A COMPREHENSIVE STUDY ON THE ZIDOVUDINE INDUCED ANEMIA IN AIDS PATIENTS

A dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI - 600 032

In partial fulfilment of the requirements for the award of degree of

MASTER OF PHARMACY
IN
PHARMACY PRACTICE

Submitted by
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Under the guidance of

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April-2014

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"A comprehensive study on the zidovudine induced anemia in AIDS patients"** submitted by **C.Sam Pushparaj**, **Reg. No: 261240205** to "**The Tamil Nadu Dr. M.G.R. Medical University**", Chennai, in partial fulfillment for the award of Degree of **Master of Pharmacy** in **Pharmacy Practice** was evaluated by us during the examination held on ……

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Date:

DECLARATION

I do here by declared that the dissertation entitled **"A comprehensive study on the zidovudine induced anemia in AIDS patients"** submitted to "**The Tamil Nadu Dr. M.G.R Medical University"**, Chennai, for the partial fulfillment of the degree of **Master of Pharmacy** in **Pharmacy Practice,** is a bonafide research work has been carried out by me during the academic year 2013-2014, under the guidance and supervision of **Dr.S.K.Senthil kumar, M.pharm.,Ph.D** Professor, Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy , Kumarapalayam .

I further declare that, this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam **C.SAMPUSHPARAJ**

Date: **Reg.no.261240205**

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Dedication

I dedicate this work to the people in my life that I appreciate and love more than words can say:
Lord Jesus, my parents and my friends for their unconditional love, sacrifices, encouragements, supports and "patience".

ACKNOWLEDGEMENTS

I express my sincere thanks to my guide **Dr.S.K.Senthil Kumar M.Pharm.,Ph.D** Professor ,Department of Pharmacy Practice, for suggesting solution to problems faced by me and providing indispensable guidance, tremendous encouragement at each and every step of this dissertation work. Without his critical advice and deep-rooted knowledge, this work would not have been a reality.

I am proud to dedicate my deep sense of gratitude to the founder, (Late) Thiru **J.K.K. Nattraja Chettiar,** providing us the historical institution to study.

My sincere thanks and respectful regards to our reverent Chairperson **Smt. N. Sendamaraai, B.Com.,** Managing Director **Mr. S. Ohm Sharravana, B.Com., LLB.,** and Executive Director **Mr. S. Ohm Singarravel, B.E., M.S.,** J.K.K. Nattraja Educational Institutions, Kumarapalayam for their blessings, encouragement and support at all times.

It is most pleasant duty to thank our beloved Principal **Dr. R. SambathKumar, M.Pharm., Ph.D.,** J.K.K.Nattraja College of Pharmacy, Kumarapalayam for ensuring all the facilities were made available to me for the smooth running of this project.

My sincere thanks to **Mr**. **N. Venkateswaramurthy, M.Pharm.** Professor and Head, Department of Pharmacy Practice. **Mrs. K. Krishna Veni, M.Pharm.** Lecturer, Department of Pharmacy Practice, **Mrs. Kavitha, M.Pharm.** Lecturer, Department of Pharmacy Practice, **Mr. kameswaran, M.Pharm.** Lecturer, Department of Pharmacy Practice, and **Dr. K. Sattanathan, M.Pharm., Ph.D.,** Associate professor, Department of pharmacy practice, for their help during my project.

I greatly acknowledge the help rendered by **Mrs. K. Rani,** Office Superintendent, **Miss. Prabha, Mrs. V. Gandhimathi, M.A., M.L.I.S.,** Librarian, and **Mrs. S. Jayakala, B.A., B.L.I.S.,** Asst. Librarian for their co-operation.

"Friends are in need are friends indeed", I am really thankful and grateful to beloved friends **R.Nithya, A.Sivakumar, Sumitha, N.Malaravan, Syed Hussain Asaf** for their constant encouragement and moral support throughout my course and stay.

I express my whole-hearted and sincere thanks to **Dr.Ajin** and **Dr.Sabila** for the complete guidance for the successful completion of the project & without whose contribution this would not have been possible.

I owe my thanks to all the technical and non-technical staff members of the institute for their precious assistance and help.

Last, but nevertheless, I am thankful to my lovable parents and all my friends for their co-operation, encouragement and help extended to me throughout my project work.

