

**ZIDOVUDINE REDUCES KETAMINE-INDUCED PSYCHOTIC SYMPTOMS IN MICE**

\*Ahmadu P.U.<sup>1,2</sup>, Ejiofor J.I.<sup>2</sup>, Chindo B.A.<sup>2,3</sup>, Husseini I.M.<sup>1</sup>, Fidelis S.A.<sup>1</sup>

<sup>1</sup>National Institute for Pharmaceutical Research and Development (NIPRD), Idu, P.M.B 21, Garki-Abuja, Nigeria.

<sup>2</sup>Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna State, Nigeria

<sup>3</sup>Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna, Kaduna State, Nigeria

\*Corresponding author:

Email; [peterjahmadu@gmail.com](mailto:peterjahmadu@gmail.com)

Phone: +2348056585359

**ABSTRACT**

**Introduction:** Infection with human immuno-deficiency virus (HIV) is associated with several neurological disorders including psychotic symptoms. Treatment or therapeutic management of these symptoms with conventional anti-psychotic drugs (APDs) is associated with drug-drug interaction and side effects that may cause treatment failure. Zidovudine (AZT) an anti-retroviral (ARV) drug, is a nucleoside analogue reverse transcriptase inhibitor (NRTI) with highest CNS penetrating ability, but few or nothing is known about its CNS effects.

**Objective of study:** To evaluate the effect of AZT on ketamine-induced depression, hyperkinesia, and cognitive function in mice.

**Method:** Acute toxicity was conducted for oral and intraperitoneal administration using Lorke's (1983) method. Acute zidovudine alone and its concurrent (AZT + Ketamine) sub-chronic (7 days) administration was investigated using forced swim test, open field locomotor test and Y-maze test. Olanzapine (5mg/kg), Haloperidol (1 mg/kg) and Eserine (0.03 mg/kg) were used as standard controls respectively with saline as normal control. Eserine was administered intraperitoneal 30 minutes before the test, while the 5 tested zidovudine doses (12.5, 25, 50, 100 and 200 mg/kg) were administered singly orally for 60 minutes prior to the acute test while ketamine 30mg/kg intraperitoneal administered concurrently for 7 days for the sub-chronic test

**Result:** The LD<sub>50</sub> for oral and intraperitoneal administration were determined to be 3807.88 mg/kg and 2154 mg/kg respectively. Concurrent AZT administration with ketamine for 7 days, significantly ( $p < 0.001$ ) reduced immobility time at AZT doses of 25 mg/kg and 12.5 mg/kg compared to the control. The 7-days AZT concurrent treatments with ketamine reduced locomotion at all AZT test groups, compared to normal control group. The mean percent alternation was severely reduced in acute AZT treatments, but increased in concurrent AZT-ketamine administration.

**Conclusion:** AZT ameliorate ketamine-induced psychotic-like symptoms in mice, but was found to cause cognitive deficits in normal controls.

**Key words:** Zidovudine, Anti-retroviral (ARV), ketamine, psychotic symptoms, HIV-infection.

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**Introduction:**

Infection with human immunodeficiency virus (HIV) has been associated with several neurological disorders and psychotic symptoms. The incidence of HIV-associated dementia (HAD) that used to occur in only about 30% of patients of HIV infections has been reported to be on the increase [10] including among children of 2 months – 5 years old with a projection of 30-50% prevalence of HIV encephalopathy with deficiency in motor functions, poor and/or impaired brain development [37]. Human immunodeficiency virus invades the central nervous system (CNS) via a ‘Trojan horse’ mechanism and causes several damaging changes to the nervous system [27]. These HIV-related CNS effects had also been reported to be caused by impact of other opportunistic infections such as toxoplasmosis, CNS neoplasm (lymphoma), progressive multifocal leukoencephalopathy (PML), (cryptococcal or tuberculous meningitis [48,52]. Some drugs used in the treatment of HIV-AIDS such as efavirenz are, themselves, known to induce schizophrenic-like symptoms such as delirium, hallucinations, nightmares, etc [36]. HIV-AIDS patients with psychosis are said to have increased morbidity and mortality due to serious impact on the immune system that could compromise therapy, as well as negative behavioural changes that may affect patient’s compliance with treatment [38]. Moreover, treatment of psychosis among patients with HIV-AIDS with current antipsychotics drugs (APDs) is associated with extrapyramidal syndrome (EPS) such as

