Effects of melatonin on metabolic abnormalities in HIV patients treated with antiretroviral drugs

ABSTRACT

Aims: Highly Active Antiretroviral Therapy (HAART) is the current care standard for treating patients with HIV/ AIDS. Although HAART has is the only regimen potent enough to decrease viral load, adverse events may limit its efficacy. Metabolic disorders are common in patients treated with HAART. Melatonin (N-acetyl-5-methoxytryptamine) was initially thought to be exclusively of pineal origin but recent studies have shown that melatonin synthesis may occur in several cells and organs. Melatonin has been shown to have a variety of functions and research during the last decade has proven the indole to be a direct free radical scavenger and indirect antioxidant. Due to these activities and possibly others that remain to be defined, melatonin has been shown to reduce toxicity and increase the efficacy of a large number of drugs. **Methodology:** Current study was carried out in a double-blind, placebo-controlled and completely randomized design. AIDS patients who had metabolic alterations were selected. Patients were divided into two groups: Group I (HAART) consisted of patients receiving placebo once a day in the evening. Group II (HAART+ Melatonin) comprised patients who received the melatonin (6mg) once a day in the evening for one month. Clinical and laboratorial evaluation was performed before and after 30 days. Clinical evaluation was performed to assess the patients´ overall clinical state. Patients were instructed to report any complications. Laboratorial evaluation was performed. Glucose levels were determined by glucose oxidase method and ELISA (Genway Biotechnology, USA), respectively, following manufacturer's instructions. Plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) were performed by the kinetic colorimetric method; triglycerides, total cholesterol and creatinine were performed by enzymatic colorimetric method, both provided by Gold Analisa Diagnóstica Ltda. **Results**: Sixty patients who had some metabolic abnormalities (glucose levels above 100.0 mg/ dL or total cholesterol above 200mg/dL or triglycerides above 200mg/dL) participated in the study. All had been using HAART therapy for at least five years, with an average 15-year infection period. Patient´s age ranged between 35 and 49 years, with a mean of 43.7 years. Fasting glucose was significantly lower in subjects in Group I treated with melatonin when compared with subjects included in the control group not treated with melatonin after one month of treatment. Levels of blood glucose were 23% lower in patients who used melatonin, with reference rates after one month of treatment. Current study revealed that 40% (12/30) of the patients had changes in AST liver enzymes (> 38 U/l), 30% (9/30) had changes in ALT levels (> 38 U/l) and 30% (9/30) had GGT levels (> 40 U/l). Results obtained after the use of melatonin suggest melatonin activity on the liver. Significant differences between groups in plasma cholesterol indicate that melatonin exerted better improvement of blood lipid composition. Melatonin would lower cholesterol in liver and decrease plasma cholesterol. Above all, melatonin could decreese oxidative stress and improve dyslipidemia. **Conclusion:** Considering the low toxicity of melatonin and its ability to reduce the side effects and increase the efficacy of the drugs, its use may be important and significant as a combination therapy with HAART. Current study which investigated the effect of melatonin associated with antiretroviral treatment demonstrated beneficent effects on metabolic abnormalities in AIDS patients.

Keywords: melatonin, HIV/AIDS, antiretroviral, metabolic abnormalities

1. INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) is the current care standard for treating patients with HIV/ AIDS. In fact, HAART has remained the only regimen potent enough to decrease viral load, even though adverse events may limit its efficacy. Metabolic disorders were commons in patients treated with HAART. Dyslipidemia and lipodystrophy may occur in patients treated with HAART since primary HIV infection. This risk should be taken into account when considering early antiretroviral treatment of HIV infection [1]. Antiretroviral therapy is significantly associated with increase in serum lipid levels and increased risk of dyslipidemia. Antiretroviral drugs increase biosynthesis and reduce hepatic clearance of serum cholesterol [2]. Use of antiretroviral therapy containing mitochondrial toxic nucleoside reverse transcriptase inhibitors might induce chronic hepatic injury, which would accelerate hepatitis C virus liver fibrosis and increase the risk of hepatic de-compensation and death [3].

Prevalence of cardiovascular diseases in HIV patients increases with aging and duration of the disease. Hypertension, high cholesterol level, obesity, diabetes, tobacco and use of alcohol are among the traditional risk factors that contribute towards cardiovascular diseases [4].Three-year outcome antiretroviral therapy in adults demonstrated good virological response featuring high toxicity rates [5].

