams of dead bodies. • Desires cold drinks, eggs, sweets; perspiration profuse, back, foot, soles; cold in general aggravates. • Baldness, hair falling; dandruff and itchy scalp; palpitation in general; painful horny corns on soles; genital eruptions; *Pains in lower extremities, thighs,* at night and rest.
Lyc.	• Quiet disposition, *desire for company,* religious minded, anger with trembling, consolation aggravates, optimistic, perseverant, sentimental, sensitive to noise, sad stories affect profoundly, self reproaches, dwells on past, *intolerant of contradiction, anger from contradiction,* cowardice, indifferent, increased sexual passion. Dreams of disease, amorous, accidents, murders, with talking in sleep. • *Lean consitution, desires sweets, constipation* from inactivity of rectum, offensive profuse perspiration, cold in general aggravates. • Painful corns. Early greying of hair. Neglected pneumonia.
Nux-v	• Sensitive to external impressions, anger violent, furious, suicidal disposition but lacks courage, jealous, delusions of persecution. • Lean constitution, warmth aggravates; desires cold food, spices; thirstlessness, diminished appetite. • Frequent dribbling urination. Unrefreshing sleep in morning.
Phos.	• *Fear* of being alone, *desires company, aversion to solitude,* sadness when alone, weepy tearful mood, *thoughts of disease,* dwells on past, desire to kill, anxiety of other, sympathy compassionate, industrious, dictatorial, mildness, *lascivious; fightful, amorous dreams,* talking in sleep. • *Lean* constitution; *Desires fish,* salt, *spices, cold drinks,* alcoholic drinks, ice; aversion to sweets, farinaceous food; thirst for large quantities, cold in general aggravates, *profuse perspiration,* diminished appetite. • Pain in extremities, after slight exertion; sleeps late, interrupted sleep with many dreams; premature ejaculations, deminished libido, haemorrhages, prolapsus uterus.
Puls.	• Reserved, *fastidious,* optimistic, *desires company,* religious natured, *consolation ameliorates;* fear of dark, of impending disease; timidity, want to self confidence, involuntary weeping; dreams of misfortune, amorous. • Desires pungent things, cold water; aversion to salty food, sweets; fats aggravate, *hot patient,* desires and better in open air, profuse *offensive* perspiration. • Orchitis, left side, from injuries. Lumbago. Sleeplessness.
Sulph.	• Bold, audacious. Hatred and revengeful; fear of misfortune, impending disease; anxious. • Desire meat, cold water, spices; aversion to sweets, bread; open air ameliorates, *thirst for large quantities,* profuse perspiration, easily perspires, foetid. *warmth* in general aggravates. • Falling asleep late, *skin-itching during sleep.* Simple toothache.

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