

Original Research Article

Study of thyroid profile in seropositive HIV adults patients on HAART regimen

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ABSTRACT

Background: Subtle alterations in thyroid function tests are more common in HIV infection and at times detectable in the early phase of disease and as well as in late phases. However, there is paucity of Indian studies.

Methods: This cross-sectional study was carried out among adult HIV positive patients attending OPD and IPD of tertiary care hospital in collaboration with ART-plus center over a period of 21 months. 100 adult HIV positive patients were interviewed and clinically examined. On the basis of CD4 count patients were divided into 3 groups {0-200 (Group A), 201-350 (Group B) and >350 cells/mm³ (Group C)}. Subjects were also divided into two groups based on type and duration of HAART regimen.

Results: Out of 100 patients included in the study 68% were males, 73% married, 12% had subclinical hypothyroidism, out of 6% of overt hypothyroidism subjects 5% were females. Among the 3 groups, thyroid abnormalities were found to be more common in group B followed by Group A and C. Patients on TLE regimen had 14% thyroid abnormalities as compared to 4% in ZLN group.

Conclusions: Subclinical hypothyroidism and overt hypothyroidism are the commonest thyroid abnormality seen, more commonly in females. CD4 counts have direct association with free T3 and free T4 and inverse association with Serum TSH level indicating trend for hypothyroidism as HIV disease progresses. Thyroid abnormalities vary with the type and duration of HAART regimen.

Keywords: HAART, HIV, Thyroid, Overt hypothyroidism, Sub clinical hypothyroidism

INTRODUCTION

India has the third largest HIV epidemic in the world. In 2013, HIV prevalence in India was an estimated 0.3% and this equates to 2.1 million people living with HIV. In the same year, an estimated 130,000 people died from AIDS-related illnesses.¹ Human immunodeficiency virus (HIV) infection can lead to involvement of multiple organs including the endocrine system.

The endocrine glands are affected in a variety of ways such as functional derangement, direct effects of HIV infection and the resultant immune suppression, effects of opportunistic infections both acute and chronic, invasion

by neoplasms and the effects of the various medications used to treat HIV or any of the opportunistic infections associated with it.

Although thyroid function tests are often abnormal in HIV patients, the prevalence of overt thyroid disorder is not significantly different from that of the general population. Most asymptomatic patients with HIV infection have normal thyroid function. Some, however, exhibit increased serum T4 and T3 concentrations. These increases are as a result of increases in serum thyroxine-binding globulin, the cause of which is unknown. However, with progression of HIV infection and as the patients become more ill, serum T4 and T3

concentrations decline, as is obtained in most if not all chronically ill patients; serum thyrotropin concentrations however remain normal or slightly depressed. These changes are as a result of reduction in serum binding proteins, decreased extra thyroidal conversion of T4 to T3, and decreased secretion of thyrotropin. Cytokines may be involved in some of these; especially the reduction in the peripheral conversion of T4 to T3.

An increasing number of patients taking anti-HIV drugs are presenting with thyroid disorders as a result of improved immune function (immune reconstitution syndrome). Graves' disease is the commonest among immune reconstitution syndromes; others include Hashimoto's thyroiditis and hypothyroidism. Autoimmune Thyroid disease (AITD) occurs in 3% of women and 0.2% of men. Goddard proposed a staging of autoimmune manifestations related to HIV/AIDS.²

Stage I - Acute HIV infection, the immune system is intact and autoimmune diseases may develop.

Stage II - The quiescent period without overt manifestations of AIDS associated with a declining CD4 count indicative of some immunosuppression. Autoimmune diseases are not found.

Stage III - Immunosuppression with low CD4 count and the development of AIDS. CD8 T-cells predominate and diseases such as psoriasis and diffuse immune lymphocytic syndrome (similar to Sjogren's syndrome) may present or even be the initial manifestation of AIDS. No autoimmune diseases are found.

Stage IV - Restoration of immune competence following HAART. In this setting, there is a resurgence of autoimmune disorders.

A high prevalence of abnormalities in thyroid function tests among HIV infected adults has been noted in previous cross sectional studies worldwide; however, there is paucity of Indian studies that are needed to evaluate the thyroid dysfunction in HIV infected Indian patients. Hence the present study was undertaken with an aim to study biosocial profile, thyroid dysfunction of study subjects and to determine the association between thyroid dysfunction with gender, age, CD4 counts, type and duration of HAART Regimen.

