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Nocturnal Sleep EEG in Patients with HIV Infection

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Summary. Nocturnal sleep was studied in 14 human immunodeficiency virus (HIV)-positive patients without opportunistic infections of the central nervous system. Seven patients had no bodily complaints at the time of the investigation. Patients exhibited an impaired nocturnal sleep with longer sleep onset latency, reduced total sleep time, reduced sleep efficiency, and more time spent awake and in stage 1. Stage 2 sleep was significantly decreased; in 2 cases, sleep spindle density was extremely low. REM latency was reduced and correlated negatively with depressive symptomatology, while the percentages of REM and slow wave sleep were normal. No significant differences in sleep parameters were present among patients in different stages of the illness, or between patients with and without bodily complaints. Ventricular size and sulcal width on computed tomography scans correlated with sleep variables indicating reduced sleep quality, and with REM density. Decreased tryptophan plasma levels were associated with shorter and less efficient sleep, and with reduced stage 2 sleep. The findings demonstrate that sleep EEG investigations can be valuable for detecting and monitoring central nervous system affection in HIV-positive individuals.

Key words: HIV infection – AIDS – Sleep EEG

Introduction

In human immunodeficiency virus (HIV) infection the central nervous system (CNS) is frequently affected, although in early stages of the illness conspicuous neurological or psychiatric symptomatology may be absent. In such stages, an intrathecal production of humoral HIV-specific antibodies could be detected in about 70% of patients (Felgenhauer et al. 1988).

Electroencephalographic (EEG) findings in HIV-positive individuals are mostly characterized by intermittent or continuous slowing of background activity (Enzensberger et al. 1985). Parisi et al. (1989) found about 25–30% abnormal EEGs in illness stages II and III (according to the CDC classification, Center for Disease Control 1987). Hartmann et al. (1988) and Schnurbus et al. (1989) presented similar results: slowing of background activity was already found in early stages of HIV infection, whereas additional focal and diffuse changes in the electrical activity of the brain occurred with progression of the infection. An analysis of topographic EEG data by Riedel and Bülau (1989) also demonstrated abnormalities in early, asymptomatic stages of the illness, as well as an evoked potential study by Maleßa et al. (1989). On the other hand, Möller et al. (1986) found that abnormal EEGs were restricted to later illness stages. Biniek et al. (1988) observed EEG slowing only in patients with secondary neurological complications. Similar results were presented by Gabuzda et al. (1988). Thus, it is still a matter of controversy as to how far EEG examinations can contribute to an early detection of an involvement of the CNS in HIV infection.

Studies on nocturnal sleep in HIV infection have yielded contradictory results. Norman et al. (1988) reported decreased sleep efficiency and increased nocturnal wakefulness in eight asymptomatic HIV-seropositive patients. Six of them exhibited comparatively large amounts of slow wave sleep. These alterations persisted in a follow-up study (Norman et al. 1990a). Moreover, severe alterations of NREM/REM sleep cycles were observed (Norman et al. 1990b). In a preliminary report, Kubicki et al. (1988) observed a remarkably small percentage of stage 2 sleep, along with an extremely low sleep spindle density. A recent study by the same group (Kubicki et al. 1989) confirmed these findings in a larger sample and demonstrated further abnormalities of nocturnal sleep:

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reduced total sleep time, less slow wave and REM sleep, more time spent awake and more stage 1 sleep than usually observed in healthy persons.

The present study was designed to investigate nocturnal sleep EEG in patients with HIV infection in different stages of the illness, including patients without bodily complaints. In addition, the relationship between sleep EEG and several parameters which probably contribute to modifications of nocturnal sleep were studied. Among these, special attention was paid to concomitant depressive symptomatology. In patients with a HIV infection, depression is frequent; in a considerable percentage of patients, criteria for DSM-III-R diagnoses of major depression or adjustment disorder with depressed mood are met (Baer 1989; Perry et al. 1990). The relationships between HIV infection and depression are complex. Depressive symptomatology can be reactive to the life-threatening implications of the infection. It can also be the expression of a mood syndrome as a direct consequence of CNS affection. A further hypothesis was put forward by Perry et al. (1990): they pointed out that individuals at perceived risk for AIDS may be vulnerable to depression independent of whether they are infected or not.

