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"Comparitive Study of Prevalence of Hyperlactatemia in HIV / AIDS Patients receiving two Antiretroviral Regimens (AZT+3TC+NVP Vs d4T+3TC+NVP)"

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Abstract: *Hyperlactatemia is one of the important metabolic abnormalities in HIV infected patients. The prevalence of hyperlactatemia in natural course of HIV disease is approximately about 2%. Aim of this study is to estimate the prevalence of hyperlactatemia in HIV patients receiving two antiretroviral regimens, advocated by NACO by monitoring the plasma lactate levels. This study was taken up with 200 patients to compare the prevalence of hyperlactatemia of two commonly used NACO regimens (zidovudine+ lamivudine+ nevirapine) Vs (stavudine+ lamivudine+ nevirapine). The plasma lactate levels were estimated between 9th to 18thmonth after initiation of antiretroviral therapy. The comparision and correlation between plasma lactate levels, CD4 counts and haemoglobin percentage in both regimens was done. There was statistically significant rise in the plasma lactate levels (p<0.05) in both regimens. The increase in plasma lactate levels is more in stavudine group compared to zidovudine group. There was low degree of positive correlation between plasma lactate and haemoglobin in Stavudine group but negative correlation between Plasma lactate and CD4 counts in both groups. More focus is needed on Pharmacovigilance of NRTIs induced hyperlactatemia especially Stavudine.*
Key words: *Hyperlactatemia, Stavudine, Zidovudine, HIV, NACO regimen.*

I. Introduction

Acquired immune deficiency syndrome (AIDS) is the most devastating disease complex that mankind has ever faced. It is caused by Human immuno deficiency virus (HIV) which belongs to the family Retroviridae and subfamily lentivirinae, shows great genetic diversity and breaks down human immune system leaving victim to vulnerable life threatening opportunistic infections, neurological disorders or unusual malignancies. [1] As per current US Centers for Disease Control and prevention (CDC) classification system for HIV infected adolescents and adults, AIDS patient is defined as 'any HIV infected individual with CD4+ T cell count of <200/ microlitre regardless of the presence of symptoms or opportunistic diseases'. [2]

HIV affects all the systems of the body and produce various metabolic abnormalities like lipodystrophy, hyperlactatemia, lactic acidosis, osteopenia and dyslipidemia. These manifestations are common throughout the course of HIV infection and may be the direct result of HIV, secondary infections and neoplasms or side effects of drug therapy, superimposed on individual characteristics such as genetic predisposition, gender and age. [3] Initiation of Highly Active Antiretroviral therapy (HAART) will lead to the reversal of most metabolic complications which are the direct result of HIV infection. HAART comprises regimens which consist of combination of 3-4 antiretroviral agents. A typical HAART combination include two nucleoside reverse transcriptase inhibitors(NRTI) with either a non nucleoside reverse transcriptase inhibitor(NNRTI) or one or two protease inhibitors(PI). This combination therapy reduces viral replication to lowest possible level and decreases chance of drug resistance. The introduction of HAART has revolutionized the treatment of HIV infected persons in the last decade.

National AIDS Control Organisation (NACO), India, recommends these regimens which achieve maximal suppression of HIV replication over a prolonged period of time. As per NACO guidelines, Zidovudine is one of the NRTIs incorporated in Regimen I and regimen II and Stavudine is one of the NRTIs incorporated in Regimen Ia and Regimen IIa.

Hyperlactatemia is one of the important metabolic abnormalities in HIV infected patients. The normal blood lactate concentration in unstressed patient is 1±0.5mmol/L. [4] Patient with critical illness can be considered to have normal concentration of lactate less than 2 mmol/L. If plasma lactate is more than 2mmol/L it is called as hyperlactatemia. It can be classified as mild to moderate with plasma lactate levels between 2-5mmol/L and more than 5mmol/L, as severe hyperlactatemia. [5] When severe hyperlactatemia is associated with decrease in blood pH it is called as lactic acidosis. Alteration in the plasma lactic acid level although asymptomatic in majority of cases, is a novel and emerging complication of HIV disease and its treatment. [6]

