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Intestinal Fluid and Glucose Transport in Albino Wistar Rats Following Long Term Administration of Nevirapine

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Abstract

Long term administration of nevirapine causes functional derangement of various tissues. This study was therefore carried out to determine the effect of long term administration of nevirapine on intestinal fluid and glucose absorption in albino Wistar rats using the everted sac technique. Twenty albino Wistar rats (both sexes) were divided into two groups of ten rats per group. The first group served as the control and was fed with normal rat chow while the second group was fed nevirapine (0.4 mg/kg body weight) by gavage once daily for 2 weeks after which the dosage was doubled by administering the drug twice daily for 12 weeks. Villus height and crypt depth were measured. The gut fluid uptake (jejunum/ileum) in nevirapine-treated rats were significantly lower ($p<0.001$) when compared to control; gut glucose uptake (jejunum/ileum) were significantly lower ($p<0.001$and $p<0.05$) in the nevirapine-treated group of rats when compared to control. The villus height (duodenum, jejunum, ileum) in the nevirapine-treated group was significantly lower ($p<0.01$, $p<0.01$, $p<0.001$) as compared to control group. The crypt depth (duodenum, jejunum, ileum) in the nevirapine-treated group was significantly lower ($p<0.001$, $p<0.01$, $p<0.01$) when compared to control. These results suggest that long term administration of nevirapine may lead to distortion in villus morphology with a concomitant mal-absorption of fluid and glucose in rats.

Keywords: Nevirapine; Intestinal fluid; Glucose absorption; Villus height; Crypt depth

Introduction

The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS–related morbidity and mortality. Unfortunately up to 25% of all patients discontinue their initial HAART regimen because of treatment failure, toxic effects or non-compliance within the first eight months of therapy [1,2]. The human immunodeficiency virus type one (HIV-1), a causal organism of acquired immunodeficiency syndrome (AIDS), destroys immune system thereby allowing any opportunistic infections leading to death of the patient [3]. HIV-1 is known to be transmitted by transfer of blood or blood products, semen, vaginal fluid, pre-ejaculated fluid, breast milk and using intravenous drug containing injections. HIV-1 infects the T-lymphocytes helper cells containing CD+ receptor on the surface [4]. Cunningham or macrophages and dendrite cells and destroy them rapidly which lead to sharp decline in their counts. When the number of CD4+ T lymphocytes declines below a critical level (<200/ul), there is a complete collapse of cell-mediated immunity and the body becomes prone to opportunistic infections by any pathogen. The entry of HIV-1 into CD4+ T cells or macrophages occurs via interaction between the glycoproteins (gp120) present on the viral envelope and the CD4 receptor present on the target cells. Certain specific co-receptors which are chemokine co-receptors such as CXCR4 (for T-lymphocytes) or CCR5 (for macrophages) are also needed for the internalization of virus into the cells after docking [5].

Nevirapine (NVP) has a proven efficacy in combination therapy for HIV [6-9], patients initiating NVP can experience a hypersensitivity reaction (HSR) that can be a serious adverse event, it is characterized by combination of rash, fever or hepatitis and typically occurs within the first 6 weeks after initiation [10,11]. Several strategies have been implemented to improve treatment duration. Due to the ongoing development of new anti-retroviral (ARV) agents, prompt understanding and management of adverse effects becomes very important. The reaction can lead to morbidity through treatment interruption, inconvenience and loss of productivity. The sustained benefits of HAART have led to far greater numbers of HIV-1 infected cases receiving at least three drugs for greater periods of time. NVP falls in the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of ARV [12]. Both nucleoside reverse transcriptase inhibitors (NRTIs) and NNRTIs inhibit the same target, the reverse transcriptase enzyme, an essential viral enzyme which transcribes ribonucleic acid (RNA) into deoxyribonucleic acid (DNA). Unlike NRTIs which bind at the enzyme's active site, NNRTIs bind allosterically at a distant site away from the active site termed the NNRTI pocket. NVP is not effective against HIV-2, as the pocket of the HIV-2 reverse transcriptase has a different structure, which confers intrinsic resistance to the NNRTI class [13]. In the book by Betram [14] NVP binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent polymerase activities by causing a disruption of the enzyme's catalytic site. The exact mechanism of NNRTI toxicity in patients under treatment is not clearly understood. However, NNRTIs such as NVP and efavirenz are known to cross the blood brain barrier even at very low concentration and reach the brains of HIV-1-infected and AIDS patients [15]. These ARV's may then exert adverse effects to the central nervous systems (CNSs) of patients and develop neurotoxic symptoms [16]. The compounds have been observed to adversely influence anxiety-related behavior and cognitive performance in mice [17]. In a research study by de Maat et al. [18] NVP is extensively bio-transformed via cytochrome p450 (oxidative) metabolism to several hydroxylated metabolite. NVP is a substrate for CYP2B6 and 3A4 and a potent inducer of these enzymes, features that favor potential production of a toxic intermediate that might cause liver injury. de