METHODS

This cross-sectional prevalence study was carried out among adult HIV positive patients attending OPD and IPD of KPS institute of medicine, GSVM Medical College in collaboration with ART-plus center, Kanpur over a period of 21 months (Dec 2014 to Aug 2016). 100 adult HIV positive patients registered at ART-plus centre during the study period were included in the study. All patients were interviewed and clinically examined. Written informed consent was obtained from all subjects.

Patient confidentiality was maintained. Data was recorded through direct personnel interview/investigation method on pre-designed and pretested questionnaire/record sheet.

Inclusion criteria

- Subjects with HIV serology positive by ELISA test
- PIHIV patient on HAART regimen
- Clinically stable with vital signs within normal limits.

Exclusion criteria

- Known cases of thyroid disorder
- Patients who were pregnant
- Patients with known thyroid disorder, hypertension, diabetes, coronary artery disease or were on drugs known to interfere with thyroid metabolism such as glucocorticoids, phenytoin, carbamazepine, etc.
- Patients on Stavudine based anti-retroviral drugs
- Abnormal liver function tests with SGOT/SGPT levels greater than 3 times normal range
- Abnormal renal function test with Serum Creatinine >1.6mg%.

Besides routine investigations, patients were subjected to specific microbiological, pathological and radiological investigations. CD4 Count (Flow cytometry), Thyroid function tests-TSH, free T4, free T3 and anti TPO antibodies were done in every patient. The data was collected on predesigned and pretested questionnaire/record sheet was compiled and master table was made on Excel accordingly. To fulfil the objectives of the present research, most appropriate statistical tools (percentages and chi square test for association) were applied to analyse the data and conclusions were drawn accordingly.

RESULTS

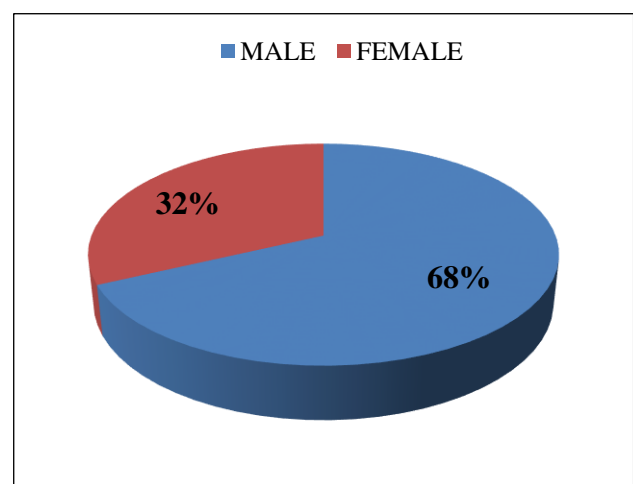


Figure 1: Distribution of subjects according to gender (n=100).

Out of 100 patients 68% of the study subjects were males and 32% of the study subjects were female. Male: female ratio was 2.125:1 (Figure 1).

Majority of the subjects belong to age group of 20-40 (72%) followed by 40-60 years (17%). Maximum number of male subjects belonged to 30-40 years of age group while maximum number of female subjects belonged to age group of 20-30 (Table 1, Figure 2).

Table 1: Distribution of subjects according to age (n=100).

Age (years)	Number of patients	Percentage (%)
<20	9	9%
20-40	72	72%
40-60	17	17%
60-80	2	2%

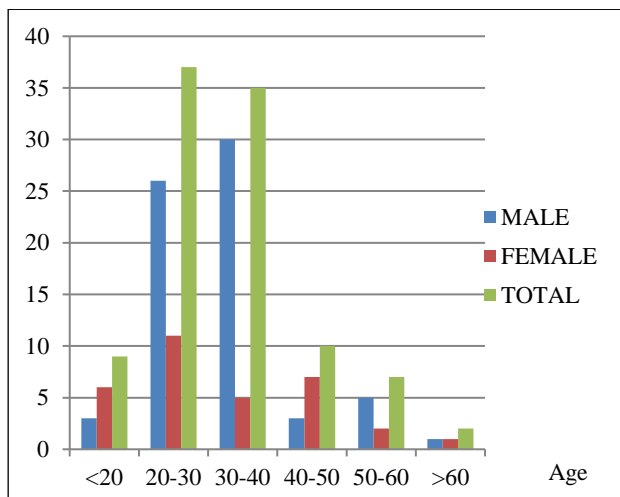


Figure 2: Distribution of subjects according to age and gender (N=100).