Another focus of interest in the present study was the relationships between sleep modifications and serum and CSF tryptophan levels, respectively. In HIV infection, serum levels of tryptophan are usually decreased, probably due to degradation induced by interferon-gamma (Werner et al. 1988; Fuchs et al., in press); this may hypothetically contribute to changes of the central serotonin metabolism and thus lead to impaired sleep regulation.

Subjects and Methods

Nocturnal sleep was studied in 14 HIV-seropositive individuals: 13 were male homosexuals, 1 was a female partner of an i.v. drug abuser. The mean age was 35.6 ± 9.3 years (cf. Table 1 for an overview). Patients with a history of drug abuse or presenting opportunistic infections of the CNS, circumscript cranial computed tomography (CT) lesions, impairment of consciousness or psychotic symptoms were excluded from the study. All were treated in the Department of Neurology of the Max Planck Institute of Psychiatry, Munich. According to the CDC case definitions (Center for Disease Control 1987), 5 patients each were in stages III (mean age 36.4 ± 10.3 years) and IV A (mean age 37.8 ± 9.9 years), and 4 were in stage IV C (mean age 31.8 ± 8.4 years). Following the Walter Reed Classification (Redfield et al. 1986), 4 patients were in stage 2, 2 in stage 4, 4 in stage 5 and 4 in stage 6. Seven patients had no bodily complaints at the time of the investigation. Four patients were treated with zidovudine. One patient met the DSM-III-R criteria (American Psychiatric Association 1987) for both major depression (296.22) and dependent personality disorder (301.60). Another patient suffered from an adjustment disorder with anxious mood (309.24). One patient exhibited an antisocial (301.70), another a borderline personality disorder (301.83). No othe patients met the criteria for any DMS-III-R psychiatric diagnosis.

Fourteen age-and gender-matched persons who were free of any neurological or psychiatric disorders served as a control group (mean age 34.2 ± 10.2 years).

Polysomnography. All patients had been free of psychoactive medication for at least 14 days; urinary analysis for psychoactive drugs (benzodiazepines, barbiturates, opiates, cocaine, amphetamines) were performed immediately before sleep recordings. After an adaptation night in the sleep laboratory, nocturnal sleep was recorded between lights out (2300 hours) and lights on (0700 hours) using a 17-channel Nihon Kohden 4417 EEG machine, including EEG (C3–A2/C4–A1), horizontal EOG and submental EMG. The sleep polygraphs were scored according to standard criteria (Rechtschaffen and Kales 1968), based on 30-s epochs. For the evaluation of sleep recordings, the following definitions of sleep parameters were used: total sleep time: time spent asleep less any awake time; sleep period time: time from sleep onset until final awakening; sleep onset latency: time from lights out until the appearance of stage 2 sleep; sleep efficiency: ratio of total sleep time to time in bed; stages awake, 1, 2, SWS (= sum of stage 3 and 4), REM are expressed in percentages of sleep period time; REM latency, time from sleep onset to the first occurrence of REM sleep; REM density, percentage of 3-s "mini-epochs" of REM sleep containing eye movements related to the total number of "mini-epochs" of REM sleep; spindle density: ratio of the number of sleep spindles during stage 2 to the stage 2 duration. Sleep spindles were identified visually using the following criteria: a frequency between 12 and 14 Hz, a duration of at least 0.5 s, a peak-to-peak amplitude of at least 25 μV.

Table 1. Description of sample

Patient	Sex	Age (years)	WR stage	CDC stage	Present complaints	Zidovudine treatment	Psychiatric diagnosis (DSM-III-R)
1	M	31	5	IV A	+	+	–
2	M	33	4	IV A	+	–	–
3	M	28	5	IV A	–	+	–
4	F	48	5	IV A	+	+	309.24
5	M	22	2	III	–	–	–
6	M	31	2	III	–	–	301.83
7	M	24	6	IV C	–	–	–
8	M	27	6	IV C	+	–	–
9	M	39	2	III	–	–	–
10	M	41	4	III	–	–	–
11	M	49	2	III	–	–	–
12	M	49	5	IV A	+	+	296.22 / 301.60
13	M	43	6	IV C	+	–	301.70
14	M	33	6	IV C	+	–	–

Psychopathology ratings. Psychopathology of the patients was assessed by means of the German version (Hiller et al. 1986) of the Inpatient Multidimensional Psychiatric Scales (IMPS) (Lorr and Klett 1967), with four major subscales covering "depressive", "manic", "paranoid-hallucinatory", and "other psychotic" symptomatology (maximum sum scores: 68, 63, 39, and 66, respectively).