Although introduction of HAART drastically reduced the AIDS related mortality and morbidity, much attention needs to be focussed on Stavudine induced metabolic toxicities especially hyperlactatemia and lactic acidosis. The severity may range from asymptomatic raised lactic acid level to fulminant lactic acidosis with multiorgan failure that leads to death.[7] Incidence of hyperlactatemia , associated with antiretroviral therapy was first described in 1993. [8] Lactic acidosis is believed to result from the over production of lactic acid as consequence of NRTI induced mitochondrial toxicity. The selective toxicity is inhibition of mitochondrialt DNA (mt DNA) polymerase γ, the enzyme responsible for replication of mt DNA. Diminished polymerase activity decreases the amount of mt DNA and its gene products, which include protein involved in oxidative phosphorylation resulting in impaired aerobic metabolism and hyperlactatemia.[9] A critical aspect of lactic acidosis is its unpredictability, sometimes may not be heralded by increased lactate level before the development of fulminant syndrome. It could be due to triggering factors like sepsis, hypoxaemia, anemia, thyrotoxicosis and exogenous intoxicants, etc. [10,11]

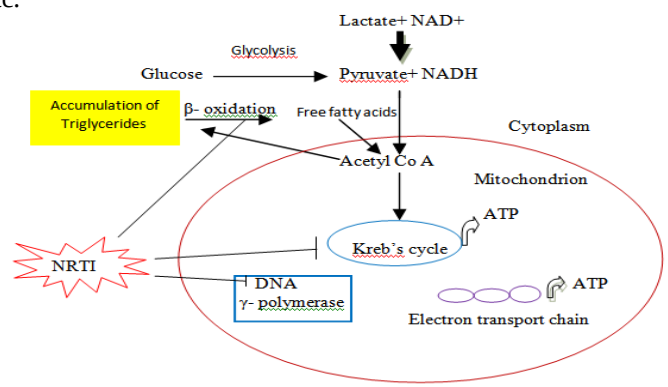

Fig.1: Mechanisms of nucleoside reverse transcriptase inhibitor (NRTI)-induced lactic acidosis.

Hyperlactatemia with no or mild symptoms is detected in 8%-21% of patients receiving atleast one NRTI versus 1-2% of patients receiving no antiretroviral therapy. Not all NRTIs precipitate hyperlactatemia equally. A rank order with Zalcitabine more likely to cause hyperlactatemia than Didanosine > Stavudine > Zidovudine > Abacavir =Lamivudine = Tenofovir. The combination of Stavudine with Didanosine is associated with markedly increased risk of lactic acidosis and hepatic steatosis[12]. According to NACO guidelines, stavudine containing Ia and IIa regimens are advocated when the haemoglobin percentage is low (< 8gm%). In resource poor areas, fixed dose combination of Stavudine plus Lamivudine and Nevirapine is most widely used regimen as it is recommended by WHO. Stavudine is substantially less toxic to the bone marrow precursors than Zidovudine. It is an important component in antiretroviral regimens due to potent and durable suppression of viremia, sustained increase in CD4+ cell counts, when combined with other nucleoside analogue plus NNRTI or PI. A unique role for Stavudine is its use in patients who harbor virus with K65R mutation and are unable to tolerate Zidovudine. When Stavudine based therapy is widely used, symptomatic hyperlactatemia is being increasingly recognized. Clinical efficacy of Stavudine is extremely good, but mitochondrial and long term toxicities remain a concern.

In this scenario, this study was taken up to compare the prevalence of hyperlactatemia of two commonly used NACO regimens (zidovudine +lamivudine +nevirapine) Vs (stavudine +lamivudine + nevirapine). And also to compare and correlate the relationship between plasma lactate levels, CD4 count and haemoglobin percentage in both regimens along with observing the clinical features in hyperlactatemia patients.

II. Materials& Methods

This was a cross sectional and observational study. The protocol was approved by the institutional ethics committee. Informed written consent was obtained from all the patients enrolled in this study in local language. This study was carried out at highly populated ART Centre, Siddhartha Medical College / Govt. General Hospital, Vijayawada functioning under NACO guidelines. The study was carried in HIV seropositive patients who received antiretroviral treatment between the period of 9th to 18th months. [13] A total number of 200 patients were enrolled in the study. These patients were divided into two groups. One group (hemoglobin> 8gm/dl) received Tab. Zidovudine + Tab. Lamivudine+ Tab. Nevirapine and other group (with heamoglobin< 8gm/dl) received Tab. Stavudine+ Tab. Lamivudine+ Tab. Nevirapine as per guidelines of NACO. In both groups, total period of the study was 6 months.