73% of the subjects were married while 27% of the subjects were unmarried. On the basis of the religion majority of the study subjects were Hindus (61%) followed by Muslims (36%) and Christians (3%). No subjects of other religion were registered (Table 2, 3).

Table 2: Distribution of subjects according to marital status (n =100).

Married	Unmarried
73	27

Table 3: Distribution of subjects according to religion.

Religion	Number of patients	Percentage
Hindu	61	61
Muslim	36	36
Christian	3	3

12% patients had subclinical hypothyroidism (TSH level in between 5-10), while 6% subjects had overt hypothyroidism (TSH values of >10). Only 2% of subjects had TSH values of <0.5. 80% patients were euthyroid. Of 12% majority (8%) of the subclinical hypothyroidism was seen in age group of 20-40 years of age. It is also seen that thyroid dysfunction was more common in females as compare to male subjects, this hypothesis was accepted as the results are statistically significant ($p<0.05$) (Table 4, Figure 3).

All 100 patients were divided in three groups according to CD4 count, arbitrarily: 0-200 (Group A), 201-350 (Group B) and >350 cells/mm³ (Group C). Out of 10 patients in group A, 6 (60%) patients had thyroid abnormalities. 4 (40%) had overt hypothyroidism and 2 (20%) had subclinical hypothyroidism. In Group B, out of 70 patients only 11 (15.71%) patients had abnormal thyroid levels. 2 (2.8%) had overt and 7 (10%) had subclinical hypothyroidism. 2 (2.8%) had TSH Levels less than 2 mIU/L. In Group C, out of 20 patients only 3 (15%) patients had subclinical hypothyroidism. No patient of overt hypothyroidism was seen (Table 5).

Table 4: Thyroid dysfunction according to gender.

S.TSH (miu/L)	Male	Female	Total (%)
<0.5	-	2	2
0.5-5	60	20	80
5-10	7	5	12
≥10	1	5	6

$X^2 = 13.83$, C.I. =95%, df =3, $p<0.05$

Table 5: Association of thyroid dysfunction with CD4 counts.

CD4 Counts (cells/mm ³)	S.TSH (mIU/L)			
	<0.5	0.5-5	5-10	>10
Group A (<200)		4	2	4
Group B (200-350)	2	59	7	2
Group C (350-500)		17	3	

$X^2 = 25.6$, C.I. =95% df =6: $p<0.05$

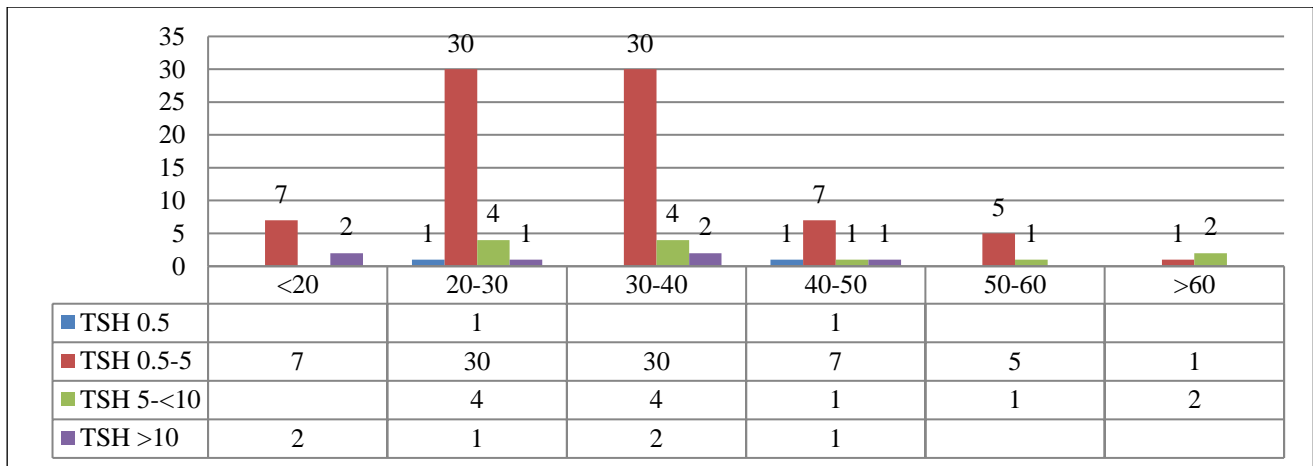


Figure 3: Association of thyroid dysfunction with age.