Computerized tomography. Cranial CT was carried out in 12 patients (General Electric 9800, 512 × 512 matrix, 5 mm slices). The measurements were performed as previously described in full detail by Krieg et al. (1988) and Möller and Backmund (1990). The following CT parameters were assessed: VBR (ventricular brain ratio): area of the lateral ventricles divided by the area of the brain × 100) (%); sulcal width: the mean width of the four largest sulci (two of the left, two of the right hemisphere) (mm)

Tryptophan measurements. The sum of free and protein-associated, but not covalently bound tryptophan was measured in serum and CSF by HPLC (for a more detailed description of the methodology, cf. Werner et al. 1988).

Table 2. Sleep in patients with HIV infection and matched healthy controls

n		Total sleep time (min)		Stage awake (%)		Stage 1 (%)		Stage 2 (%)		Slow wave sleep (%)		REM sleep (%)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Controls	14	429.0	22.6[a]	3.2	2.5[b]	6.4	4.4[c]	57.9	7.5[d]	12.2	8.3	19.2	5.0
Patients	14	390.0	22.7[a]	9.4	8.7[b]	12.5	7.8[c]	45.4	9.5[d]	10.4	6.5	20.8	6.1
CDC stage III	5	410.4	24.4	7.9	6.7	13.8	5.2	53.1	4.5	7.1	4.8	16.5	2.0
CDC stage IV A	5	381.6	65.2	8.1	7.4	14.3	12.1	40.4	9.8	12.5	8.1	22.9	5.1
CDC stage IV C	4	375.0	55.8	12.6	13.2	8.6	1.4	41.8	8.7	12.1	6.1	23.5	8.5
		Sleep onset latency (min)		REM latency (min)		REM density		Sleep efficiency (%)		Number of awakenings		Sleep spindle density	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Controls	14	15.6	12.2[e]	95.9	37.1[f]	27.6	7.7	93.4	2.9[g]	9.0	5.0[h]	3.5	1.4
Patients	14	29.9	17.9[e]	69.2	31.6[f]	30.6	13.2	83.1	10.4[g]	15.4	6.1[h]	2.7	1.6
CDC stage III	5	24.9	15.4	91.9	31.0	32.0	11.9	86.2	4.7	16.8	5.9	2.9	0.9
CDC stage IV A	5	37.4	23.8	48.9	24.7	26.9	14.7	81.5	13.6	14.2	8.7	1.7	2.0
CDC stage IV C	4	26.9	13.3	66.1	25.8	33.4	15.4	81.3	13.0	15.3	2.8	3.9	1.4

Significant differences between patients and controls: [a] $t = 2.67$, $df = 26$, $P < 0.02$; [b] $t = -2.56$, $df = 26$, $P < 0.02$; [c] $t = 2.56$, $df = 26$, $P < 0.02$; [d] $t = 3.87$, $df = 26$, $P < 0.001$; [e] $t = -2.48$, $df = 26$, $P < 0.02$; [f] $t = 2.05$, $df = 26$, $P < 0.05$; [g] $t = 3.57$, $df = 26$, $P < 0.003$; [h] $t = -3.05$, $df = 26$, $P < 0.005$

Statistics. Differences between patients and healthy conrols, as well as between patients with and without bodily complaints, were analysed by using Student's *t*-test. For the analysis of differences between patients of different groups according to the CDC classification, a one-way analysis of variance was applied. In the correlational analyses, Spearman's rank correlation coefficients were computed. The level of significance was set at 5% (two-tailed).