Severe hepatotoxicity in HIV-infected patients treated with highly active antiretroviral therapy occurs in 5-10% of cases. Liver transaminases should be closely monitored after the start of highly active antiretroviral therapy. Light to moderate transaminase rise may improve under continued therapy, but life-threatening liver injury associated with jaundice or high transaminase rates above 10 times the upper normal limit makes the de-continuation of antiretroviral therapy mandatory [6].

Hepatotoxicity has been associated with the use of human immunodeficiency virus-protease inhibitors. However, the complexity of the HIV-infected patient´s conditions and the combination of medicines to treat HIV complicate the evaluation of the effects of drug-induced liver injury [7].

A retrospective cohort study investigated whether particular antiretroviral agents were associated with a higher risk for the development of grade 4 liver enzyme elevations in patients with human immunodeficiency virus type 1 infection who started receiving HAART. Regimen of nevirapine or high-dose ritonavir was a risk factor [8].

Several antiretroviral drugs have been linked to serious adverse events such as efavirenz [9], nevirapine [10] tipranavir/ritonavir [11], atazanavir [12], ritonavir [13], zidovudine/lamivudine[14], lopinavir/ritonavir[15].

Melatonin (N-acetyl-5-methoxytryptamine) is a molecule with a very wide phylogenetic distribution from plants to man. In the case of vertebrates, melatonin was initially thought to be exclusively of pineal origin, but recent studies have shown that melatonin synthesis may occur in a variety of cells and organs. Melatonin has been shown to have several functions, and research in the last decade has proved the indole to be a direct free radical scavenger and an indirect antioxidant. Due to these activities and possibly others that remain to be defined, melatonin has been shown to reduce toxicity and increase the efficacy of a large number of drugs. Side effects are well documented [16] [17] [18] [19].

There are many beneficial effects of melatonin when combined with the following drugs: doxorubicin, cisplatin, epirubicin, cytarabine, bleomycin, gentamicin, cyclosporine, indomethacin, acetylsalicylic acid, ranitidine, omeprazole, isoniazid, iron and erythropoietin, phenobarbital, carbamazepine, haloperidol, capside-50, morphine, cyclophosphamide and L-cysteine [20]. While most studies were conducted on animals, several investigations were also done on humans.

Melatonin was chosen for its antioxidant and anti-apoptotic action on renal tissue [21] and injury of myocardical cells. In the experimental model, melatonin reduces obesity and improves the metabolic profile. Melatonin also lowers mitochondrial oxidative status by reducing nitrite levels and by increasing superoxide dismutase activity. Results demonstrate that chronic oral melatonin improves mitochondrial respiration and reduces the oxidative status and susceptibility to apoptosis in white and beige adipocytes [22].

Many physiological and pathological conditions may alter melatonin levels. Decrease in levels of this indolamine has been observed in subjects with low tryptophan intake, subjects with insomnia, depression, coronary heart disease, rheumatoid arthritis and liver cirrhosis [23].

Current study evaluates the effect of the use of oral melatonin in HIV patients undergoing antiretroviral therapy.

2. MATERIAL AND METHODS

2.1 Subjects

HIV / AIDS patients were treated at the Center for Studies and Support to HIV Patients of the State University of Maringá - Department of Basic Health Sciences. The Center attends approximately 200 patients who freely seek the sector to participate in the project. All patients are evaluated clinically and laboratory tests are performed prior to their participation in the projects.

2.2 Study model

Current study was carried out in a double-blind, placebo-controlled and completely randomized design. AIDS patients who had metabolic alterations were selected. The patients were divided into two groups: Group I (HAART) consisted of patients receiving placebo once a day, in the evening. Group II (HAART+ Melatonin) comprised patients who received melatonin (6mg) once a day, in the evening, for one month.

2.3 Preparation of Melatonin

Melatonin® 6 mg was manipulated by Medformula compounding pharmacy.

2.4 Antiretroviral Therapy

The therapeutic scheme follows the standard protocol used in Brazil (ritonavir 100mg+zidovudine 300mg+lamivudine 150 mg+ atazanavir 300 mg/day).

2.5 Evaluation

Clinical and laboratorial evaluation was performed before and after 30 days

2.5.1 Assessment of body weight: patients were weighed on scale Sensimax 130 before the start of treatment and at the end of the experiment.