1. Inclusion Criteria

1.1. Patients who were declared as HIV-I positive as per NACO guidelines in the Department of Microbiology, Siddhartha Medical College, Vijayawada, Andhra Pradesh, India.

1.2. Both male and female patients between the age group of 15 and 60 years.
1.3. Patients who were on highly active antiretroviral therapy (HAART) receiving I and Ia NACO regimens

2. Exclusion Criteria
2.1. Patients below 15 years of age group
2.2. Pregnant and lactating women.
2.3. Patients receiving drugs like ethanol, nalidixic acid, isoniazid, metformin, ethylene glycol, niacin, theophylline, paraldehyde etc.
2.4. Patients who have undergone major abdominal surgeries.
2.5. Patients suffering from tuberculosis, diabetes mellitus, malignancies like lymphoma and kaposis sarcoma during study period.
2.6. Patients with history of epilepsy.
2.7. History of strenous muscle exercises within 24 hours of enrollment into the study.

3. Drugs
3.1. **Zidovudine group**
Each tablet contains Zidovudine 300 mg
Lamivudine 150 mg
Nevirapine 200mg
} twice daily after food
Name of the pharmaceutical company – CIPLA
Trade Name - DUOVIR –N
3.2 **Stavudine group**
Each tablet contains Stavudine 30mg
Lamivudine150mg
Nevirapine200mg
} twice daily after food
Name of the pharmaceutical company – CIPLA
Trade Name - -TRIOMUNE

4. Measurement of cd4 counts CD4 cell count was measured with Becton & Dicknson flow Cytometer, model BD Fluorescent Activated cell stores (FACS), caliber machine, which was done at Department of Microbiology, Siddhartha Medical College, Vijayawada.
5. Haemoglobin estimation Hemoglobin percentage was estimated by Sahli's haemoglobinometer.
6. Measurement of plasma lactate levels Plasma lactate estimation was done with K LAB KIT of Company Chemelex, S.A.Pol .Ind.Can.Castelles C/Industries 113, Nanj 08420 Canovelles, BARCELONA by LO-POD, enzymatic colorimetric method.

Heparinised plasma, free of hemolysis was prepared by drawing 2 ml of blood without using tourniquet and without clinching fist into the heparinised tubes. Immediately the sample was placed in a refrigerator, centrifused and plasma was separated within 15 minutes to prevent blood cells to metabolise glucose to lactic acid. Lactic acid was estimated in assay conditions of wave length 505nm, cuvette 1 cm light path and temperature 37^0. 25µl of plasma was mixed with Reagent I and Reagent II mixture. This was incubated for 10 minutes in room temperature and the observation was read in digital calorimeter. Adsorbance of sample was read and caliber against blank.
Calculation:

$$Lactate\ \left(\frac{mg}{dl}\right) = \frac{A\ sample}{B\ standard}\ x\ 10\ (calibrator\ )$$

Conversion factor = mg/dl x 0.111 = mmo1/L
6.1. Clinical Significance: Lactate is a metabolic intermediary, originated in the lactic fermentation from glucose which accumulated during high intensity exercises as a result of associated increase in glycolytic activity. The formation of ATP is linked to generation of lactate. Sensitivity of test is = 1 mg/dl = 0.01A.
7. Clinical features were observed in all the patients with hyperlactatemia for abdominal pain, fatigue, vomiting, dyspnoea and weight loss
8. Statistical analysis:
8.1. 'Z' test was done for the plasma lactate parameter in both Zidovudine and Stavudine group.
8.2. Correlation coefficient test done for Plasma lactate and Hemoglobin percentage and for Plasma lactate and CD4 counts in both groups.

IV. Results

A total of 200 patients were enrolled in the study. Out of 200 patients, 37.5% (n=75) were aged 20-30 years, 50% (n=100) of 31-40 years age, 11.5% (n=23) 41-50 years and 1% (n=2) of 51-60 years old. Maximum number of patients were in the age group of 31-40 years.

Equal number of males and females were included to eliminate the influence of gender on the study. 50% (n=100) patients were males and 50% (n=100) patients were females.

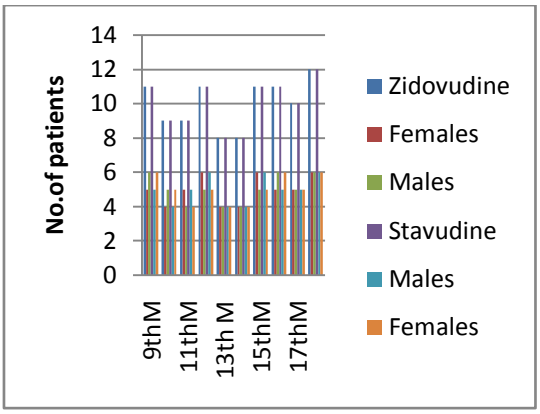

Fig no.2: Distribution of cases according to sex, month and regimen wise.

