International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 10 (2): March-April 2020

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 12-03-2020; Revised: 30-03-2020; Accepted: 02-04-2020

DIDANOSINE AS AN ANTI- HIV DRUG: A REVIEW

Rahul V. Sonawane*, Amol S. Chaudhari, Harshal L. Tare.

TSPM's, Trimurti Institute of Pharmacy Jalgaon, Maharashtra, India

Keywords:

Didanosine, Nucleoside Analogue, Reverse Transcriptase Inhibitor, HIV

For Correspondence:

Rahul V. Sonawane

TSPM's, Trimurti Institute of Pharmacy Jalgaon, Maharashtra, India

ABSTRACT

Didanosine is a Nucleoside Analogue Reverse Transcriptase Inhibitor (NRTI).In the target cell for HIV, didanosine is converted to its active moiety.dideoxyadenosine-5'-triphosphate (ddATP),which inhibits HIVreverse transcriptase and terminate viral dna growth.it is now well established that didanosine therapy produces beneficial effect on virological and immunological markers of HIVdisease and improves clinical outcome in adults or children with HIVinfection.in numerous clinical trials, pronounced and sustained decreases in plasma HIVrna levels and increases in cd4+ cell counts occurred in previously untreated or antiretroviral therapy-experienced patients treated with didanosine in combination with at least 1 other. antiretroviral drug; zidovudine, stavudine, lamivudine, nevirapine. HIVrna levels decreased to below the limits of detection in some patients receiving triple or dual therapy with didanosine-containing regimens in double blind,placebo-controlled trials,triple therapy with didanosine,zidovudine and nevirapine was significantly more effective than dual therapy with various combinations of these agents in improving surrogate disease markers in treatment-naïve patients and in delaying disease progression or death in treatment experienced patients with advanced disease

INTRODUCTION

Didanosine is a synthetic purine nucleoside analogue active against a human immunodeficiency virus (hiv) didanosine chewable/dispersible buffered tablet are available for oral administration in strength 20, 50,100,150 and 200 mg of didanosine. Each tablet is buffered with calcium carbonate and magnesium hydroxide, didanosine tablet also contain aspartane, sorbitol microcrystalline cellulose, polyplasdone, mandarin orange flavor, and magnesium striate. Didanosine is as a white crystalline powder with the molecular formula c10h12n4o3 and molecular weight of 236.2,the aq. Solubility of didanosine at 25c and ph of approximately 6 is 27.3mg 1ml.didanosine is unstable in acidic solution for example at ph<3 and 37c,10% of didanosine decomposes to hypoxanthine is less than 2 minutes. Didanosine buffered powder for oral administration in single dose packets containing 100,167, or 250mg of didanosine. Packets of each product strength also contain a citrate phosphate buffer (composed of dibasic sodium phosphate, sodium citrate, citric acid) and sucrose. Didanosine pediatric powder for oral solution is supplied for oral administration in 4-or 8-ounce glass bottles containing 2or 4 grams of didanosine, respectively.

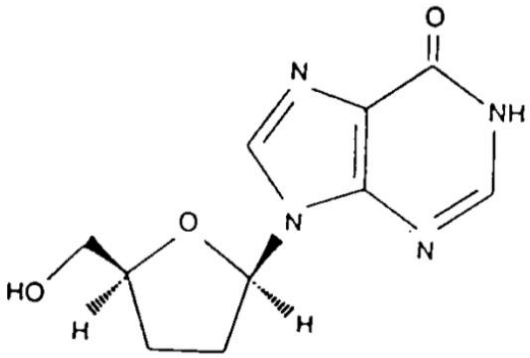

Fig. 1: Structure of Didanosine

1. History

The related pro-drug of didanosine, 2',3'-dideoxyadenosine (ddA), was initially synthesized by morris j.robins (professor of oraganic chemistry at brigham young university) and R.K. robins in 1964. Subsequently, Samuel broder,hiroaki mitsuya,and Robert yarchoan in the national cancer institude (NCI) found that ddA and ddI could inhibits HIVreplication in the test tube and conducted initial clinical trials showing that didanosine had activity in patients infected with HIV. On behalf of the NCI, they were awarded patents on these activitites. Since the NCI does not market products directly,the national institutes of health (NIH)

awarded a ten-year exclusive license to Bristol-myers squibb co.(BMS) to market and sell ddi as didanosine tablets.