Results

Table 2 demonstrates that patients and healthy controls differed significantly in several sleep parameters. Patients had a shorter total sleep time, they spent more time awake and in stage 1, whereas stage 2 sleep was reduced. Their sleep onset latency was longer whereas REM latency was shorter [one patient exhibited a sleep onset REM (SOREM) period with a REM latency of 5.5 min]. Sleep in patients was less efficient, and they woke up more frequently during the night. There was no difference in slow wave sleep, percentage REM sleep and REM density. An extremely reduced sleep spindle density (0.14 and 0.33 spindles/min stage 2, respectively) was observed in two cases. Among these was the only patient meeting the criteria for major depression who exhibited a total number of only 13 sleep spindles during 90 min of stage 2 sleep. Group statistics, however, did not reveal a significant difference in sleep spindle density between patients and controls.

When analysing the differences in sleep variables between patients in different illness stages according to the CDC classification, an analysis of variance yielded no significant results. However, a trend was present for stage 2 sleep (reduced in stages IV A and IV C, $F = 3.72$, $df = 2; 11$, $P = 0.06$) and REM latency (shorter in stages IV A and IV C, $F = 3.10$, $df = 2; 11$, $P = 0.09$). When dichotomizing the total group into patients with and without bodily complaints at the time of the investigation, no significant differences were found. (These data are not represented in the table.)

There were no significant differences in sleep variables between patients receiving zidovudine ($n = 4$) and drug-free patients. However, REM latency and percentage stage 2 tended to be shorter in the zidovudine group ($P < 0.20$ in either case). Moreover, both patients with an extreme paucity of sleep spindles were in this group.

Table 3 describes psychopathology, CT scan measures and tryptophan levels in the total patient group and in the subgroups according to the CDC classification. Levels of depressive symptomatology were fairly high in the patients. In CDC stage III, depression was significantly less pronounced than in higher stages. Depression scores also differed significantly between patients with and without bodily complaints ($t = -2.49$, $df = 12$, $P = 0.03$). Manic symptomatology was far less pronounced, without any differences between subgroups. In the remaining IMPS subscales (paranoid-hallucinatory symptomatology and other psychotic symptomatology) most patients scored zero; thus, the results for these subscales are not presented and discussed here.

Table 4 gives the correlations between psychopathology scores and selected sleep variables. Depressive symptomatology correlated positively with percentage REM sleep, whereas there was a negative correlation with REM latency; no significant correlations emerged for manic symptomatology.

Ventricular and cortical CT scan measures were highly intercorrelated ($r = 0.88$, $df = 11$, $P = 0.004$). No differences were present between CDC classification subgroups or between patients with and without bodily complaints.

Table 3. Psychopathology, cranial CT scan measures and tryptophan levels in patients with HIV infection

	Psychopathology					CT scan measures					Tryptophan levels					
	n	Depressive (sum scores)		Manic (sum scores)		*n*	VBR[a] (%)		Sulcal width (mm)		*n*	Plasma (μmol/l)		*n*	CSF (μmol/l)	
		Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD		Mean	SD
Total	14	21.5	12.1	6.1	7.4	12	6.4	2.9	2.58	0.61	10	48.7	14.7	9	1.4	0.5
CDC stage III	5	11.2[b]	2.4	4.0	6.8	4	6.6	1.6	2.53	0.41	1	81.5	–	2	1.7	0.4
CDC stage IV A	5	25.8	10.8	8.0	4.4	5	5.8	4.1	2.60	0.93	5	47.7	11.7	5	1.4	0.6
CDC stage IV C	4	29.0	13.5	6.5	11.7	3	7.1	2.6	2.62	0.26	4	41.7	7.3	2	1.3	0.5

[a] Ventricular brain ratio: area of the lateral ventricles divided by the area of the brain × 100
[b] Significant group effect: $F = 4.47$, $df = 2, 11$, $P = 0.04$

Table 4. Correlations of sleep variables with psychopathology, cranial CT scan measures and tryptophan levels