2.5.2 Clinical evaluation: Clinical evaluation was performed to assess the overall clinical state of the patient and patients were instructed to report any complications.

2.5.3 Laboratory evaluation: After an approximately 10-h overnight fast, 5 ml of venous blood were obtained from each patient. Glucose levels were determined respectively by glucose oxidase method and ELISA (Genway Biotechnology, USA), following the manufacturer's instructions. Plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) were assessed by the kinetic colorimetric method; triglycerides, total cholesterol and creatinine were evaluated by the enzymatic colorimetric method, both provided by Gold Analisa Diagnóstica Ltda.

2.6 Statistical Analysis

Groups were compared with Graph Pad Prism 6.0 (Graph Pad, San Diego, CA, USA) using Student´s *t* test at 95% significance.

3. RESULTS AND DISCUSSION

Sixty patients with certain metabolic abnormalities (glucose levels above 100.0 mg/ dL or total cholesterol above 200mg/dL or triglycerides above 200mg/dL) participated. All patients had been using HAART therapy for at least five years and their average infection period was 15 years. Patients´ age ranged between 35 and 49 years, with mean 43.7 years. Patients were separated into two groups (treated with and without melatonin) with 30 patients each, in a paired form for age and gender. All patients were followed up by a clinical evaluation during the 30 days of treatment.

Effect of Melatonin on Fasting Blood Glucose

Diabetes and changes in glucose tolerance are common in adult populations. They are associated with increased mortality from cardiovascular disease and microvascular complications. The diagnosis may be made early. Fasting plasma glucose measurement is used as a fast and easy test, with altered rates when higher than 110mg / dL. On the other hand, rates over 100mg / dL should be monitored. The introduction of antiretroviral therapy has triggered the emergence of some metabolic complications, including hyperglycemia and diabetes mellitus, among HIV-positive patients. Hyperglycemia, especially pre-diabetes is very frequent among people with HIV. Forty-three percent of patients (13/30) in current study presented changes in glycemic levels (> 100mg / dL) at the start of the study.

Table 1 shows fasting blood glucose. Fasting glucose was significantly lower in subjects contained in Group I treated with melatonin when compared to subjects included in the control group who were not treated with melatonin after one month of treatment. Levels of blood glucose were 23% lower in patients who used melatonin reference values after one month of treatment

Table 1. Blood glucose levels in HIV/AIDS patients treated by antiretroviral therapy with and without melatonin

Patients HIV/AIDS	Glucose Levels (mg/dL) Before 30days	After 30 days	p
HAART	107 ± 15.53	113.8± 11.1	0.5486
HAART + melatonin	105 ± 17.76	80.8 ± 7.7*	0.0264

Table 1: Glucose levels in the experimental groups after 30 days. Comparison between experimental groups: Group I treated with HAART (ritonavir 100mg+zidovudine 300mg+lamivudine 150 mg+ atazanavir 300 mg/day); Group II treated with HAART (ritonavir 100mg+zidovudine 300mg+lamivudine 150 mg+ atazanavir 300 mg/day) + Melatonin 6mg, once a day. Results are given as mean ± SD of 30 patients. *p<0.05

Pineal hormone melatonin exerts its influence on the periphery through the activation of two specific trans-membrane receptors: MT1 and MT2. The two isoforms, expressed in the islets of Langerhans, are involved in the modulation of insulin secretion from β-cells and in glucagon secretion from α-cells. De-synchrony of receptor signaling may lead towards the development of Type 2 diabetes [24] [25]. Most authors agree that the pineal gland has a suppressive effect on the activity of the pancreatic insulin-producing β-cell, because melatonin reduces insulin levels and glucose tolerance in rats [26]. Due to increased insulin level that exerts an inhibitory effect on the melatonin synthesis of the pineal gland, a functional antagonism between insulin and melatonin is presumed. This antagonism is in line with the fact that, in humans, low insulin levels at night and high levels during the day coincide with elevated nocturnal melatonin concentrations and reduced levels during the day [27]. Moreover, diabetic patients generally lack a circadian melatonin rhythm [28].