Didanosine became the second drug approved for the treatment of HIVinfection in many other countries, including in the united states by the food and drug administration (FDA) on October 9,1991. Its FDA approval helped bring down the price of zidovudine(AZT), the initial anti-HIVdrug.

Didanosine has weak acid stability and is easily damaged by stomach acid. Therefore,the original formula approved by the FDA used chewable tablets that included an antacid buffering compound to neutralize stomach acid. The chewable tablets were not only large and fragile, they also were foul-tasting and the buffering compound would cause diarrhea. Although the FDA had not approved the original formulation for once a day dosing it was possible for some people to take it that way.

At the end of its ten year license, BMS reformulated didanosine as didanosine EC and patented that, which reformulation the FDA approved in 2000. The new formulation is a smaller capsule containing coated microspheres instead of using a buffering compound. It is approved by the FDA for once a day dosing.also at the end of that ten-year period, the NIH licensed didanosine to BRR laboratories under a non-exclusive license, and didanosine became the first generic anti-HIVdrug marketed in the united states.

2. Mechanism of Action

Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxyadenosine in which the 3'-hydroxyl group is replaced by hydrogen.intracellularly,didanosine is converted by cellular enzyme to the active metabolite,dideoxyadenosine 5'-triphosphate.Dideoxyadenosine 5'-triphosphate inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate,dexoyadenosine 5'-triphosphate,and by its incorporation into viral DNA causing termination of viral DNA chain elongation.

3. Pharmacokinetics

Didanosine is rapidly absorbed,with peak plasma concentration generally observed from 0.25 to 1.50 hours following oral dosing.increases in plasma didanosine concentration were dose

proportional over the range of 50 to 400mg.steady state pharmacokinetic parameters did not differ significantly from values obtained after a single dose.binding of didanosine to plasma proteins in vitro was low (<5%).based on data from in vitro and animal studies,it is presumed that the metabolism of didanosine in a men occurs by the same pathways responsible for the elimination of endogenous purines.

The pharmacokinetic parameters of didanosine are summarized in table 1.

Table 1: Pharmacokinetics parameters for didanosine in adults and pediatric patients

Parameter	Adults Patients	n	Pediatric patients	n
Oral bioavaibility	42+12%	6	25+20%	46
Apperent volume of distribution	1.08+0.22l/kg	6	28+15L/m2	49
CSF-plasma ratio	21+0.03%	5	46% (range 12-85%)	7
Systemic clearance	13.0+1.6ml/min/kg	6	516+184ml/min/m2	49
Renal clearance	5.5+2.1 ml/min/kg	6	240+90 ml/min/m2	15
Elimination half life	1.5+0.4h	6	0.8+0.3h	60
Urinary recovery of didanosine	18+8%	6	18+10%	15

Effect of on absorption of didanosine:

Didanosine peak plasma concentration and area under the plasma concentration time curve (AUC) were decreased by approximately 55% when didanosine tablets up to 30 minutes before a meal did not result in any significant changes in bioavailability. Didanosine should be taken on an empty stomach, at least 30 minutes before or 2 hours after eating.

4. Dosage and root of Administration

All didanosine formulations should be administrated on an empty stomach, at least 30 minutes before or 2 hours after eating. for either a once-daily or twice-daily regimen, patients must taken at least two of the appropriate strength tablets at each dose to provide adequate buffering and prevent gastric acid degradation of didanosine. Because of the need for

adequate buffering, the 200-mg strength tablet should only be used as a component of a once-daily regimen. To reduce the risk of gastrointestinal side effects, patients should taken no more than four tablets at each dose.

Adults: the preferred dosing frequency of didanosine is twice daily because there is more evidence to support the effectiveness of this dosing regimen. Once daily dosing should be considered only for adult patients whose management requires once daily dosing of didanosine.

The daily dose in adult patients is dependent on weight as outlined in table 2

Table 2: Adult dosing

Patient weight	Didanosine tablets	Didanosine buffered powder
Preferred dosing		
> 60 kg	200 mg twice daily	250 mg twice daily
< 60 kg	125 mg twice daily	167 mg twice daily
Dosing for patients whose management requires once-daily frequency		
>60 kg	400 mg once daily	B
< 60 kg	250 mg once daily	B

a) The 200-mg strength tablet should only be used as a component of a once daily regimen.

b) Not suitable for once daily dosing except for patients with renal impairment.