	Psychopathology				CT scan measures				Tryptophan levels			
	Depressive ($n = 14$)		Manic ($n = 14$)		VBR[a] ($n = 12$)		Sulcal width ($n = 12$)		Plasma ($n = 10$)		CSF ($n = 9$)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Total sleep time	−0.12	0.66	0.09	0.73	−0.64	0.03	−0.73	0.01	0.68	0.04	0.13	0.71
Sleep onset latency	0.45	0.10	0.03	0.89	0.43	0.15	0.61	0.04	−0.16	0.63	0.28	0.43
Sleep efficiency	0.01	0.93	0.25	0.37	−0.57	0.05	−0.69	0.02	0.66	0.04	0.07	0.83
Stage awake (%)	−0.01	0.93	−0.06	0.82	0.48	0.11	0.57	0.05	−0.56	0.09	−0.13	0.71
Stage 1 (%)	−0.02	0.89	0.11	0.70	0.48	0.11	0.26	0.40	0.06	0.83	−0.20	0.57
Stage 2 (%)	−0.33	0.23	−0.01	0.93	−0.07	0.80	−0.27	0.38	0.78	0.02	0.39	0.27
Slow wave sleep (%)	−0.01	0.92	−0.06	0.81	−0.47	0.12	−0.22	0.46	0.14	0.68	0.37	0.30
REM sleep (%)	0.61	0.03	0.36	0.19	−0.33	0.27	−0.27	0.37	0.05	0.84	0.06	0.84
REM latency	−0.68	0.01	−0.28	0.32	−0.12	0.70	−0.17	0.57	−0.09	0.78	−0.38	0.28
REM density	0.21	0.46	−0.05	0.85	0.75	0.01	0.69	0.02	0.10	0.75	0.25	0.49
Sleep spindle density	0.15	0.59	−0.17	0.55	−0.15	0.61	−0.01	0.92	−0.05	0.84	0.40	0.26

[a] Ventricular brain ratio: area of the lateral ventricles divided by the area of the brain × 100

Both VBR and sulcal width were negatively correlated with total sleep time and sleep efficiency (Table 4), whereas they correlated positively with REM density. In addition, patients with a greater sulcal width exhibited longer sleep onset latencies and spent more time awake.

Tryptophan plasma levels correlated with total sleep time, sleep efficiency and stage 2 sleep. For CSF tryptophan, no significant correlation with any of the sleep variables was present. The intercorrelation between both tryptophan measurements was not significant ($r = 0.50$, $df = 7$, $P = 0.18$).

Discussion

The results demonstrate clear abnormalities of nocturnal sleep in patients with HIV infection. In summary, it was found that sleep quality was impaired in a rather unspecific way since similar sleep abnormalities are present in various other conditions, e.g. depression, several forms of dementia and normal aging (Franceschi 1988; Gillin et al. 1981). Surprisingly, we did not observe a reduction of slow wave sleep which is usually present in the conditions mentioned.

This is at variance with findings by Kubicki et al. (1988, 1989) who reported reduced slow wave sleep in patients with HIV infection. However, the comparability of the studies is limited because of a number of methodological differences. There were no controls in the study of Kubicki et al. Our impression is that their patients were more severely ill than those of our sample. However, this cannot be verified since the authors applied stage definitions which are not compatible with the usual classifications. Time in bed varied largely since the beginning of sleep recordings was variable (between 2200 hours and midnight) whereas the termination was fixed at 0700 hours. There was no adaptation night, and patients were not controlled for use of psychoactive drugs before sleep recordings. (The authors mention that they suspected the abnormally high quantities of sleep spindles in two patients to be due to benzodiazepines; nevertheless, these cases were included in their analysis.) Finally, the authors deviated from the standard definition of slow wave sleep.

Our data concerning slow sleep wave also contradict the findings of Norman et al. (1988), who observed large amounts of slow wave sleep in asymptomatic HIV-positive individuals (i.e. more than 19% slow wave sleep in six out of eight patients). However, age and other fac-

tors which may be relevant were not controlled for in the study of Norman et al.

As was the case for slow wave sleep, the percentage of REM sleep was normal in our sample. In contrast, Kubicki et al. (1989) reported smaller amounts of REM sleep. The methodological differences mentioned above may account for this divergence (especially the lack of an adaptation night in their study, which may have led to first-night effects).