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Maat et al. [19] had also reported that NVP may cause severe or life threatening, usually emerging in the first six weeks of treatment.

There is a causal relationship between toxicity of NVP administration and the metabolite content in rats suggesting a potential cytotoxic effect associated with long term administration of NVP [20]. Several reports have been documented on the effect of NVP administration on various functional and structural alterations [21-28]. The gastrointestinal tract (GIT) functionality is dependent on the integrity of its lateral intercellular spaces, connective tissues, enzymatic actions among others [29]. These factors may considerably affect the rate of fluid transport and glucose absorption within the intestinal wall. Since damage to internal tissues may affect their functions, this study was therefore designed to investigate the effect of NVP administration on absorption of glucose and fluid transport using albino Wistar rats as a model.

Materials and Methods

Experimental animals/source of acquisition of nevirapine

Twenty albino Wistar rats (both sexes) of initial body weight between 50-125 g from the start of the experiment were used for this study. They were obtained from the animal house of Physiology Department, University of Calabar, Nigeria, after approval for the study was obtained from the College of Medical Sciences Ethical Committee. They were kept in improvised plastic metabolic cages with wire net covers. They were maintained in the animal facility of Physiology Department, University of Calabar, at a temperature of 28 ± 2°C and 12 hours light/dark cycles. NVP was sourced from Strides Arcolab Ltd., Bangalore, India. It was obtained free from the Pharmacy Unit of the University of Calabar Teaching Hospital Permanent site, Calabar, Cross River State.

Measurement of fluid and glucose transport

The everted intestinal sac technique described by Wilson and Wiseman [30] used by Barry et al. [31] and modified by Adeniyi and Olowokurun [32] was used in this study in the measurement of fluid and glucose transport. The animals were rendered unconscious by stunning, and their abdomens quickly cut open to obtain the intestinal segments. Four segments (i, ii, iii and iv) each10 cm long were cut out as shown in Figure 1 for sac

In all, the following weighing was measured: W_1=weight of dish + 2 ligatures; W_2 = weight of dish + empty sac + 2 ligatures; W_3=weight of dish + initial full sac + 2 ligatures; W_4=weight of dish + final full sac + 2 ligatures; W5=weight of dish + final empty sac + 2 ligatures. The fluid and glucose transfer was expressed as ml/g sac/30 minutes) and mg/g sac/30 minutes) respectively, according to Parsons et al. [33] and as used by Barry et al. [31] also, Adeniyi and Olowokurun [32]. Fluid and glucose transfers were determined as measures of volume transferred by a unit wet weight of intestine for a given period.

The mucosal fluid transfer (MFT), serosal fluid transfer (SFT), and gut fluid uptake (GFU) were determined by using the results of the weighing as follows:

Initial wet weight (IWW) = $W_2 - W_1$;

Initial serosal volume (ISV) = $W_3 - W_2$;

Final serosal volume (FSV) = $W_4 - W_5$;

Serosal fluid transfer (SFT) = FSV – ISV;

Gut fluid transfer = $W_5 - W_2$;

Mucosal fluid transfer (MFT) = SFT + GFU.

MFT, SFT and GFU were expressed as volume /g sac /30 minutes. The terms used for glucose transfer are mucosal glucose transfer (MGT), seroal glucose transfer (SGT) and gut glucose uptake (GGU). MGT is the amount of glucose that disappeared from the mucosal fluid, while the SGT is the amount of glucose that entered the serosal fluid. GGU is the difference in glucose concentration between mucosal and serosal fluids after incubation. This value includes glucose metabolized and those found in the gut wall at the end of the experiment.