As the CD4 counts decreases mean values of T3 and T4 also decreases while S.TSH level increases. 4% patients with CD4 count <200 had overt hypothyroidism and Therefore, CD4 counts have direct association with T3 and T4 and inverse association with S.TSH level. This association was found to be statistically significant (Figure 4).

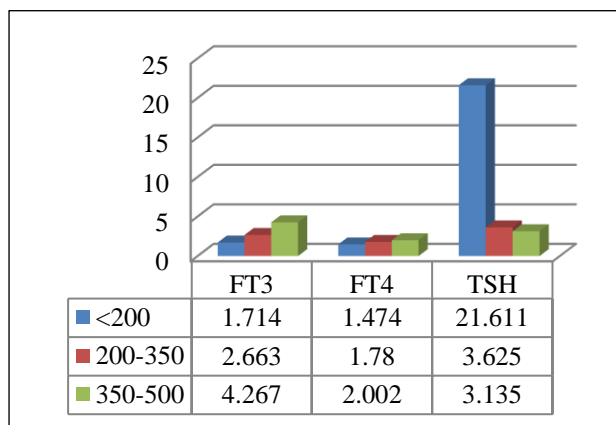


Figure 4: Comparison of CD4 counts with mean values of thyroid function test.

All the patients included in the study were on HAART. Out of 100, 58 patients were on ZLN (Zidovudine, Lamivudine, Nevirapine) and 42 were on TLE (Tenofovir, Lamivudine, Efavirenz). Out of 58 patients on TLE regimen 14 (24.13%) patients had thyroid abnormalities. 6 (10.34%) patients had overt hypothyroidism, 8 (13.79%) had subclinical hypothyroidism whereas 2 (3.44%) had TSH levels less than 0.5 mIU/L. Among ZLN regimen, only 4 (9.42%) had subclinical hypothyroidism none had overt hypothyroidism. Thyroid dysfunction was more common in subjects with TLE regimen (27.58%) than with ZLN (9.42%) (Table 6, 7).

Table 6: Distribution of subjects based on HAART regimen.

HAART regimen	Number of patients
TLE	58
ZLN	42

TLE- Tenofovir, Lamivudine, Efavirenz.

ZLN- Zidovudine, Lamivudine, Nevirapine.

Table 7: Distribution of Thyroid function abnormality with the type of HAART regimen.

Regimen	S.TSH (mIU/L)			
	<0.5	0.5-5	5-10	>10
TLE	2	42	8	6
ZLN	-	38	4	-

Out of 58 patients on TLE regimen 23 patients were on treatment for less than one year whereas 35 of them were for more than one year. Similarly, In ZLN regimen - 17 patients were on treatment for less than one year and 25 of them were for more than one year. It was observed that thyroid dysfunction was associated with TLE regimen when given for > 1year.

Hence, we can say that thyroid dysfunction was associated with prolonged treatment of TLE regimen and this result was found to be statistically significant ($p < 0.05$). It was also observed that thyroid dysfunction was associated with ZLN regimen of <1year. Hence, we can say that thyroid dysfunction was associated with initiation of ZLN therapy. This observation was also found to be statistically significant. ($p < 0.05$). It was also observed that thyroid dysfunction was associated with ZLN regimen of <1year. Hence, we can say that thyroid dysfunction was associated with initiation of ZLN therapy. This observation was also found to be statistically significant. ($p < 0.05$). (Table 8).

Table 8: Association of thyroid function test with type and duration of HAART.