Tardive dyskinesia [49,47]. Several drug-drug interaction problems result from combining most APDs with ARVs leading to failure of anti-retroviral therapy and/or ineffective treatment of the schizophrenic-like symptoms among these patients [2]. Hence, there is need for an agent that would cause fewer or no side effects and that could be effective in the management of spontaneously occurring psychotic-like symptoms associated with HIV-without compromising anti-retroviral therapy. Zidovudine, a member of the nucleotide reverse transcriptase inhibitors (NRTIs). Zidovudine is the first antiretroviral approved for treatment of HIV in humans has not been well studied; zidovudine (azidothymidine) is a deoxythymidine analogue that inhibits the RNA dependent DNA polymerase and incorporates itself into the viral genetic chain resulting in chain termination and it is the highest BBB penetrating ARV in the class of NRTIs [59]. Certain ameliorative effect of highly active anti-retroviral therapy (HAART) on HIV-associated CNS disorders has been attributed to ability to penetrate the CNS by some components of HAART. Zidovudine is member of NRTI with the highest central nervous system penetrating effectiveness (CPE) ranking and it was a component of highly active anti-retroviral therapy (HAART) [59,39], few specific CNS effects have been studied. Zidovudine can be used by mouth or by slow injection into the vein. Common side effects of AZT are headache, fever, nausea and sometimes its use can be associated with serious side effects such as liver problems, diarrhea (especially among children),

constipation, muscle damage, and high blood lactate levels. Others are stomach pain or cramps, difficulty falling asleep or staying asleep. Some commonly reported adverse reaction associated with AZT includes anemia and neurotopenia. The mechanism of action is via inhibition of the enzyme reverse transcriptase that HIV uses to make DNA and therefore decreases replication of the HIV virus.

Ketamine is a non-selective antagonist of NMDA receptors. Antagonists of N-methyl d-aspartate (NMDA) receptors such as ketamine and phencyclidine (PCP) mimic psychotic behavioural symptoms including depression, hyper-locomotion and cognitive deficit. Sub-chronic administration of higher doses of ketamine (15 - 50 mg/kg body weight) had been reported to produce these symptoms in rodents [18,56,1,11] and thus this study evaluated the effect of zidovudine on ketamine-induced symptoms of depression, hyper-locomotion and cognitive function in mice. A pre-acute experiment was conducted to ascertain the effect of zidovudine alone on depression, hyper-locomotion and cognitive deficits to serve as baseline data of the effect of zidovudine.

The aim of the present study was to evaluate the effect of AZT in ketamine-induced psychotic-like symptoms in mice.

## Materials and Methods

### Materials

### Animals

Swiss albino male and female mice (20-25g) obtained from the Animal Facility Centre (AFC) of the National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria, were used for the study. Animals were housed under conditions of temperature ( $22 \pm 1$  °C), and light approximately (12/12 hr light/dark cycle); and fed on standard maintenance diet and water ad libitum. Animals were approved by the AFC committee of the Institute (ACE number: NIPRD.05.03.05-43). All procedures involving the animals were carried out in line with the National Institute of Health Guide for the care and Use and of laboratory Animals (NIH Publications No. 80-23) revised 1996. All efforts were made to minimise the number of mice used and their suffering.

### Equipment

Forced swim apparatus, open-field apparatus, and Y-maze apparatus used were made by National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria. Opaque screen for separating cylinders, Metric balance (accurate to 0.1 g), 1-ml syringes and needles for i.p injection.