Preparations of tissues for microscopic examination

Tissue preparation for microscopic examination was done according to the method of Drury and Wallington [34]. At the end of 14 week feeding period, rats were anaesthetized by inhalation of chloroform and decapitated. The small intestine was removed and placed in cold normal saline. Tissue blocks from the small intestine were fixed in 10% neutral formation after which they were dehydrated using alcohol and then cleared in xylene. The sections were then stained with hematoxylin thereafter, viewed under the microscope and photomicrographs were taken.

Determination of villus height and crypt depth

The villus height was taken as the distance from the crypt opening to the tip of the villus while the crypt depth was measured from the base of the crypt to the level of the crypt opening [35]. Five villi were selected from segment for each rat in the three groups for microscopic analysis. The villi height and crypt depth were measured.

Statistical analyses

All results are presented as mean ± standard error of mean. The data were analyzed using the unpaired Student's t-test and $p<0.05$ was considered statistically significant.

Results

Fluid transfer in the intestine of control and nevirapine-treated groups

As shown in Table 1 and Figure 2, mean values for serosal fluid transfer (SFT) in jejunum and ileum for control group of animals (ml/g sac/30 minutes) was (-0.232 ± 0.052 and -0.44 ± 0.012) respectively. Mean values for SFT in jejunum and ileum for NVP-treated group of animals (ml/g sac/30 minutes) was (-0.019 ± 0.018 and 0.4004 ± 0.167) respectively, this was significantly lower ($p<0.01$ and $p<0.001$) when compared to control. The mucosal fluid transfer (MFT) in jejunum of NVP-treated group of animals (ml/g sac/30 minutes) was (-0.088 ± 0.022) this was not significantly different from the control (-0.069 ±

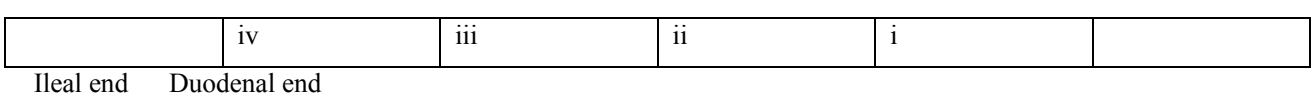

Figure 1: Measurement of fluid and glucose transfer.

Groups	Body weight range (g)	Serosal fluid transfer- Jejunum (ml/g sac/30 minutes)	Serosal fluid transfer- Ileum (ml/g sac/30 minutes)	Mucosal fluid transfer- Jejunum (ml/g sac/30 minutes)	Mucosal fluid transfer- Ileum (ml/g sac/30 minutes)	Glucose fluid uptake-Jejunum (ml/g sac/30 minutes)	Glucose fluid uptake- Ileum (ml/g sac/30 minutes)
Control	100-210	-0.232 ± 0.052	-0.44 ± 0.012	-0.069 ± 0.049	-0.127 ± 0.090	0.270 ± 0.012	0.225 ± 0.024
NVP-treated	100-300	-0.019 ± 0.018**	0.404 ± 0.167***	-0.088 ± 0.022^{NS}	0.336 ± 0.161*	-0.068 ± 0.004*	-0.064 ± 0.018*

Table 1: Fluid transfer in the intestine of the rats treated with nevirapine.