Regimen	Duration of treatment	S.TSH mIU/L				
		<0.5	0.5-5	5-<10	>10	
TLE	<1y	2	21	0	0	$X^2=14.1$, C.I. =95%, df= 3, $P<0.05$
	>1y	0	21	8	6	
ZLN	<1y	0	13	4	0	$X^2=6.5$, C.I. =95%, df= 1, $P<0.05$

DISCUSSION

The study aims at recognizing association of Thyroid dysfunction in patients with HIV infection and to determine whether Thyroid function test can be used as surrogate marker for the severity of infection.

100 seropositive HIV study subjects on HAART regimen were included in the study and were divided on the basis of CD4 counts as per CDC classification; type and duration of HAART regimen. Study population was divided into 3 groups on the basis of CD4 counts: Group A - CD4 counts <200 cells/mm³, Group B - CD4 counts 200-350 cells/mm³ and Group C - CD4 counts 350-500 cells/mm³. Study population was also divided according to duration of HAART therapy as <1 year and >1 year and according to type of HAART regimen {TLE (Tenofovir, Lamivudine, and Efavirenz) and ZLN (Zidovudine, Lamivudine and Nevirapine)}.

In our study 68% of the subjects were males and 32% were females with male to female ratio of 2.125:1, comparable with the study of Shukla Y et al and Michèle G, et al.^{3,4} Male to female ratio in their study was 2.6. Majority of the study population (72%) belong to the age group of 20-40 years, with mean age of 33.91±10.4 comparable with the study of Shukla Y et al in which majority of the cases (81.45%) were between 20-45 years and Michèle G et al in which mean age was 40.8 years (SD = 9.54).⁷ 3% of our study population was married (including widowed and divorcee) and 37% of the subjects were unmarried, these observations was also comparable with the study of Shukla Y et al.^{3,4}

Majority of the patients were found to be euthyroid (80%). 12% had subclinical hypothyroidism while 6% subjects had overt hypothyroidism. Only 2% had subclinical hyperthyroid (TSH values of 0.21 and 0.11 with normal T3 and T4). Overall incidence of thyroid dysfunction was 20%. These results are comparable to Meena LP et al.⁵ They evaluated the thyroid function in 150 HIV infected male patients at different levels of CD4 counts. Overall 30% were found to have subclinical hypothyroidism and 10% had overt hypothyroidism. Beltran S, et al conducted a cross sectional study to determine the prevalence of and risk factors for hypothyroidism in 350 HIV infected patients grouped according to CDC staging.⁶ Results showed 16% of them having hypothyroidism, 2.6% had overt hypothyroidism, 6.6% had subclinical hypothyroidism. Madge S et al,

studied 1565 patients.⁷ Out of which, 2.5% had overt hypothyroidism, 4% had subclinical hypothyroidism, normal function was found in 75% of the patients. Varthakavi PK concluded that abnormal thyroid function tests are encountered often in HIV positive individuals.⁸ Study conducted by Mandal SK et al also found endocrine dysfunction in 48 patients.⁹ Among them, 33% had hypogonadism, 20% had hypothyroidism and 15 patients had diabetes. Grappin et al reported thyroid dysfunction in 10.4% patients, 8.5% with subclinical hypothyroidism and four patients with elevated antithyroperoxidase antibody serum levels.⁴ No hyperthyroidism was found. Similar findings were also found by Sharma N et al.¹⁰ They screened 527 patients, 359 patients, having good immune function. Subclinical hypothyroidism was the commonest thyroid dysfunction (14.76%) followed by sick euthyroid syndrome (SES) (5.29%). Therefore, high incidence of thyroid dysfunction may contribute to the morbidity of the patient and poor quality of life.

Overall thyroid dysfunction in our study was more common in females (12%) than in males (8%) and this observation was found to statistically significant ($p<0.05$). It was also more common in younger age group (<40 years), this finding in contrast to the results seen in study of Tripathy SK et al.¹¹ Thyroid dysfunction was more common in males than females.