### Drugs/chemicals

Zidovudine tablet, Physostigmine (Eserine) from (sigma Aldrich, USA), Ketamine Hcl (UK), Olanzapine (Oretim Yeri; Lilly S.A Alcobendas, Madrid, Spain), Haloperidol tablet B.P (XL laboratory PVT, LTD, Rajasthan, India. NAFDAC No. A4-4638; Batch no: T644, manufacture date; November, 2014; Expiry date; January, 2019, and 70% alcohol (sigma

Aldrich, U.S.A), Ketamine (Rotex Pharma Germany).

## Methods

### Acute Toxicity Test

Phases I and II of the adopted Lorke's method [55] of acute toxicity test were conducted with 13 mice each for oral and intraperitoneal administration. Nine (9) mice were used in phase I in 3 groups of 3 mice per group and were administered 10, 100 and 1000 mg/kg AZT with a 24 h observation for obvious signs of toxicity such as tremor, rigors, convulsion or death. The 2<sup>nd</sup> phase of the test was conducted with the remaining three mice administered with higher doses of 1600, 2900 and 5000 mg/kg ( $n=x/\text{dose}$ ). The obtained outcome was then used for the estimation of the median lethal dose ( $LD_{50}$ ) by calculating the geometric mean of the highest non-lethal and the lowest lethal doses as:

$$LD_{50} = \sqrt{\text{maximum nonlethal dose} \times \text{minimum lethal dose}}$$

### Assessment of the Effect of Zidovudine 60 minutes after oral administration (AZT Alone) and Sub-acute (7-days) Concurrent Administration with Ketamine in Mice

Antagonists of N-methyl d-aspartate (NMDA) receptors such as ketamine and phencyclidine (PCP) mimic psychotic behavioural symptoms including depression, hyper-locomotion and cognitive deficit. Subchronic administration of higher doses of ketamine (15 - 50 mg/kg body weight) had been reported to produce these

symptoms in rodents [1,11,18,56] and thus this study evaluated the effect of zidovudine on ketamine-induced symptoms of depression, hyper-locomotion and cognitive function in mice. A pre-acute experiment was conducted to ascertain the effect of zidovudine alone on depression, hyperlocomotion and cognitive deficits to serve as baseline data of the effect of zidovudine.

### Assessment of antidepressant activity of zidovudine

Forced swim test is a validated model used in investigating anti-depressant activity of agents in rodents [57,58]. The forced swim test (FST) apparatus consists of transparent glass cylinders (13 cm diameter  $\times$  24 cm high) containing water ( $22^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ) to a depth of 10 cm. All the mice were individually placed (2 mice dropped simultaneously) in the glass cylinder for 15 minutes for acclimatization and removed, body cleaned with small towel and placed in a cage. This was done to all the mice 24 hours before the test. For this test, 35 of the acclimatized mice were randomized into 7 groups (5 mice /group). The test group received zidovudine (12.5, 25, 50, 100 and 200) mg/kg while the control groups received saline 10 ml/kg and 5 mg/kg olanzapine orally respectively as negative and positive control one hour before test. Two mice were placed simultaneously in the two narrow cylinder separated by an opaque diaphragm and observed for immobility for 6 minutes. The mean time the mouse did not swim calculated as the immobility period for the treatment groups was then compared with the normal control. Low value of the

immobility period indicates antidepressant activity. Similar treatment, but with concurrent administration of 30 mg/kg ketamine given to another 7 groups of mice for 7 consecutive days was used to evaluate the effect of zidovudine on ketamine-induced depression. The animals were left untreated on the 8<sup>th</sup> day for a 24 hour wash out period prior to the forced swim performance as previously and the mean immobility period for the treatment groups was then compared for all the groups and with the baseline data from the preliminary (acute zidovudine treatment).