Pediatric patients:

The recommended dose of didanosine in pediatric patients is 120 mg/m2 twice daily. there are no data on once daily dosing of didanosine in pediatric patients.

Dose adjustment:

Clinical and laboratory signs suggestive of pancreatitis should prompt dose suspension and careful evaluation of the possibility of pancreatitis.didanosine use should be discontinued in patient with confirmed pancreatitis.patients with sympytoms of peripheral neuropathy may

tolerate a reduced dose of didanosine after resolution of the symptoms of peripheral neuropathy upon drug discontinuation. if neuropathy recurs after resumption of didanosine, permanent discontinuation of didanosine should be considered.

Renal impairment:-in adult patients with impaired renal function, the dose of didanosine should be adjusted to compensate for the slower rate of elimination. The recommended doses and dosing intervals of didanosine in adult patients with renal insufficiency.

5. Pharmacodynamics

Didanosine is a nucleoside reverse transcriptase inhibitor (NRTI) with activity against human immunodeficiency virus Type 1 (HIV-1). Didanosine is a hypoxanthine attached to the sugar ring,unlike other nucleoside analogues. Didanosine is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIVreverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. Didanosine is effective against HIV, and usually used in combination with other antiviral therapy. Switching from long term AZT treatment to didanosine has been shown to be beneficial. Didanosine has weak acid stability and therefore, it is often combined with an antacid.

6. Route of elimination

Based on data from in vitro and animal studies, it is presumed that the metabolism of didanosine in man occurs by the same pathways responsible for the elimination of endogenous purines. Purines are eliminated by the kidney.

7. Half life

30 minutes in plasma and more than 12 hours in intracellular environment

8. Toxicity

Side effects include pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia and hepatic dysfunction

9. Physiochemical properties

Appearance: didanosine is a white, crystalline powder

Solubility: the aqueous solubility of didanosine at 25*C and pH of approximately 6 is 27.3 mg / ml. didanosine is unstable in acidic solutions. For example, at pH <3 and 37*C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes.

10. Drug Interaction

Refer the corresponding product monographs of other drug in the regimen for drug interaction information. The most conservative recommendation among all the components of the regimens should be followed.

The concomitant use of didanosine and other drugs may results in known or potentially significant drug interactions, some of which may lead to loss of therapeutics effect of didanosine and possible development of resistance, dosage adjustments of concomitant medications, or clinically significant adverse reactions from greater exposures of concomitant drugs.

11. Drug contraindication with didanosine:

Table 3: Didanosine is contraindicated with the co-administration of certain drug

Drug Class/Drug Name	Effects on Exposure	Clinical comment
Antivirals		
Ribavirin	Didanosine ↑	Co administration of didanosine and ribavirin is contraindicated due to increases in didanosine associated toxicities.
Antiretrovirals		
Stavudine	Didanosine ↔	Co administration of didanosine and stavudine is contraindicated due to increases in didanosine associated toxicities.
Antigout agents		
Allopurinol	didanosine ↑	Co administration of didanosine and allopurinol is contraindicated due to increases in didanosine toxicities.

a) allpurinol has been shown to increase the plasma exposures of ddi and as a consequence,increase the risk of pancreatitis. When allopurinol is given with didanosine,the

plasma exposure (AUC) of didanosine was increased 4-fold in renally impaired patients (CLcr=15 and 18 ml/min) and 2-fold in healthy subject. the coadministration of didanosine and allopurinol is contraindication due to increases in didanosine associated toxicities

b) the administration of didanosine with stavudine is associate with fatal events of lactic acidosis,liver abnormalities, pancreatitis and peripheral neuropathy and coadministration with didanosine is contraindicated both didanosine and stavudine have been associated with a high risk of mitochondrial toxicity.contraindication and warnings and precautions.