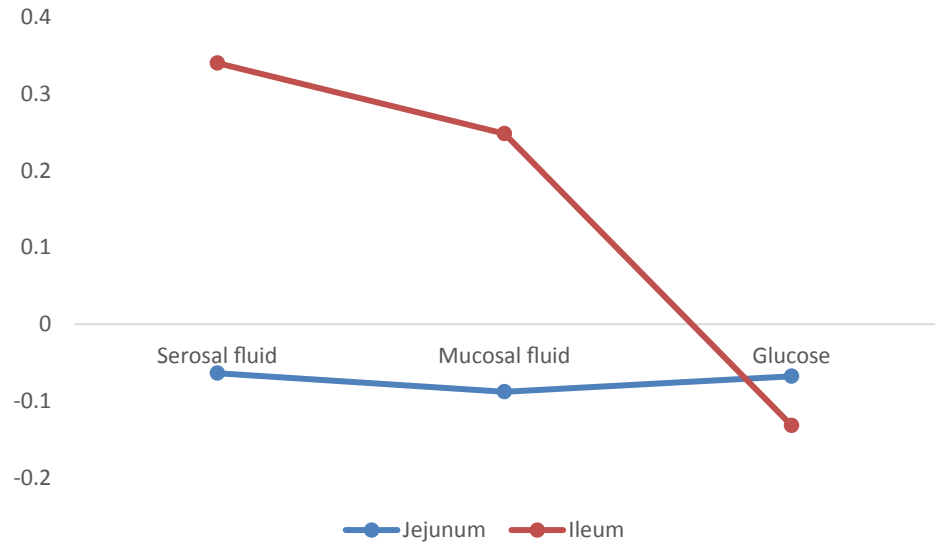

Figure 2: Fluid transfer in the intestine of rats treated with nevirapine.

Groups	Body weight range (g)	Glucose transfer – jejunum (mg/g sac/30 minutes)	Glucose transfer – ileum (mg/g sac/30 minutes)	Gut glucose uptake – jejunum (mg/g sac/30 minutes)	Gut glucose uptake - ileum (mg/g sac/30 minutes)
Control	100-210	8.14 ± 0.17	7.82 ± 0.19	8.14 ± 0.169	7.82 ± 0.191
NVP-treated	100-300	2.84 ± 0.24***	6.18 ± 0.45*	2.84 ± 0.242***	6.18 ± 0.946*

Table 2: Glucose transfer in the intestine of rats treated with nevirapine.

0.049). The MFT in ileum of NVP-treated group of animals (ml/g sac/30 minutes) was (0.336 ± 0.161) this was significantly higher ($p<0.05$) when compared to control (-0.127 ± 0.090). The gut fluid uptake (GFU) in jejunum and ileum of NVP-treated group of animals (ml/g sac/30 minutes) was (-0.068 ± 0.004 and -0.064 ± 0.018) respectively, this was significantly lower ($p<0.05$) when compared to control (0.270 ± 0.024 and -0.225 ± 0.024) respectively.

Each value represents mean ± SEM, for 20 sacs in 5 rats; NS: not significant versus control; ***$p<0.001$ versus control; **$p<0.01$ versus control; *$p<0.05$ versus control.

Glucose transfer in the intestine of control and nevirapine-treated group

The mean values of glucose transfer in jejunum of control group of animals (mg/g sac/30 minutes) was (8.14 ± 0.17). Glucose transfer in jejunum of NVP-treated animals (mg/g sac/30 minutes) was (2.84 ± 0.24). This was significantly lower ($p<0.001$) when compared to control. Glucose transfer in ileum of NVP-treated animals and control group (mg/g sac/30 minutes respectively) was (6.18 ± 0.45 and 7.82 ± 0.19) respectively, this was significantly lower ($p<0.05$) when compared to control. Gut glucose uptake (GGU) in jejunum of NVP-treated group of animals (mg/g sac/30 minutes) was (2.84 ± 0.242) this was significantly lower ($p<0.001$) when compared to control (8.14 ± 0.169). GGU in ileum of NVP-treated group of animals (mg/g sac/30 minutes) was (6.18 ± 0.946) this was significantly lower when compared to control (7.82 ± 0.191) Table 2 and Figure 3.

Each value represents mean ± SEM, for 20 sacs in 5 rats; ***$p<0.001$ versus control; *$p<0.05$ versus control; NS: not significant versus control.

Villus height and crypt depth in the intestine of rats administered with nevirapine

In Figure 4, the villus height in the duodenum, jejunum and ileum for control group was (272.01 ± 17 mm, 359.60 ± 33 mm and 193.03 ± 57 mm) respectively. In the NVP-treated rats, villus height in the duodenum, jejunum and ileum was (248.83 ± 39 mm, 259.76 ± 12 mm and 163.97 ± 18 mm) respectively, showing significant ($p<0.05$, $p<0.05$ and $p<0.001$) reduction when compared to control. The crypt depth in the duoenum, jejunum and ileum for control group was (408. 17 ± 26 mm, 255.67 ± 34 mm and 256.57 ± 81 mm) respectively. In the NVP-treated rats, crypt depth in the duodenum, jejunum and ileum was (259.67 ± 49 mm, 224.23 ± 89 mm and 233.20 ± 11 mm) respectively, showing significant ($p<0.05$, $p<0.05$ and $p<0.001$) reduction when compared to control (Figure 5).