Animal models of diabetes have been used to examine the influence of diabetes on melatonin levels and, in turn, the effect of melatonin treatment on glucose homeostasis and the diabetic status in these models. A combined treatment of insulin and melatonin of STZ-induced diabetic rats had beneficial effects on blood glucose levels and body weight. Melatonin, or insulin alone, provided limited protection against hyperglycemia and induced oxidative damage in diabetic rats, whereas combined treatment with insulin and melatonin suppressed hyperglycemia, prevented oxidative damage, and restored endothelium function. Beneficial effects of the combined treatment are thus demonstrated [29].

In STZ-rats insulin-positive, β-cells appeared degranulated and degenerated or necrotic, revealing decreased insulin secretion and increased blood glucose levels. Melatonin administration, however, ameliorated the diabetic phenotype by causing a partial regeneration/proliferation of pancreatic β-cells, a decrease in serum glucose and an increase in insulin concentrations [30]. Treatment with melatonin resulted in the appearance of high-intensity insulin and anti-apoptotic Bbcl-xL-positive cells in the pancreas, whereas the number of apoptotic cells decreased [31].

As a whole, the above studies indicate that melatonin may have a positive impact on β-cell neogenesis and proliferation and on the prevention of apoptosis.

Our results demonstrate a beneficial effect of melatonin on blood glucose levels in patients using HAART therapy.

Effect of the Melatonin on hepatic enzymes

The clinical use of lopinavir/ritonavir as a component of antiretroviral regimens was found to be associated with the occurrence of hepatotoxicity ranging between 1% and 9.5% in clinical trials. Hepatotoxicity, characterized by increase in hepatocellular cytolysis rates and significant increases in serum transaminase levels, is a common complication in HIV-positive patients receiving HAART. An increase in hepatic enzymes has been registered in about 6% to 30% of patients

receiving antiretroviral therapy. Severe hepatotoxicity (defined as an increase in transaminases levels five times greater than the normal limit) has been reported in less than 10% of patients receiving treatment [32].
In current study, 40% (12/30) of patients had changes in AST liver enzymes (> 38 U/l); 30% (9/30) had changes in ALT levels (> 38 U/l); and 30% (9/30) in GGT levels (> 40 U/l). Results obtained after the use of melatonin suggest the impact of melatonin on the liver (table 2).

Table 2. Hepatic enzymes in HIV/AIDS patients treated by antiretroviral therapy with and without melatonin

Patients HIV/AIDS	Hepatic enzymes					
	AST(U/l)		ALT(U/l)		GGT(U/l)	
	Before 30days	After 30 days	Before 30days	After 30 days	Before 30days	After 30 days
HAART	57.33±13.19	64.21±33.43	37.33±7.34	36.67±15.7	51.29±14.28	58.14±35.73
HAART + melatonin	41.79±5.17	24.85±3.48*	34.03±5.15	25.34±1.7*	45.93±6.37	22.10±19.46

Table 2: Hepatic enzymes in experimental groups after 30 days. Comparison between experimental groups: Group I treated with HAART (ritonavir 100mg+zidovudine 300mg+lamivudine 150 mg+ atazanavir 300 mg/day); Group II treated with HAART (ritonavir 100mg+zidovudine 300mg+lamivudine 150 mg+ atazanavir 300 mg/day) + Melatonin 6mg, once a day. Results are given as mean ± SD of 30 patients. *p<0.05

The liver is a vital organ of the human body and is responsible for several fundamental and important roles, including digestive and excretory functions, nutrient storage and metabolic functions, synthesis of new molecules and purification of toxic chemical [33]. Liver steatosis, fatty liver, hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma are the most prevalent liver diseases. They have also been investigated extensively.

Despite all the studies performed up to now, therapy choices for liver injuries and diseases are very few. Melatonin is a well-known natural antioxidant and has many bioactivities. Several studies have investigated the effects of melatonin on liver injuries and diseases. In fact, melatonin may regulate various molecular pathways, such as inflammation, proliferation, apoptosis, metastasis and autophagy in different pathophysiological situations. Melatonin may also prevent and treat liver injuries and diseases. Several studies have shown that melatonin has a hepatoprotective effect [34-38].

Animals treated with antiretroviral therapy and melatonin had higher body weight gain, less hepatomegaly, less anxiety, lower levels of triglycerides, cholesterol and hepatic enzymes, when compared to animals treated with antiretroviral therapy [39].