#### **Assessment of effect of Zidovudine on Locomotor activity**

Open field locomotor assessor model of Siegel (1946) was used for this study. The apparatus is made of plywood (72cm × 72cm × 36cm) with transparent Perspex-glass walls and cardboard-paper floor covered also with Plexiglas. The number of crossings of squares on the floor and the 16 other equal (15cm × 15cm) squares bordering it was used in assessing locomotor activity. A total of thirty-five mice (male and female) were used for this experiment. Following the pre-acute test to establish the baseline-data in one set of 7 treatment groups of 5 mice in each, orally treated with saline (10 ml/kg) and five AZT doses (12.5, 25, 50, 100 and 200 mg/kg). Haloperidol (1 mg/kg), was used as a positive standard control [30] for 60 minutes. Thereafter, concurrent administration of 30 mg/kg ketamine to same treatment groups of mice for 7 consecutive days before evaluation of zidovudine on ketamine-induced changes in locomotion. The animals were left

untreated on the 8<sup>th</sup> day for a 24 hour wash out period prior to the open field observation. Each mouse placed at the Centre square of the open field apparatus was observed for number of square crossings in 5 minutes. The apparatus was wiped with 70% ethyl alcohol between each mouse. The mean number of crossings of the treatment groups was then compared.

#### **Assessment of effect of Zidovudine on cognitive function**

This test was carried out using the method described by Heo [50]. The objective of this test was to determine the immediate spatial working (short) memory effect of AZT in mice. The Y-maze is a three-arm horizontal maze (40 cm long and 5 cm wide with walls 10 cm high) in which the three arms are symmetrically separated at 120°. Thirty-six mice (male and female) were used in this experiment. Mice were initially placed within one arm (A), and the arm entry sequence (e.g., ABC CAB, where letters indicate arm codes) and the number of arm entries were recorded manually for each mouse over a 5-minute period. The maze arms were cleaned with 70% ethanol between tasks to avoid error due to odours. Alternations were determined from successive entries into the three arms on overlapping triplet sets in which three different arms are entered. An actual alternation was defined as entries into all three arms consecutively (i.e., ABC, CAB, or BCA). If an animal entered an arm and return for example in an order BAB, CAC, it was not recorded as alternations. An entry was defined as placing all four paws within the boundaries of the arm. One hour before this test, mice were

treated with graded doses of AZT (12.5, 25, 50, 100, and 200) mg/kg body weight. The normal control group received saline 10 ml/kg body weight, while an ant-cholinesterase agent, Eserine (physostigmine) 0.03 mg/kg administered intraperitoneally was used as positive control. Eserine prevent hydrolysis of acetylcholine hence, making it available for synaptic transmission for cognitive function. Results obtained were used as base-line (preliminary) data. Thereafter, the same mice groups (6 mice per group) were concurrently administered 30 mg/kg ketamine daily for 7 consecutive days before testing for the effect of zidovudine on ketamine-induced changes in cognitive function. The animals were left untreated on the 8<sup>th</sup> day for a 24 hour wash off period prior to the Y-maze assessment. The apparatus was wiped with 70% ethyl alcohol between each mouse. The percentage alternation for each mouse was determined (as the ratio of actual to possible alternations (defined as the total number of arm entries minus 2), multiplied by 100 as shown below;

$$\% \text{ Alternation} = \frac{[\text{Number of alternations}]}{[\text{Total arm entries} - 2]} \times 100 \quad [54,50].$$

### Summary and routes of drug administration

For acute experiments, each group received AZT or any other drug once before the test, while for sub-acute experiments, each group received graded doses of AZT (12.5, 25, 50, 100, and 200) mg/kg + ketamine 30 mg/kg i.p body weight. (For example, group that received 12.5 mg/kg AZT p.o + 30 mg/kg

ketamine i.p daily for seven (7) days, then, a wash-off period of 12 hours was allowed before tests were carried out. Similarly, groups the groups were treated as follows:

25 mg/kg AZT p.o + ketamine 30 mg/kg i.p daily for 7 days

50 mg/kg AZT p.o + ketamine 30 mg/kg i.p daily for 7 days

100 mg/kg AZT P.o + Ketamine 30 mg/kg i.p daily for seven days

200 mg/kg AZT P.O + Ketamine 30 mg/kg i.p daily for seven days

1 mg/kg haloperidol p.o + ketamine 30mg/kg daily for 7 days

5 mg/kg olanzapine p.o + ketamine 30 mg/kg daily for 7 days

0.03mg/kg Eserine (physostigmine) i.p + ketamine 30 mg/kg daily for 7 days

In each case, wash-off period of 12 hours was allowed to pass before the tests were carried out

**Key:** p.o =Per oral (oral route of administration)

i.p =intraperitoneal route of administration

AZT= Azidothymidine (Zidovudine)

### Statistical Analysis

The data obtained were expressed as mean  $\pm$  SEM. Data obtained were analyzed using one-way analysis of variance (ANOVA) followed by Dunnet's post hoc test. T-test was used to analyze the difference between acute and sub-chronic (7-day concurrent) ketamine

administration. The level of statistical significance for all tests was set at  $p < 0.05$ .

## Results

### Acute Toxicity Test

The oral and intraperitoneal median lethal doses of Zidovudine in mice was calculated to be 3,807.88 and 2154 mg/kg body weight respectively and based on these preliminary studies, the test doses (12.5, 25, 50, 100 and 200) mg/kg body weight were used throughout the study.

### The Effect of Zidovudine on Depression Following Acute (60 Minutes) AZT Alone and Sub-chronic (7-days) Concurrent Administration with Ketamine in Mice

This result showed that saline (control) alone treatment did not alter immobility time in mice, but on concurrent administration with

ketamine, immobility time was increased. The standard reference (antidepressant) drug, olanzepine, significantly ( $p < 0.001$ ) reduced the immobility time in both its acute treatment alone and 7-days concurrent treatment with ketamine (F value for acute treatment=2.412, F value for 7-days treatment=16.90). Acute AZT administration did also not have significant effect on immobility time at its various doses tested and this was in line with the saline control group. However, following concurrent AZT administration with ketamine for 7 days, significantly ( $p < 0.001$ ) reduced immobility time was observed at AZT doses of 25 mg/kg and 12.5mg/kg as with (T-test: Acute Vs 7-days treatment;  $X = p < 0.05$ , degree of freedom  $t = 0.5981$ ,  $df = 6$ ). This result showed that AZT at these two doses produced significant antidepressant activity similar to olanzepine (table1).

**Table 1: Effect of Zidovudine on duration of immobility in forced-swim test**

Acute AZT alone treatment		7-days Concurrent AZT and ketamine treatment	
Saline (Control) (10 ml)	226.80 ± 8.17	saline (control) (10 ml) + Ket	261.80 ± 3.92
AZT (200 mg)	219.00 ± 8.30	AZT (200 mg) + Ket	223.80 ± 22.11
AZT (100 (mg)	217.40 ± 10.86	AZT (100 (mg) + Ket	243.00 ± 20.14
AZT (50 (mg)	201.00 ± 25.85	AZT (50 (mg) + Ket	225.40 ± 10.35
AZT (25 mg)	211.20 ± 22.34	AZT (25 mg) + Ket	164.60 ± 10.37*
AZT (12.5 mg)	214.80 ± 9.57	AZT (12.5 mg) + Ket	121.80 ± 10.58*X