Discussion

Effect of NVP administration on intestinal fluid and glucose absorption in rat was studied. Results on the study showed a decrease

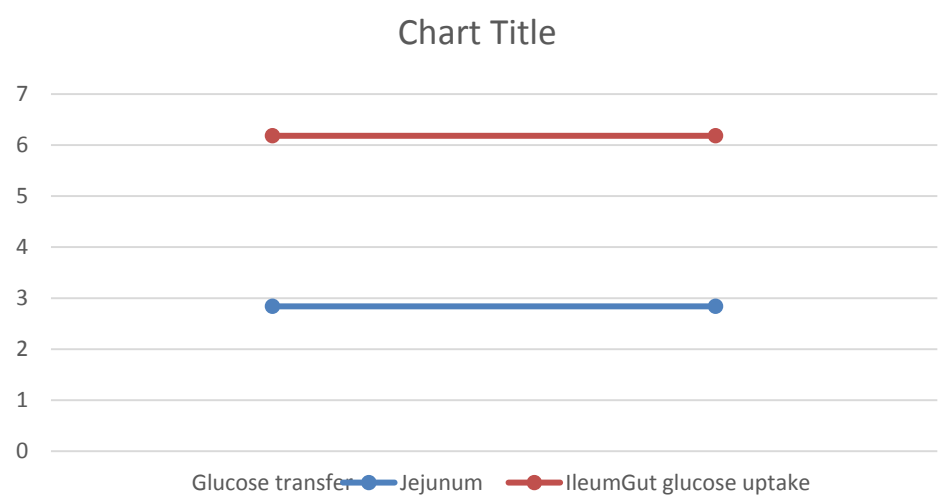

Figure 3: Glucose transfer in the intestine of rats treated with nevirapine.

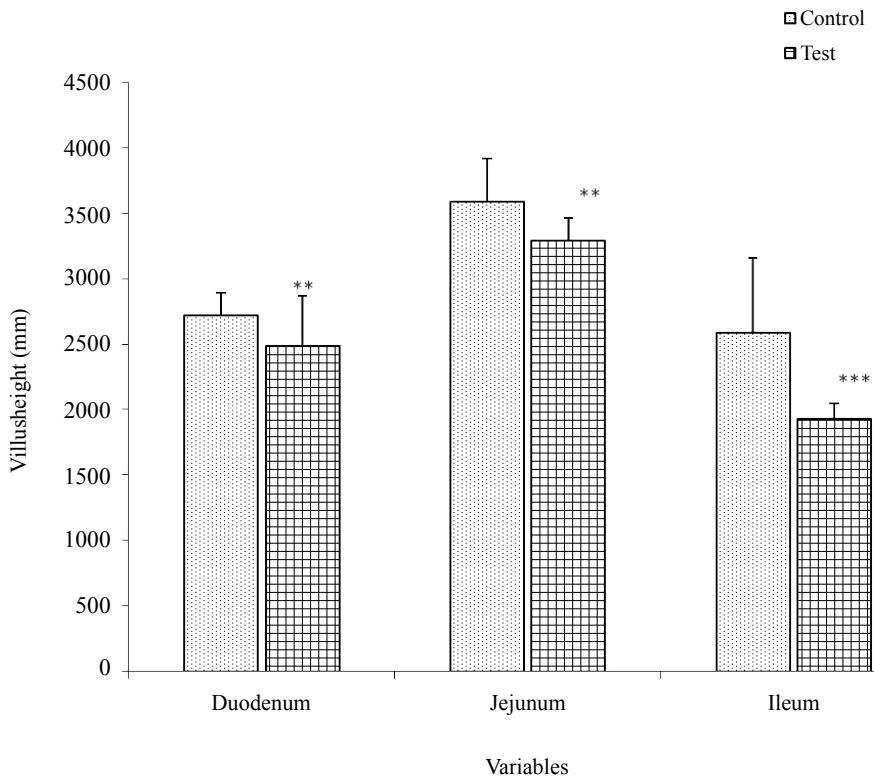

Figure 4: Duodenal, ileal and jejunal villus heights of control and NVP-treated groups. Values are mean ± SEM, n = 10 *p<0.05, ***p<0.001 vs control.