The patients of our samle had shorter mean REM latencies than matched healthy controls. This effect was statistically significant, yet less pronounced than REM latency shortening observed in major depression (Gillin et al. 1979). Shorter REM latencies correlated with higher depression scores, and the same was true for higher percentages of REM sleep. This confirms the close connections between REM sleep regulation and depressive symptomatology, which have been extensively discussed in the context of pathophysiological hypotheses on depression (Gillin et al. 1982; McCarley 1982). Our data support the view that concomitant depressive symptomatology in HIV infection may be mediated by pathophysiological processes related to those in major depression. However, REM latency shortening is not obligatory in secondary depression. Thus, Lauer et al. (1989) did not find such a relationship in patients with eating disorders, and Wiegand et al. (in press) failed to observe short REM latencies in patients with Huntington's disease exhibiting pronounced depressive symptomatology.

In this context, our finding of a clear decrease in stage 2 sleep is of interest, since this has as yet only been observed in major depression (de Maertelaer et al. 1987; Lauer et al., in press). We failed to confirm the drastic reduction of mean sleep spindle density described by Kubicki et al. (1989). Yet our data point in the same direction, as in single cases sleep spindles were remarkably sparse or even virtually absent.

There is no ready interpretation of the stage 2 and spindling abnormalities, since not much is known about specific functions of stage 2 sleep (in contrast to slow wave and REM sleep, which have aroused more attention in sleep research and have been the object of extensive hypothesizing). The same applies to sleep spindles, whose function is far from clear. Their occurrence seems to be important for the maintenance of sleep during certain stages, and drugs improving sleep continuity (e.g. benzodiazepines) have a stimulating effect on sleep spindles. On the other hand, an increase in sleep spindles has been observed in disorders of the basal ganglia where sleep is generally impaired (Jankel et al. 1983; Emser et al. 1988; Wiegand et al. 1989).

The possibility cannot be excluded, however, that sleep spindle and stage 2 reduction (as well as shorter REM latencies) are partly due to zidovudine medication, since these effects were more pronounced in patients treated with this drug ($n = 4$). There are as yet no polygraphic data on zidovudine effects on sleep; subjective impairment of sleep under this drug has been reported by Richman et al. (1987).

Throughout the stages of the illness, no significant differences in sleep parameters emerged. Patients who had no bodily complaints at the time of the investigation exhibited the same abnormalities in sleep as patients with such complaints. This demonstrates that sleep EEG investigations can reveal CNS affection even in patients who are free of any conspicuous symptomatology.

In a previous study, Möller et al. (1990) were able to demonstrate that cerebral atrophy is present in HIV infection, but seems to be restricted to later stages of the illness. Our data show close connections between reduced sleep quality and both ventricular and cortical measures of brain morphology in patients with HIV infection. However, there are no significant correlations with slow wave sleep, unlike in several other neuropsychiatric conditions where relationships between abnormal slow wave sleep and changes in brain morphology (as assessed by cranial CT) have been found [e.g. in eating disorders (Lauer et al. 1989), schizophrenia (van Kammen et al. 1988), chronic alcoholism (Ishibashi et al. 1987), Huntington's disease (Wiegand et al., in press)]. This supports the view that in HIV infection, slow wave sleep appears to be untouched by the illness process and its influence on brain morphology.

The unexpected observation that larger VBR and sulcal width measurements correlate with higher REM density may be interpreted in the context of oculomotor disturbances which are frequent in HIV infection (Currie et al. 1989). Since percentage REM sleep and REM latency are not correlated with CT measures, an explanation of higher REM density as an indicator of a generally elevated "REM pressure" appears implausible.

The significant positive correlations between serum tryptophan levels and total sleep time, sleep efficiency and stage 2 sleep warrant a cautious interpretation, since peripheral tryptophan levels do not allow direct conclusions on central serotonin metabolism; moreover, we did not find significant correlations of sleep parameters with CSF tryptophan levels. Peripheral tryptophan levels are only one factor among a variety of others (e.g. the ratio of tryptophan to other large aminoacids) determining tryptophan influx into the brain (Wurtman et al. 1981). However, it appears plausible that peripheral decrease of tryptophan levels can indirectly contribute to an altered brain serotonin metabolism which is likely to induce a variety of neurological and psychiatric symptoms. It can thus be hypothesized that sleep alterations in HIV infection are partly mediated by an impaired serotonin metabolism. This supports the view that the associations between immunological processes and serotonin metabolism in HIV infection represent a crucial pathway in the pathophysiology of neuropsychiatric symptoms in HIV infection, incuding disturbed mood and impaired sleep regulation.

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