C.SAMPUSHPARAJ

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LIST OF ABBREVIATIONS

1	AIDS	Acquired immune deficiency syndrome
2	HIV	Human immuno deficiency virus
3	NRTI s	Nucleoside reverse transcriptase inhibitors
4	ARV	Anti-retroviral
5	ZDV	Zidovudine
6	d4T	Stavudine
7	HAART	Highly active antiretroviral therapy
8	DNA	Deoxy ribonucleic acid
9	RNA	Ribonucleic acid
10	AZT	Azidothymidine
11	TB	Tuberculosis
12	PRCA	Pure red cell aplasia
13	NVP	Nevirapine
14	EFV	Efavirenz
15	ELISA	Enzyme linked immuno sorbent assay
16	RBC	Red blood cells
17	WBC	White blood cells
18	ESR	Erythrocyte sedimentation rate
19	SGOT	Serum glutamic oxaloacetic transaminase
20	SGPT	Serum glutamic pyruvic transaminase
21	Hb	Hemoglobin
22	PLHA	Patient living with HIV-AIDS
23	ZLN	Zidovudine, Lamivudine, Nevirapine

24	SLN	Stavudine, Lamivudine, Nevirapine
25	ZLE	Zidovudine, Lamivudine, Efavirenz
26	SLE	Stavudine, Lamivudine, Efavirenz
27	TLN	Tenofovir, Lamivudine, Nevirapine

1. INTRODUCTION

AIDS is a life threatening disease caused by HIV (human immunodeficiency virus).HIV makes it difficult for the body to fight off infections. The high prevalence and mortality of HIV/AIDS led to a revolution in the care of patients with HIV/AIDS[1].

PREVALENCE OF AIDS [2]

- HIV disease continues to be a serious health issue for parts of the world.

- About 34.2 million people are living with HIV around the world. In 2010, there were about 1.8 million deaths in persons with AIDS, and nearly 30 million people with AIDS have died worldwide since the epidemic began.

- In 2012, there were 35.3 million [32.2 million–38.8 million] people living with HIV. 1.6 million [1.4 million–1.9 million] people died from AIDS-related cause worldwide.

- India has 2.4 million HIV positive people. It's estimated that out of these 61% are male, 39% are female and 3.5% are children.

TABLE 1: Prevalence of HIV-AIDS in the world

	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
(in millions)								
People living with HIV	32.5	32.8	33.2	33.5	34	34.4	34.9	35.3
New HIV infections (total)	2.9	2.8	2.7	2.6	2.6	2.5	2.5	2.3
New HIV infections (adults)	2.3	2.3	2.2	2.2	2.2	2.2	2.2	2.0
New HIV infections (children)	540000	520000	480000	450000	400000	360000	310000	260000
AIDS related deaths	2.3	2.3	2.2	2.1	2.0	1.9	1.8	1.6
People accessing treatment	1.3	2.0	2.9	4.1	5.3	6.6	8.1	9.7