in fluid and glucose uptake in NVP-treated group as compared to control. Results on the villus height and crypt depth in the small intestine (duodenum, ileum and jejunum) of the NVP-treated group showed a significant decrease as compared to control. This result is in consonance with the works [36,37] who attributed toxicity problems to be associated with a broad spectrum of antiretroviral (ARV) compounds. Also, Umoren et al. [38], Deborah et al. [39] have attributed NVP administration with alteration in gastrointestinal system. Hoffman and Kamp [40] also reported that in the early stages of chemotherapy with nucleoside analogs, NNRTIs, and PIs, symptoms of gastrointestinal disorders, such as abdominal discomfort, loss of appetite, diarrhea, nausea and vomiting, Heartburn, abdominal pain, meteorism, dehydration, malnutrition with weight loss, low plasma drug levels, and constipation may also develop. However, some of their reports are in disparity to our earlier results. From our previous laboratory studies, NVP-treated rats showed increase food and water uptake resulting in increased body weight gain [41]. The disparity in the result could be specie specific. According to Hoffmann and Kamps [40], diarrhea occurs frequently with zidovudine, didanosine, and all PIs (nelfinavir, saquinavir, and lopinavir), whereas nausea is

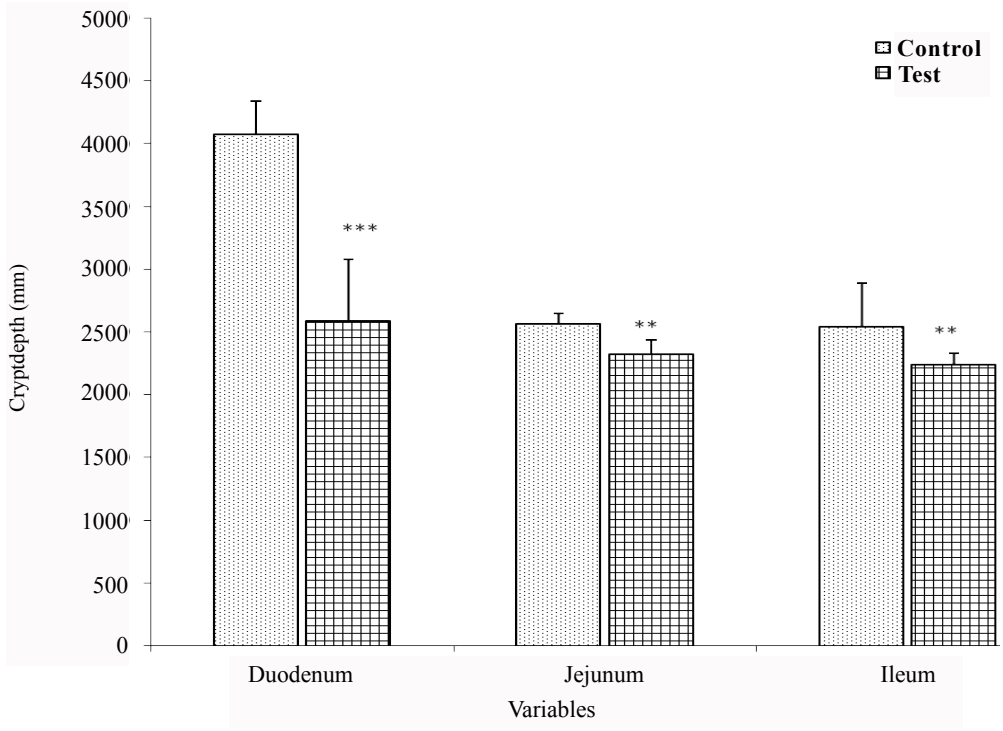

Figure 5: Duodenal, ileal and jejunal crypt depths in control and NVP-treated groups.Values are mean ± SEM, n = 10. *p<0.05, ***p<0.001 vs control.

commonly produced by zidovudine. In many cases such disorders are resolved between 1 month and 6 weeks of treatment.