Melatonin alleviates liver injuries and diseases by preventing oxidative damage, improving mitochondrial physiology, inhibiting liver neutrophil infiltration, necrosis and apoptosis, reducing the severity of morphological alterations and suppressing liver fibrosis. However, related studies of melatonin applied to clinical treatment for liver injuries and diseases are limited. Further clinical trials should be conducted to assess the effects of melatonin in this field.

Effect of the Melatonin on Lipid profile

Diabetes and elevated triglycerides were the metabolic syndrome components most strongly linked with global increase in HIV patients. In current study, 83% of patients (25/30) presented changes in triglycerides levels (> 200mg / dL) and 76% (23/30) presented changes in total cholesterol levels (> 200mg / dL) at the start of the study.

Table 3. Metabolic parameters in HIV/AIDS patients treated by antiretroviral therapy with and without melatonin

Patients HIV/AIDS	Lipid profile					
	Total Cholesterol (mg/dL)		p	Triglycerides (mg/dL)		P
	Before 30days	After 30 days		Before 30days	After 30 days	
HAART	255.3±18.37	261.7±43.3	0.7310	364.8±49.84	353.7±88.63	0.8240
HAART + melatonin	205.0±14.29	157.7±9.34*	0.0102	272.0±19.45	242.8±18.49	0.2910

Table 3: Lipid profile in the experimental groups after 30 days. Comparison between experimental groups: Group I treated with HAART (ritonavir 100mg+zidovudine 300mg+lamivudine 150 mg+ atazanavir 300 mg/day).; Group II treated with HAART (ritonavir

100mg+zidovudine 300mg+lamivudine 150 mg+ atazanavir 300 mg/day) + Melatonin 6mg, once a day. Results are given as mean ± SD of 30 patients. *p<0.05

Table 3 shows significant differences between groups in plasma cholesterol and indicates that melatonin exerts better improvement of blood lipid composition. Melatonin may lower cholesterol in liver and decrease plasma cholesterol. Above all, melatonin may decrease oxidative stress and improve dyslipidemia.

Effect of Melatonin on Renal Function

Acute kidney and chronic kidney diseases are more common in the HIV-infected population than in the general population. Renal dysfunction is common in HIV-positive patients who receive antiretroviral therapy. Glomerular and tubular diseases are often identified in HIV-infected patients. Several antiretroviral agents have been associated with the progression of kidney disease, inhibition of renal tubular transporters that mediate creatinine secretion or with impaired reabsorption of phosphate and low-molecular weight proteins. Tenofovir and atazanavir may cause acute tubular injury, tubule-interstitial nephritis or nephrolithiasis [40]. Tenofovir is associated with severe acute kidney injury in a small percentage of patients and with subclinical abnormalities in many more [41]. Some antiretroviral agents are related to kidney disease, hyperlipidemia, diabetes mellitus and hypertension, which may intensify the occurrence of chronic kidney disease [42].

In current study, 10% of patients (3/30) presented high creatinine levels (> 1.2mg / dL) at the start of the study. The authors would like to highlight a patient who had presented a rate of 5.25mg/dL. Rates were within the normal range (1.1mg/dL) after the use of melatonin.
Subsequently, dysfunction of the melatonergic system is often associated with sleep and circadian dysfunction.

Table 4. Renal Function in HIV/AIDS patients treated by antiretroviral therapy with and without melatonin

Patients HIV/AIDS	Renal function		
	Creatinine(mg/dL)		p
	Before 30days	After 30 days	
HAART	0.8567±0.11	0.8913±0.25	0.7564
HAART + melatonin	1.471±0.44	1.135±0.57*	0.0482

Table 4: Creatinine levels in the experimental groups after 30 days. Comparison between experimental groups: Group I treated with HAART (ritonavir 100mg+zidovudine 300mg+lamivudine 150 mg+ atazanavir 300 mg/day); Group II treated with HAART (ritonavir 100mg+zidovudine 300mg+lamivudine 150 mg+ atazanavir 300 mg/day) + Melatonin 6mg, once a day. Results are given as mean ± SD of 30 patients. *p<0.05

Although melatonin is a neuro-hormone primarily synthesized by the pineal gland, other cell-types are also capable of synthesizing. Pineal synthesis in mammals is under the control of the master circadian pacemaker, which is located in the suprachiasmatic nucleus of the hypothalamus. Two types of G protein-coupled receptors named MT1 and MT2 mediate the action of melatonin. These receptors are expressed in many different organs and tissues. In fact, melatonin modulates multiple aspects of human physiology. In addition to the action mediated by MT1 and MT2 receptors, melatonin may also act as a free-radical scavenger and thus as an antioxidant.