Association of thyroid dysfunction with CD4 counts is shown in Table 5. Results showed that there was increased incidence of thyroid dysfunction with lower CD4 counts i.e. thyroid dysfunction increases with severity of the disease, these observations were found to be statistically significant ($X^2 = 25.6$, C.I. = 95% df = 6: $p<0.05$). Results were comparable with the study of Jain G et al in which a direct correlation between CD4 count and free T3 and free T4 values and an inverse correlation of CD4 counts with serum thyroid stimulating hormone (TSH) levels was seen.¹² They concluded that thyroid dysfunction is frequent in HIV infection and with progression of disease there is a primary hypothyroid like stage. Palanisamy P et al concluded that thyroid dysfunction is frequent in HIV infection and that with progression of disease there is a primary hypothyroid like stage that occurs in patients with HIV infection.¹³ Therefore free T3, free T4 and serum TSH can be used as a surrogate marker of progression of the disease. Thongam S et al, reported that thyroid dysfunction may be a marker of severity or progression of HIV.¹⁴ TSH,

total T4, and T3 were analyzed in 60 HIV cases: 30 on HAART and 30 HAART naïve. Thyroid function abnormality was seen in five out of 30 patients in both patients on HAART or without HAART therapy. Among patients on HAART, three had hypothyroidism, and two had biochemical feature of sick euthyroid syndrome. Among the HAART naïve group, sub-clinical hypothyroidism was seen in four, and one had biochemical feature of sick euthyroid syndrome. There is a highly significant correlation ($P = 0.01$) between TSH and CD4 count. Raffi F et al concluded that endocrine dysfunction in HIV-infected patients is rarely of clinical significance, that it is related more to cachexia and advanced disease than to HIV or opportunistic infections, and that it could serve as a prognostic marker.¹⁵ According to the study of Dev N et al the overall prevalence of thyroid dysfunction was 75.5% in the study group and 16% in the control group.¹⁶ Subclinical hypothyroidism was the commonest abnormality noted in almost 53%. Significant correlation was observed between CD4 count and, free triiodothyronine, and free thyroxine levels ($r = -0.86$, $r = 0.77$, and $r = 0.84$, respectively, $p < 0.0001$ for all). The study demonstrated high prevalence of thyroid dysfunction in HIV-positive patients. The dysfunction is subclinical in most cases and correlates well with declining CD4 counts.

There is a significant association of thyroid function with type and duration of HAART regimen. Significant association was observed between the TLE regimens when giving for duration of more than 1 year. Therefore, we conclude that prolonged treatment with TLE regimen could result in thyroid dysfunction. This observation was found to be statistically significant ($X^2 = 14.1$, C.I. = 95%, $df = 3$, $p < 0.05$). It was also found that thyroid dysfunction was associated with ZLN regimen when given for less than 1 year. Hence, we concluded that thyroid dysfunction was associated with initiation of ZLN therapy. This observation was also found to be statistically significant ($X^2 = 6.5$, C.I. = 95%, $df = 1$, $p < 0.05$). Similar observation was reported by Shujing Ji et al¹⁷ in which Thyroid dysfunction was significantly more frequent in the HAART group (41/104, 39.4%) than in the HAART-naïve group (18/74, 24.3%; P value < 0.05). The mean CD4 cell count was significantly lower in patients with hypothyroidism ($372 \pm 331/\mu L$) than in the other patients (P value < 0.05). The FT4 level was significantly lower in the HAART group than in the HAART-naïve group. FT3/FT4 levels were negatively related to HIV duration and FT3 levels were positively related to CD4 cell (P value < 0.05). HBV patients had lower FT3 levels, while HCV patients had higher FT3 and FT4 levels (P value < 0.05). Thyroid dysfunction is more common in HIV patients on HAART, mainly manifested as hypothyroidism. But association of thyroid dysfunction with type of HAART regimen still needs to be substantiated by large longitudinal study.

This study had some limitations. The study group was small and the study was conducted purely on Indian

ethnic background. All the subjects in this research were on HAART (either TLE or ZLN) with no HAART naïve patients and long-term follow-up of the study.

CONCLUSION

Abnormal thyroid function test results are common in PLHIV patients. Subclinical hypothyroidism and overt hypothyroidism are the commonest thyroid abnormality seen, more commonly in females as compared to males. CD4 counts have direct association with free T3 and free T4 and inverse association with S.TSH level indicating trend for hypothyroidism as HIV disease progresses. Thyroid dysfunction was associated with initiation of the ZLN and with prolonged treatment with TLE regimen. Since patients on HAART have high prevalence of Thyroid dysfunction, larger studies are needed to confirm the findings to examine the epidemiology and health consequences of mild thyroid dysfunction in HIV-infected patients.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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