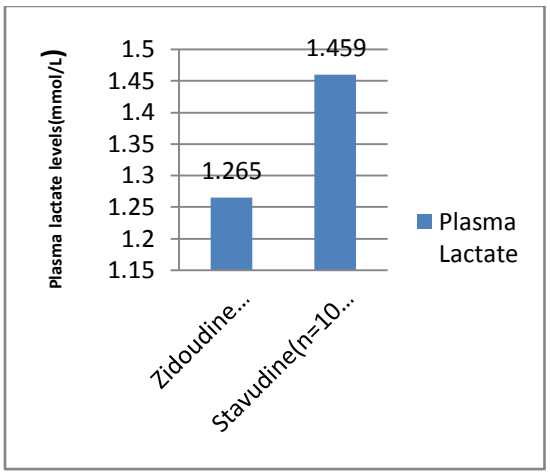

Fig no.3: Mean Plasma Lactate levels in both groups

There was statistically significant rise in the plasma lactate level ($p<0.05$) in both regimens. The increase in plasma lactate level is more in Stavudine group compared to Zidovudine group.

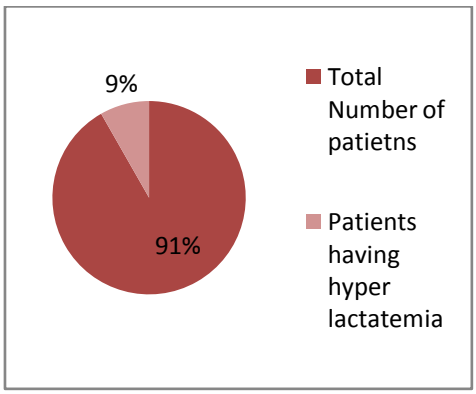

Fig no. 4: No. of patients having hyperlactatemia in Zidovudine group

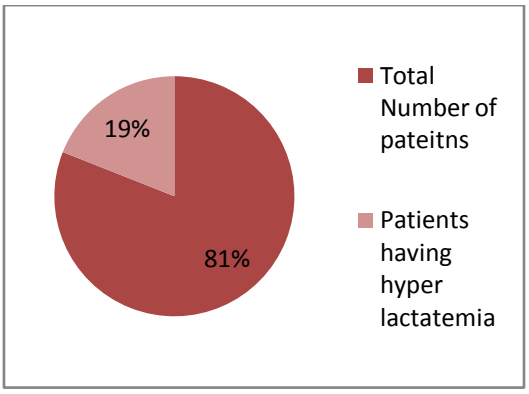

Fig no. 5: No. of patients with hyperlactatemia in Stavudine group

There was a low degree of negative correlation between plasma lactate level and hemoglobin percentage and correlation coefficient 'r' value is -0.181, which is not statistically significant in the Zidovudine group. There was a low degree of negative correlation between plasma lactate level and CD4 count and correlation coefficient 'r'value is -0.115, which is not statistically significant in the same group as in Table no.1.

Table no. 1: Correlation between Plasma lactate and Hb level and between Plasma lactate and CD4 count in Zidovudine group

S.no.	Variable	Zidovudine n=100	Correlation coefficient'r'	Interpretation	Statistical significance
1.	Plasma Lactate(Mean)	1.265	-0.181	Low degree of negative correlation	Not significant(p<0.3)
	Haemoglobin %	9.023			
2.	Plasma Lactate(Mean)	1.265	-0.115	Low degree of negative correlation	Not significant(p<0.36)
	CD4 count(Mean)	227.310			

There was a low degree of positive correlation between plasma lactate and hemoglobin percentage and the a low degree of negative correlation between plasma lactate level and CD4 count in Stavudine group as indicated in Table no. 2.