From the present study, there was mal-absorption of fluid and glucose in the NVP-treated group. This may result from the apparent disorganization of cyto-architecture of the villus height and crypt depth. Umoren et al [22] had earlier reported distortion of morphology of cyto-architecture of the liver and small intestine resulting from NVP administration. Damage affecting the height and depth of villi may be caused by increased serum concentrations of low density cholesterol (LDL-c) [20]. Oxidation of LDL-c occurs *in vivo* and modified LDL-c is cytotoxic to various organs including the liver [42]. It is conceivable that this cytotoxic LDL-c as present in NVP [20] may cause damage on intestinal tissues (villus height and crypt depth). This was evident in the result of the present study.

Absorption is dependent on the rate of change of basolateral spaces which in turn is determined by connective tissues present and absorption is impeded when there is altered morphology of the intestine [43]. Intestinal absorption of fluid is usually passive and dependent on absorption of solutes like sodium or glucose which means that if glucose absorption is disturbed, the fluid absorption would also be affected [43]. From our laboratory studies, morphology of intestinal tissues was damaged. This may explain the observed reduction in fluid and glucose absorption in the NVP-treated group of animals. On the other hand, there was improved transfer of fluid and glucose uptake in the control group. This may be due to the fact that the integrity of intestinal tissues in this group of animals was not affected as our result showed normal cyto-architecture [22]. Results from the present study suggest that long term administration of NVP may lead to distortion in villus morphology with a concomitant mal-absorption of fluid and glucose in rats.

It is however recommended that since NVP administration usually portends hypersensitivity and toxic reactions, and for the fact that NVP administration has also led to greater reduction in morbidity and mortality rate in HIV-1 infected patients [12]. Users should be closely monitored for toxicity reactions and treatment discontinued. According to Sharma [44], toxicity due to long term treatment with anti-HIV-1 drugs in general and HAART in particular is a common problem in HIV medication. Treating HIV-1- infected individuals is sometimes highly complicated, as many of them do not adhere to the treatment, switch over to a new regimen within a few weeks of starting therapy, or even refuse to begin HAART [45]. Some of the options to overcome or reduce anti-HIV-1 drug-induced toxicity may include early diagnosis, monitoring of treatment by an HIV clinician at quarterly intervals, and standard evaluations of patient's history, physical examinations, and measurement of vital signs and body weight [40]. To avoid these complications, the medication should not be taken on an empty stomach. Coffee, smoking, alcohol, aspirin, very spicy or fatty foods, and dairy products should be avoided. For symptomatic treatment, metoclopramide, dimenhydrinate, cimetidine, ranitidine, or ondansetron is normally prescribed. Antiemetic drugs can be taken 30-45 minutes before HAART regularly, but after a few weeks they can be gradually withdrawn. In cases of PI-associated diarrhea, oat bran tablets or psyllium may be useful. Nelfinavir-associated diarrhea is alleviated by calcium, taken as calcium carbonate, at a dosage of 500 mg bid. To inhibit bowel movements arising due to PI usage, loperamide or opium tincture or pancrelipase, a synthetic pancreatic enzyme, may be taken on the advice of a physician. To avoid significant dehydration and loss of electrolytes, soft drinks, salty crackers, sport drinks, herbal teas, and electrolytes, solutions may be useful [40,46,47].

In conclusion, these results suggest that long term administration of NVP may lead to distortion in villus morphology with a concomitant mal-absorption of fluid and glucose in rats.

HIV-1/AIDS patients are currently being treated with a single drug or different combinations of 22 ARV agents approved by the FDA for clinical use. These drugs have been developed to target viral enzymes such as HIV-1RT, protease, and integrase encoded by the pol gene of the virus. Several small molecules have also been developed against different stages of the viral life cycle. Some of them have entered into various stages of basic and clinical development. Most of these drugs have been found to induce moderate to severe toxic effects after long term use and therefore pose a challenge to chemotherapy. Because of the side effects, adherence to treatment has always been at stake, and discontinuation of treatment in many cases further aggravates the drug resistance problem. Therefore, knowledge about the mechanisms of action of these drugs, their interactions with other concomitantly administered drugs, development of newer and safer ARVs, and effective management practices to combat drug-induced toxicity are urgently required for successful treatment of the disease.

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