C) ribavirin has been shown to increase the plasma exposures of ddI and, as a consequence, increase the risk of pancreatitis. Based on in vitro data, ribavirin increases the intracellular triphosphate levels of didanosine. Fatal hepatic failure,as well as peripheral neuropathy, pancreatitis and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving didanosine and ribavirin with or without stavudine.the coadministration of didanosine and ribavirin is contraindicated due to increases in didanosine associated toxicities

Carcinogenesis and mutagenesis

Lifetime carcinogenicity studies were conducted in mice and rats for 22 and 24 months, respectively. In the mouse study, initial doses of 120, 800, and 1200 mg/kg/day for each sex were lowered after 8 months to 120,210, and 210 mg/kg/day for females and 120,300 and 600 mg/kg/day for males. The two higher doses exceeded the maximally tolerated dose in females and the high dose exceeded the maximally tolerated dose in females and the high dose exceeded the maximally tolerated dose in males. The low dose in females represented 0.68-fold maximum human exposure and the intermediate dose in males represented 1.7-fold maximum human exposure based on relative AUC comparisons. In the rat study, initial doses were 100, 250, and 1000mg/kg/day, and the high dose was lowered to 500mg/kg/day after 18 months. The upper dose in male and female rats represented 3-fold maximum human exposure. Didanosine induced no significant increases in neoplastic lesions in mice or rats at maximally tolerated doses.

Didanosine was positive in the following genetic toxicology assays: 1) the Escherichia coli tester strain wp2 uvr A bacterial mutagenicity assay, 2) the L5178Y/TK+/- mouse lymphoma mammalian cell gene mutation assay, 3) the in vitro chromosomal aberrations assay in cultured human peripheral lymphocytes; 4) the in vitro chromosomal aberrations

assay in Chinese hamster lung cells; and 5) the BALB/c 3T3 in vitro transformations assay. No evidence of mutagenicity was observed in and ames salmonella bacterial mutagenicity assay or in rat and mouse in vivo micronucleus assays.

12. Drug – food interaction

Ingestion of didanosine EC with food significantly reduces the amount of didanosine absorbed (see Action and clinical pharmacology).

Didanosine should be administrated at least 1.5 hours before or 2 hours after eating (see dosage and administration).

Drug –herb interactions

Interactions with herbal products have not been estabilished.

Drug –laboratory test interactions

Interactions with laboratory btests have not been estabilished.

13. ADME (Absorption, Distribution, Excretion, Metabolism)

Absorption:

The didanosine contained within the beadlets of didanosine EC capsules is protected against gastric acid by an enteric coating,which dissolve when the beadlets empty into the higher pH of the small intestine,the site of drug absorption. The time to reach Cmax (Tmax) is 2 hours following administration of the EC capsules.

Effect of food on absorption of didanosine:

Didanosine Ec should be taken on an empty stomach, at least 1.5 hours before or 2 hours after a meal. Compared to the fasting condition, the administration of didanosine Ec capsules with a high-fat meal significantly decreased the didanosine Cmax (46%) and AUC (19%). Co administering didanosine EC capsules with light meal, 1.5 hours before a light meal, or 2 hours after a light meal resulted in significant decrease in both Cmax (22%, 15%, and 15% respectively) and AUC of didanosine (27%, 24%, and 10% respectively) compared to the fasting condition. Administration of didanosine Ec capsules 1, 5, 2 or 3 hours before a light meal resulted in equivalent Cmax and AUC values compared to those obtained under fasting

conditions. Compared to the intact capsule administered in fasting conditions, co administration of didanosine EC beadles with yogurt or apple sauce resulted in a significant decrease in Cmax (30% and 24% respectively) and AUC of didanosine (20% and 18% respectively).

Distribution:

Because in vitro human plasma protein binding is less than 5% with didanosine, drug interaction involving binding site displacement are not anticipated.

Excretion:

The intracellular half life of ddATP, the metabolite presumed to be responsible for the antiretroviral activity of didanosine, is reported to be 8 to 24 hours in vitro. The half life of intracellular ddATP in vivo has not been measured.

Metabolism of didanosine (ddI) by erythrocytes:

Danosine is a nucleoside analogue wih potent inhibitory effect against the human immunodeficiency virus (HIV). Its is converted within target cells to its active form ddA-triphosphate , which is thought to act as a chain terminator and inhibitor of reverse transcriptase. In addition to the intracellular formation of ddA-TP, didanosine may be broken down to hypoxanthine and uric acid by the enzymes Purine nucleoside phosphorylated (PNP) and xanthine oxidase. As PNP is found in relatively high concentrations in human erythrocytes. We have previously investigated the metabolism of ddI in vitro using human blood when incubated with whole blood at 37*C, ddI was extensively metabolized, principally to hypoxanthine (50% formed at 6 h). Metabolism of hypoxanthine occurred within red blood cells and was temperature dependent. Following this in vitro study we suggested that the metabolic degradation of ddI within red blood cells may have implication for the interrelation of the results of ddI pharmacokinetic studies.