Olanzapine (5 mg)	136.40 ± 35.13*	Olanzapine (5 mg) + Ket	114.20 ± 15.34*
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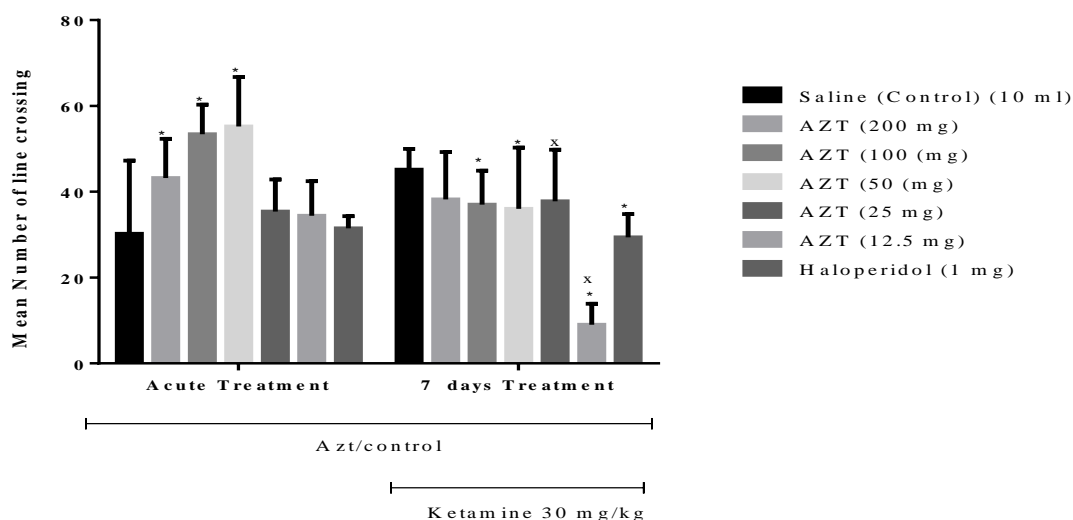
Data are represented as Mean ± SEM duration of immobility. n=5, statistical tool = One-way ANOVA was used to analyze within group \*= p<0.05 significant level of difference from saline (F values for Acute = 2.412, 7-days Concurrent; F= 16.90. T-test (multiple t-test) analysis was used to compare between acute and 7 days' treatment,  $\chi^2$ =p<0.05, degree of freedom; t=0.5981, df=6.

### The Effect of Zidovudine on locomotion 60 minutes after (Acute) AZT Alone and after 7- days (sub-chronic) Concurrent Administration with Ketamine in Mice

As expected, locomotion did not change with saline control alone treatment, but it increased on concurrent ketamine administration. Haloperidol (antipsychotic drug) reduced locomotion to almost same level as with the saline control group as expected. However, locomotion was slightly increased at doses 12.5

and 25mg/kg in the AZT alone treated groups compared to the saline control group while statistically significant locomotion was observed at AZT doses of 50, 100 and 200 mg/kg [figure 1] [F value for acute and 7-days treatment= 5.456 and 7.771]. The 7-days AZT concurrent treatments with ketamine reduced locomotion at all the AZT test groups and much more drastically at 12.5 mg/kg AZT dose (T-test (Acute and 7-days treatment,  $\chi^2$ =p<0.05, degree of freedom t=1.37, df=6).

**Figure 1: Changes in Locomotor Activity of Zidovudine in open field test**



Data are represented as Mean ± SEM number of line crossings. n=5, statistical tool; One-way ANOVA was used to analyze within group \*= p<0.05, significant level of difference from saline (F values for Acute = 5.456, 7-days Concurrent F= 7.771). T-test (multiple t-test) analysis was used to compare between acute and 7-days treatment;  $\chi^2$  = P<0.05, degree of freedom t=1.37, df=6.