Table no. 2: Correlation between Plasma lactate and Hb level and between Plasma lactate and CD4 count in Stavudine group

S.no.	Variable	Stavudine n=100	Correlation coefficient'r'	Interpretation	Statistical significance
1.	Plasma Lactate(Mean)	1.459	0.034	Low degree of positive correlation	Not significant(p<0.36)
	Haemoglobin %	8.276			
2.	Plasma Lactate(Mean)	1.459	-0.159	Low degree of negative correlation	Not significant(p<0.36)
	CD4 count(Mean)	218.570			

Out of 100 patients in Zidovudine group, 9 patients had hyperlactatemia. Among these 9 patients, 4 patients were male and 5 patients were female. Out of 9 patients with hyperlactatemia, 8 patients were associated with clinical features like nausea, anorexia, abdominal bloating, fatigue, malaise and dyspnoea. Out of 9 patients with hyperlactatemia, 6 (66.6%) patients were associated with anemia .

Out of 100 patients in Stavudine group, 19 patients had hyperlactatemia. Among these 19 patients, 4 patients were male and 5 patients were female. Out of 19 hyperlactatemia patients, 17 patients were associated with clinical features nausea, anorexia, abdominal bloating, fatigue, malaise and dyspnoea and 15 (78.8%) patients were associated with anemia.

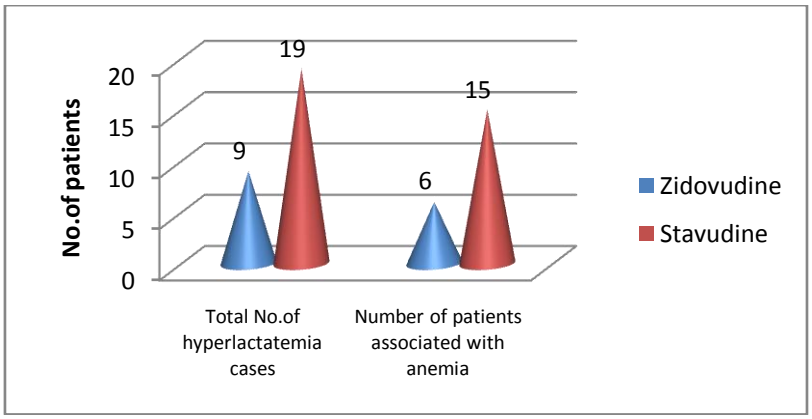

Fig no. 5: Hyperlactatemia associated with anemia.

In Stavudine group, one female patient was associated with severe hyperlactatemia (>5mmol/L) with clinical features like abdominal pain, fatigue, vomiting, dyspnoea and weight loss. Patient was anemic (Hb-7g%) . She was moderately dehydrated and on clinical examination hepato-splenomegaly was present.

V. Discussion

HIV affects all the systems and produces various metabolic abnormalities like lipodystrophy, hyperlactatemia, lactic acidosis, osteopenia and dyslipidemia. Metabolic disorders are very common in advanced HIV disease. Typically, all these are reversible. [3] The median time for developing lactic acidosis on HAART regimens is 9 months (range7-11.6months). [14] Similarly, complete histopathological mitochondrial dysfunction develops after 18 months of initiation of HAART. Hence, this study was done in HIV patients who are on HAART regimens between 9th to 18th months after initiation of treatment.

The results in this study were comparable with a study done by Muthu Sundaram et al., estimated hyperlactatemia as 15.5% in HIV patients who received HAART in their study. [14] Arenas Pinto et al., observed 9-16% of hyperlactatemia in their study. [6] In Swiss cohort study conducted by Boubacker et al., the prevalence of hyperlactatemia was 15.4%. [15] In the present study, the estimated prevalence of hyperlactatemia was 14%, which was comparable with the above studies.

Not all NRTIs precipitate hyperlactatemia equally. A rank order with zalcitabine more likely to cause hyperlactatemia than didanosine > stavudine > zidovudine > abacavir = lamivudine = tenofovir. [12] Stavudine is one of the common drug incorporated in NACO regimens. There is an increase in plasma lactate levels in Stavudine group compared to Zidovudine group according to Rose Mary et al., who revealed in their study that, all the NRTIs do not precipitate hyperlactatemia uniformly. [7] In a cross sectional study conducted by Eric Wool Torton et al., incidence of hyperlactatemia was found to be 1-2% in an year in the Stavudine therapy when compared to 1% in another group of NRTIs. [5] In this study, there was significant increase in prevalence of hyperlactatemia in Stavudine group (19%) when compared to Zidovudine group (9%).