We have now investigated this possibility in a pharmacokinetic study of three men who were infected with HIV and who took ddI (250mg twice daily) following zidovudine intolerance. Approval for the study was granted by the local ethics committee and all patients provided written informed consent. Each patients attended for study on two occasions separated by at least 2 weeks. After an overnight fast and following the insertion an

intravenous cannula, blood samples were taken at 15 min intervals for 2 h,half hourly for another 2 h, and at 5and 6 h after didanosine 250 mg.

Each blood sample was divided into two aliquots, one was centrifuged immediately (3000 rev min for 10 min) and the other was left at room temperature and centrifuged when the and the other was left at room temperature and centrifuged when the pharmacokinetic study was completed. The separated plasma samples were exposed to a temperature of 58*C for 30 min to inactivate the human immunodeficiency virus and then analysed for ddI for using a commercial radioimmunoassay (sigma, London). Plasma samples were initially diluted 1:100 with blank plasma. The assay has a limit of detection of less than 1 nm. The interassay coefficient of variations was less than 10% at a concentration of 10 nm.

14. Adverse reactions

The most common adverse events with didanosine are diarrhea,nausea, vomiting,abdominal pain,fever, headache,and rash.peripheral neuropathy occurred in 21-26% of participants in key didanosine trials. A serious toxicity of didanosine is pancreatitis which may be fatal other important toxicitites include lactic acidosis/severe hepatomegaly with steatosis; retinal changes and optic neuritis; and peripheral neuropathy.

When didanosine is used combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when didanosine is used alone. Thus,patients treated with didanosine in combination with stavudine, with or without hydroxyurea,may be at increased risk for pancreatitis, which may be fatal, and hepatotoxicity. Patients treated with didanosine in combination with stavudine may also be at increased risk for peripheral neuropathy.

Adults: selected clinical adverse events that occurred in adult patients in clinical studies with didanosine are provided in table 4

Clinical trial adverse drug reaction

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction

information from clinical trials is useful for identifying drug related adverse events and for approximating rates.

Table 4: Selected clinical adverse events from monotherapy studies

Adverse events	Didanosine N=197	Zidovudine N=212	Didanosine N=298	Zidovudine N=304
Diarrhea	19	15	28	21
Peripheral neurologic	17	14	20	12
Rash /pruritus	7	8	9	5
Abdominal pain	13	8	7	8
pancreatitis	7	3	6	2

Pancreatitis

In clinical trials using a buffered formulation of didanosine, pancreatitis resulting in death was observed in one patient who received didanosine plus stavudine plus nelfinavir one patients who received didanosine plus stavudine plus indinavir, and 2 of 68 patients who received didanosine plus stavudine plus indinavir plus hydroxyurea. In an early access program, pancreatitis resulting in death was observed in one patients who received didanosine plus stavudine plus hydroxyurea plus ritonavir plus indinavir plus efavirenz.

The frequency of pancreatitis is dose related. In phase 3 studies with buffered formulations of didanosine, incidence ranged from 1% to 10% with doses higher than are currently recommended and 1% to 7% with recommended dose.

Post-market adverse drug events:

The following events have been identified during post approval use of didanosine buffered formulations. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to

their seriousness, frequency of reporting, casual connection to didanosine, or a combination of these factors.

Body as a whole: abdominal pain, alopecia, anaphylactoid reaction, asthemia, chills/fever, and pain.

Digestive disorders: anorexia, dyspepsia, and flatulence.

Endocrine disorders: lipoatrophy, endocrine metabolism lipoatrophy.

Exocrine gland disorders: pancreatitis (including fatal cause), sialoadenitis, parotid gland enlargement, dry mouth, dry eyes.

15. Storage and stability:

Didanosine EC beadlets capsules are available for oral administration in strength of 400,250,200 and 125 mg of didanosine.

Inactive ingredients in the beadlets include carboxy methyl cellulose sodium, diethyl phthalate, methacrylic acid polymer, sodium hydroxide, sodium starch glycolate and talc.