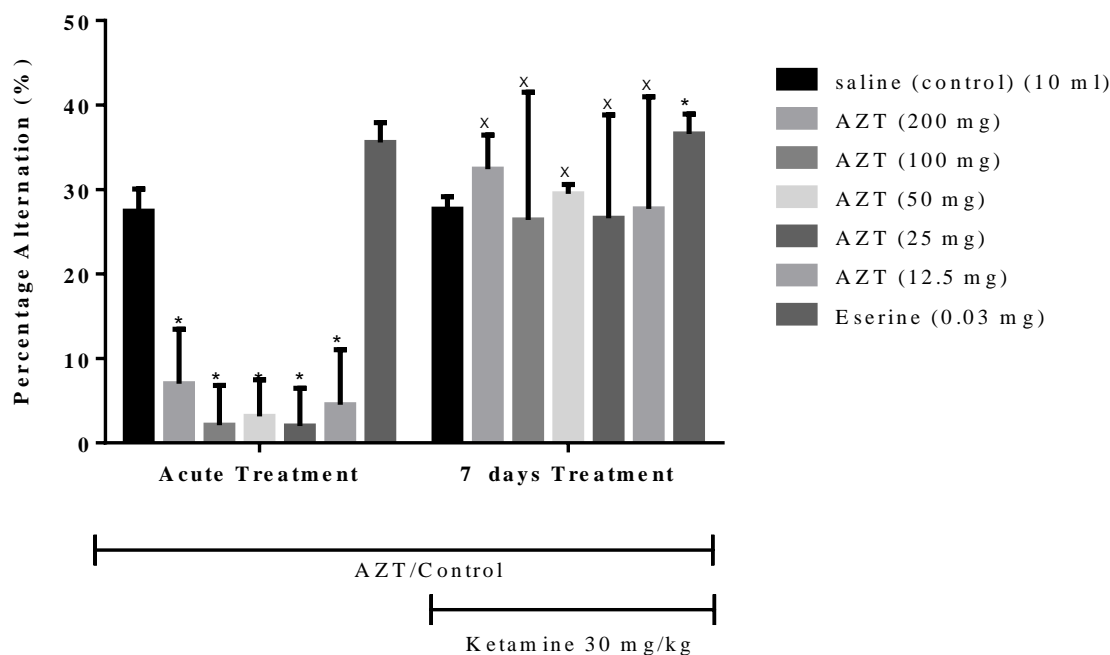


**The Effect of Zidovudine on Cognitive function 60 minutes after AZT Alone (acute) and 7-days (Sub-chronic) Concurrent Administration with Ketamine in Mice**

From the acute study, AZT treatment groups showed lower percentage alternation compared to saline (control), but on concurrent saline (control) with ketamine administration, reduction in percent alternation was seen

( $p < 0.05$ , F value=42.49 for acute treatment, 7-days treat F value=0.9069). The reference standard, Eserine (physostigmine), showed increased percentage alternation compared to the saline (control). However, the mean percentage alternation was severely reduced in zidovudine alone (acute) treatment as against the normal saline control group, but it increased in concurrent AZT-ketamine administration. ( $X = P < 0.05$ , degree of freedom  $t = 3.401$ ,  $df = 6$ ).

**Figure 2: Cognitive Function: Effect of Zidovudine on Y-maze test**



Data are represented as Mean  $\pm$  SEM percentage alternation.  $n = 5$ , statistical tool = one-way ANOVA was used to analyze within group  $* = p < 0.05$ , (F values for Acute = 42.49, 7-day concurrent; = 0.9069) significant level of difference from saline (control). T-test (multiple t-test) analysis was used to compare between acute and 7 days' treatment,  $x = p < 0.05$ , degree of freedom  $t = 3.401$ ,  $df = 6$ .

## DISCUSSION

Psychotic-like symptoms such as depression, hyperlocomotion and cognitive deficits occurs

frequently among human immunodeficiency virus (HIV) sero-positive patients [22,29,36,41] There are several underlying dysfunctions of

nervous systems linked with schizophrenic-like symptoms [27, 51]. Manifestation of psychotic symptoms has been associated with abnormal dopamine transmission [23], and also with glutamate hypofunction [34,53]. Repeated use of phencyclidine (PCP), a glutamate antagonist in humans leads to persistent symptoms similar to psychotic symptoms such as depression, hyperkinesia and cognitive deficits seen among psychiatric patients [18]. Moreover, N-Methyl-D-aspartate (NMDA) receptor hypo function, such as that induced by NMDA receptor antagonists, PCP or ketamine are known to provide useful schizophrenic-like models of these symptoms [8,26,35]. Thus, sub-chronic, concurrent administration of ketamine and zidovudine followed by 24h wash-out period had been shown to produce depression, hyper locomotion and cognitive deficit symptoms of schizophrenia in rodents as seen in this study with Swiss mice.