Melatonin is currently used by millions of people around the world as a natural supplement for circadian and sleep disturbance. However, the mechanisms responsible for the beneficial effect of melatonin are still not fully understood. Hundreds of reports have appeared lately that documented melatonin's ability to neutralize directly free radicals and related toxicants. The first indication that melatonin may be a direct free radical scavenger actually appeared in 1991 [43], after which definitive evidence that melatonin functioned as a direct scavenger of hydroxyl radicals was provided [44] [45].

The significance of melatonin as an OH scavenger is related to the fact that the reactant is generally considered to be the most damaging of all endogenously generated reactive agents.

Chemically, melatonin is characterized as an amphiphilic molecule, that is, thanks to the presence of methoxy groups at carbon 5 and the acetyl group attached to the nitrogen of the amine group, the molecule has the property of diffusing with

equal capacity both in media hydrophilic and lipophilic. Since it is produced in the pineal gland, melatonin is immediately secreted and may be found in all compartments of the organism, in the intercellular nuclei and even in cellular ones. Another characteristic is its high reducing or antioxidant capacity due to carbons 2 and 3 of the pyrrole ring that have a high capacity to donate electrons. Consequently, melatonin is considered one of the most powerful natural antioxidants [46].

The mechanisms whereby melatonin stimulates enzyme activity that detoxify oxygen-based reactants remain unknown but it is likely to be mediated via specific receptors. Although membrane receptors for melatonin have been identified in many cells, nuclear binding sites for the indole have also been documented [47].

Finally, the importance of a number of endogenously generated melatonin metabolites in terms of their scavenging action should not be overlooked, since they likely contribute, via the antioxidant cascade defined above, towards the total capacity of melatonin to reduce oxidative damage.

When organisms are exposed to drugs or other free radical generating agents or processes (excessive exercise, hyperoxia, ionizing radiation, inflammation, ischemia, toxins, trauma), the number of reactants produced overwhelms the capacity of the system to defend itself. In such situations, supraphysiological levels of an antioxidant must be given to prevent plundering by the large number of induced toxic reactants. So that an antioxidant neutralizes a toxic reactant before it mutilates a bystander molecule, it must be very near to where the reactant was generated. Since it is amphiphilic, melatonin seems to be ubiquitously distributed, albeit unevenly, in subcellular compartments.

Another important factor in melatonin's role as an antioxidant within a vertebrate organism is its ability to transverse established morphophysiological barriers. Melatonin penetrates in the brain minutes after its administration [48].

The authors assume that physiological levels of melatonin have a function similar to those of the pharmacological concentrations used. It may be relevant that endogenous melatonin levels change substantially throughout a lifetime. There are sometimes substantial differences in the quantity of melatonin produced by different individuals [49].

Studies on melatonin´s bioavailability have shown that it is completely absorbed in the gastrointestinal tract. Its plasma peak occurs 60 minutes after its administration. The usual oral dosages range between 2 and 4 mg, with only 15% reaching the circulatory system, probably due to first-pass hepatic metabolism [50].

Studies on the administration of melatonin in normal subjects indicate the absence of significant adverse effects (SEABRA et al., 2000).

Considering melatonin´s low toxicity and its ability to reduce side effects and increase the efficacy of the drugs, its use as a combination therapy with HAART may be important and significant. In fact, current analysis on melatonin's effects associated with antiretroviral treatment has proved to have a good effect on the metabolic abnormalities in AIDS patients.

4. CONCLUSION

Our study suggests that melatonin reduced HAART´s toxic effects. Most studies show that melatonin reduces the toxicity of a wide variety of currently used drugs. Our study would seem to justify the use of melatonin as a co-treatment with antiretroviral therapy. Besides its high safety margin, melatonin is inexpensive to produce in a pharmacologically pure form. Melatonin´s disadvantage is the fact that it is a naturally occurring, non-patentable molecule. Thus, pharmaceutical interest in this agent is per se low, despite its low toxicity and high efficacy.

COMPETING INTERESTS

Authors have declared that there are no competing interests.

ETHICAL APPROVAL

All authors hereby declare that "Principles on laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate Committee for Ethics.

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