Inactive ingredients in the capsule shell include; gelatin, sodium lauryl sulfate and titanium dioxide. Capsules are imprinted with edible ink.

Didanosine EC 125 mg capsules are white, opaque capsules with tan markings Bottles of 30 capsules.

Didanosine EC 200 mg capsules are white, opaque capsules with green markings Bottles of 30 capsules.

Dianosine EC 250 mg capsules are white, opaque capsules with blue markings Bottles of 30 capsules.

Didanosine EC 400 mg capsules are white, opaque capsules with red markings Bottles of 30 capsules.

CONCLUSION:

Didanosine inhibits the in vitro replication of HIVin human primary cells culture and estabilished cells lines. The active antiviral metabolites, dideoxyadenosine-triphosphate

(ddATP), are formed in several steps by phosphorylation of didanosine by cellular enzymes. Inhibitions of HIVreverse transcriptase by ddATP is through competition with endogenous deoxyadenosine triphosphate for binding to the active site of the enzyme. In addition, ddATP is a substrate for reverse transcriptase and is incorporated into the growing DNA chain. binding of didanosine to plasma proteins in vitro was low less than 5%. Based on data from in vitro and animal studies, it is presumed that the metabolism of didanosine in man occurs by the same pathways responsible for the elimination of endogenous purines.

REFERENCE:

1. Hirch Ms. Chemotherapy of human immunodeficiency virus infections :current practice and future prospects, J infect Dis 1990; 161; 845-857.
2. Cooney DA, ahluwalia G, Mitsuya H et al. initial studies on the cellular pharmacology of 2',3' –dideoxyinosine, an inhibitor of HIT V-III infectivity. Biochem pharmac 1987; 36: 1765-1768.
3. Hartman NR,Yarchon R, pluda JM et al. pharmacokinetics of 2',3' dideoxyinosine in patients with severe human immunodeficiency virus infection clin pharmacy ther 1990; 47: 647-654.
4. Simmonds AA, Fairbanks LD, Morris GS, Webster DR, Harley EH. Altered erythrocytes nucleotide patterns are characteristics of inherited disorders of purine or pyrimidine metabolism. Clin chim acta 1998; 171 : 197-210
5. Back DJ ormesher S, TJIa JF, Macleod R. metabolism of 2'-3' –deoxyinosine in human blood. BR J clin pharmacy 1992;23;189-193
6. Mc dougal JS, Martin Ls, Cort SP, Mozen M, heldebrant CM, Evatt BL. Thermal inactivation of the acquired immunodeficiency syndrome virus, human T lymphotropic virus III/lymphadenopathy associated virus, with special reference to antihaemophilic factor. J clin invest, 1985; 76: 875-877.
7. Bach MC, clinical response to dideoxyinosine in patients with HIVinfection resistant to zidovudine New engl j med 323:275,1990.
8. Cooley TP, kunches LM, saunders CA, et al . once daily administration of 2'-3'-dideoxyyinosine (ddI) in patients with acquired immunodeficiency syndrome or AIDS related complex. New eng j med 322:1340:1345

9. Hartman NR, Yarchon R, pluda JM, et al. pharmacokinetics of 2'-3'-dideoxyadenosine and 2',3' – Dideoxyinosine in patient with severe human immunodeficiency virus infection. Clin pharm Ther 47:647:654, 1990
10. Singlas E, et al. Didanosine pharmacokinetics in patient with normal and impaired renal function. Antimicrob agents chemother 36:1519-1524,1992.
11. Johnson MA, Ahluwalia G, Connelly MC, et al. metabolic pathway for the activation of antiretroviral agent 2-3 dideoxyadinosine in human lymphoid cells J. Biol chem. 263:15354-15357, 1988
12. Nunez M, Lana R, Mendoza JL, Martin caronera L, Soriano V risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. J. acquir immune defic syndr: 2001 :426-431
13. Podzamczer D, Ferrer E, et al. early virologic failure with a combination of tenofovir, didanosine and efavirenz antiviral therapy 10: 171-177-2005.
14. Yarchoan R, mitsuya h, Thomas RV, et al. in vitro activity against HIVand favorable Toxicity profile of 2-3- dideoxyinosine science 245:412-415, 1989.
15. Bland JM, Altman DG, Statistical method for assessing agreements between two methods of clinical measurement. Lancet 1986: I- 307-310.