The reduced locomotor activity observed with the zidovudine and ketamine co-administration may be due to sustained elevation of dopamine function as a result of NMDA receptor blockade. A relationship between NMDA receptor blockade and an improved dopamine function had been reported and other studies had also reported reduced locomotion in rats administered with subchronic PCP and amphetamine [25,61,62].

This study had shown that zidovudine reduced the memory function significantly as seen in the normal control of this study and in a similar manner as scopolamine, a muscarinic receptor antagonist. However, in conditions of

derangement or impairment, it tends to increase memory function as indicated by the significant increase in percentage alternation at all tested doses in this study (Table, 3). Atypical anti-psychotic drugs (APDs) has been reported to improve PCP-induced cognitive impairments in novel object recognition paradigm in rats [14,16,17].

From previous studies, attenuation of NMDA antagonist-induced behavioural deficits was linked to ability to decrease  $D_1$  and to increase  $5-HT_{1A}$  receptor binding [7, 32,43]. Thus, zidovudine might have acted in the same manner to this mechanism by inhibiting the effect of the subchronically administered ketamine. Another mechanism through which zidovudine might have antagonized ketamine-induced cognitive deficits is via augmentation of NMDA receptor-evoked currents through a  $D_1$  receptor mechanism [44].

The mechanism of action of several atypical APDs such as clozapine, ziprane, aripirazole and quetiapine had been associated with stimulation of the  $5-HT_{1A}$  for their positive cognitive effects [17,32]. Interestingly, the activity of zidovudine from this study was similar with reports from other studies that APDs differ in their effects on healthy individuals as opposed to schizophrenic patients [19,31,33,45]. An example of such APDs is Asenapin known for its adverse effects on cognitive function in normal individuals, but effective in patients with impaired cognitive function [13,43].

Zidovudine at doses 12.5 mg/kg and 25 mg/kg exhibited pronounced antidepressant effect on ketamine-induced depression in mice as with olanzepine, the reference standard drug which also decreased immobility time in both the non-induced and ketamine-induced normal control mice. In this study, the increase in the immobility time seen with the normal control mice was an indication of depression from the sub chronic administration of ketamine and which was found ameliorated with zidovudine. Depression is a negative symptom of schizophrenia and it is usually difficult to treat using the typical APDs such as haloperidol. Antidepressants like monoamine uptake blockers and monoamine oxidase inhibitors have been reported to have significant effect in reducing immobility as seen with zidovudine in this study [20]. Therefore, the ability of zidovudine to reduce ketamine-induced immobility may have been through any of their mechanisms-namely, inhibition of monoamine oxidase and/or blockade of monoamine uptake [20].

## CONCLUSION

Zidovudine demonstrated significant ameliorative effects on both the negative and cognitive deficit symptoms induced by sub-chronic administration of ketamine in mice as can be seen in this study. Since negative and cognitive deficit symptoms of schizophrenia are related to the dopamine released in the prefrontal cortex [21], zidovudine might have acted like the atypical APDs such as olanzepine and risperidone used in these conditions. These drugs act by modulating combined D<sub>2</sub> and

serotonin 5-HT<sub>2A</sub> receptor antagonism and/or partial D<sub>2</sub> receptor antagonism in addition to preferential blockade of inhibitory dopamine auto receptors (in a serotonergic pathway) to increase striatal dopamine release and/or improve both negative and cognitive deficit symptoms of schizophrenia [12,21]. Although further study is required to elucidate the exact mechanism of zidovudine effect, the pro-cognitive and antidepressant effects of zidovudine seen in this study and possible other beneficial psychotic effects suggests multiple receptor modulation mechanism.

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