It was noticed that there was a strong association between gender and abnormal lactate level. In a cross sectional study conducted by Muthu Sundaram et al., 74% of men and 83% of women showed hyperlactatemia.[14] In this study, there was increased hyperlactatemia in female patients (5%), compared to male (4%) in Zidovudine group and 13% females compared to 6% male in Stavudine group. With this observation, we can suggest practitioners to monitor female patients' plasma lactate levels.

One female patient (0.5%) was found to have severe hyperlactatemia with symptoms like nausea, abdominal pain, and abdominal bloating. Patient was moderately dehydrated and was associated with anemia and hepato-spleenomegaly. According to David L Blazes et al., there was symptomatic hyperlactatemia estimated in 8-14 /1000 per year. [7] Geofferoy Marceau et al., observed 0.7% patients with symptomatic severe hyperlactatemia. [10] In this study, out of 9 hyperlactatemia patients in Zidovudine group, 8 patients presented with clinical features and out of 19 patients in Stavudine group, 17 patients presented with clinical features. Sometimes, lactic acidosis may not be preceded by hyperlactatemia. This could be due to acute infections, hypoxemia, exogenous intoxicants and other uncontrolled coexisting morbidities. [10]

Muthu Sundaram et al., observed that there was influence of CD4 count on lactatemia, In low counts, there was increase in the incidence of hyperlactatemia. According to Bonnet et al, in their study CD4 count was not predictive for hyperlactatemia. [17] Patric Chariot et al., found that there was no correlation between CD4 count and lactatemia. [18] In the present study, there was a low degree of negative correlation between plasma lactate and CD4 count in both groups.

1. Limitations of the study:

1.1. As HIV/AIDS patients are living longer with ART, the period of observation was not sufficient to assess lactic acid homeostasis disturbances.

1.2. Arterial blood is more reliable for estimation of plasma lactate compared to venous blood. As intra arterial blood drawing procedure is difficult and cumbersome and may prone to produce bleeding, I could not draw the intra arterial blood.

1.3. Continuous monitoring of plasma lactate is more reliable than single estimation to assess lactic acid homeostasis disturbance.

1.4. Complete correlation of clinical features in hyperlactatemia patients was not possible as majority of the studied patients coexisted with anemia, which reflects similar clinical features of hyperlactatemia.

1.5. Lack of facilities to carry out blood gas analysis to detect electrolyte disturbances for sensitive diagnosis of lactic acid homeostasis disturbances.

VI. Summary and Conclusion

As per the NACO guidelines in India, fixed dose combination of AZT + 3TC + NVP and d4 + 3TC + NVP are commonly dispensed drug regimens in ART centres. The same situation exists in other resource poor countries in the world. As a part of National Pharmacovigilance programme, it is our responsibility to detect, assess, understand and to prevent short term and long term adverse effects of the antiretroviral drugs.

It is important to study and understand the extent to which Stavudine associated hyperlactatemia and lactic acidosis is likely to be problematic not only because there is an access to a growing number of regimens that include Stavudine, a relevant fact, when Stavudine related toxicities are still of concern. In the case of symptomatic hyperlactatemia associated with Stavudine use, restarting HAART with Zidovudine seemed to be safe and effective for patients with limited nucleoside reverse transcriptase inhibitor alternatives. Measurement of lactate, under standard conditions may be useful in optimizing the management of HIV positive persons on antiretroviral therapy[38].

Accordingly, this study focused on identified hyperlactatemia patients with their plasma lactate levels were informed to the concerned medical officers/coordinators of ART centre, Siddhartha Medical College, Government General Hosptial, Vijayawada for regular monitoring of plasma lactate level for further follow up and advice.

Unfortunately, majority of ART centres functioning under NACO guidelines have lack of diagnostic facilities to estimate the plasma lactate levels periodically. Hence, all diagnostic facilities at ART centres should be facilitated for the estimation of plasma lactate levels.

NACO and Government of India are concentrating mainly on the provision of antiretroviral drugs to the HIV/AIDS patients. But, there is a less focus on the management of malnutrition, opportunistic infections and coexisting morbidities and Pharmacovigilance on antiretroviral drugs.

Infact, the incidence of adverse drug reactions including metabolic abnormalities like hyperlactatemia is increased in HIV /AIDS patients when malnutrition, opportunistic infections, and other co-existing morbidities are not managed properly.

In addition, there is a need for NACO to incorporate better antiretroviral drugs in place of existing drugs to increase efficacy and to decrease adverse drug reactions which in turn increase the patient compliance and better prognosis.

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