COMPLICATIONS OF AIDS

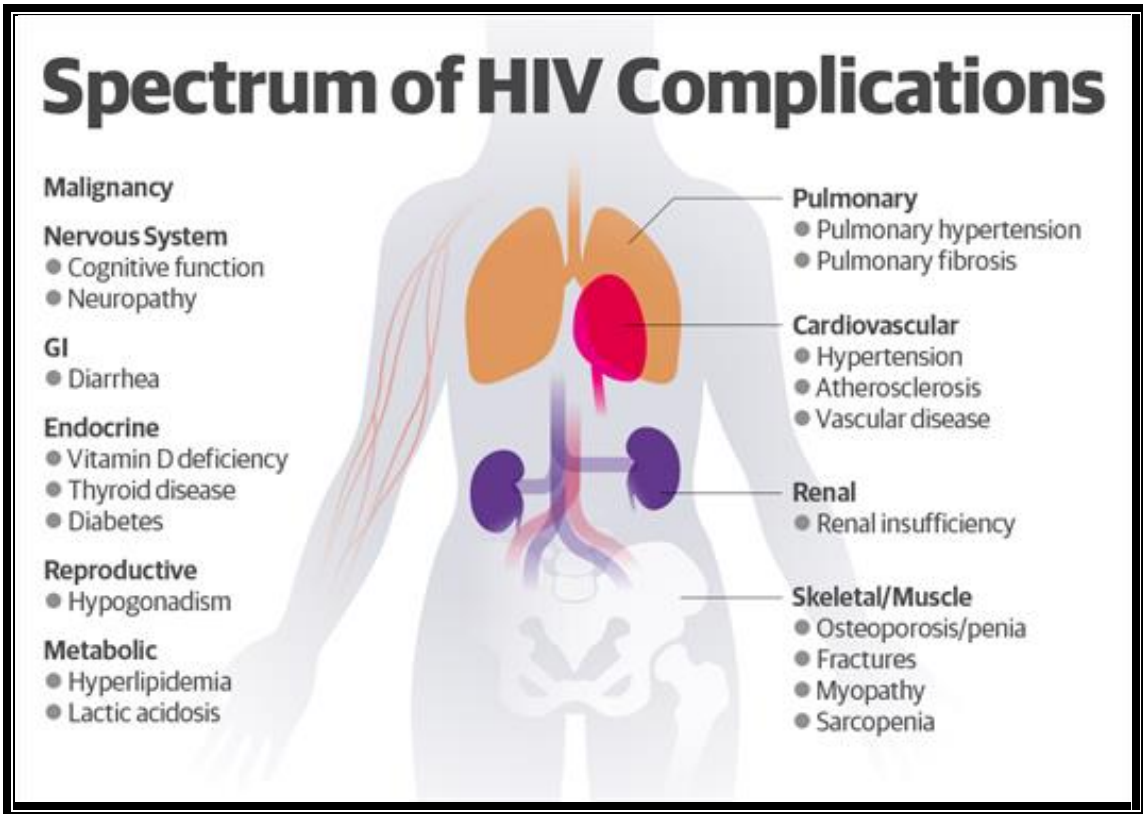


Fig 1: Complications of HIV

TREATMENT [3-5]

The reason HIV has become a more manageable disease instead of a death knell is because of something called anti-retroviral therapy in which a cocktail of drugs are given to HIV positive people which helps them manage their condition and prevents HIV from becoming AIDS.

NRTIs form the backbone of antiretroviral (ARV) cocktail and zidovudine (ZDV) and stavudine (d4T) are the most preferred NRTIs widely used in the first line management for HIV treatment.

Nucleoside reverse transcriptase inhibitors (NRTIs) in combinations with other antiretrovirals (HAART) are the cornerstones of acquired immunodeficiency syndrome (AIDS) therapy, turning HIV infection into a manageable chronic illness.

AZT which is the thymidine analogue (a potent inhibitor of the replication of human immunodeficiency virus) is the first U.S. government-approved treatment for HIV therapy, prescribed under the name Retrovir. AZT was the first breakthrough in AIDS therapy, significantly reducing the replication of the virus in patients and leading to clinical and immunologic improvements.

MECHANISM BY WHICH ZIDOVUDINE WORKS? [6]

AZT works by selectively inhibiting HIV's reverse transcriptase, the enzyme that the virus uses to make a DNA copy of its RNA. Reverse transcription is necessary for production of HIV's double-stranded DNA, which would be subsequently integrated into the genetic material of the infected cell (where it is called a provirus).

WHY ZIDOVUDINE IS GIVEN IN COMBINATION? [7, 8]

AZT is not potent enough to prevent all HIV replication, and may only slow the replication of the virus and the progression of the disease. During prolonged AZT treatment, HIV has the potential to develop resistance to AZT by mutation of its reverse transcriptase. To slow the development of resistance, physicians generally recommend that AZT be given in combination with another reverse transcriptase inhibitor and an antiretroviral from another group, such as a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor; this type of therapy is known as **HAART** (Highly Active Anti Retroviral Therapy).

Azidothymidine (AZT) was first administered to patients in 1985. It remains the primary drug and the only antiviral agent approved for initial treatment of human immunodeficiency virus (HIV) positive patients. However, serious side effects have occurred in clinical studies with AZT, resulting in dose reduction or discontinuation of the drug completely.

ANEMIA AND AIDS [9-11]

Fig 2: Anemia

One of the side effects is anemia. Anemia is a frequent complication of infection with the human immunodeficiency virus type 1 (HIV-1) and may have multiple causes.

Anemia has been associated with progression to AIDS and shorter survival times for HIV-infected patients

HIV infection and its direct effects on HSCs and stromal elements can lead to anemia. Opportunistic infection and myelosuppressive drugs might also cause anemia.
The anemia associated with zidovudine treatment is macrocytic, and indeed the red cells may be macrocytic even without anemia. Finally, anemia can be a result of red cell destruction, or hemolysis, as opposed to an aberration of production.

The etiology of anemia in HIV infection is multifactorial and typically the anemia may result from low production of red blood cells, increased RBC destruction, or ineffective RBC production. Other mechanisms for HIV-associated anemia, although uncommon, include vitamin B12 deficiency and the autoimmune destruction of erythrocytes. Direct infection of marrow precursor cells. Red blood cells develop from immature cells in the bone marrow called erythroid progenitor cells. When the number or maturation of these progenitor cells is impaired, anemia can result.

PATHOPHYSIOLOGY OFANEMIA IN HIV INFECTED PERSONS [12]

An obvious cause of anemia in patients with HIV infections blood loss. Pathophysiology of HIV-associated anemia may involve 3 basic mechanisms.

(a) Decreased RBC production

(b) Increased RBC destruction

(c) Ineffective RBC production

Table 2: Pathophysiology of anemia in HIV infected persons

DECREASED RBC PRODUCTION	INCREASED RBC DESTRUCTION	INEFFECTIVE RBC PRODUCTION
• Infiltration of bone marrow by infection- • Use of myelosuppressivedrug • HIV infection itself • Decreased production of erythropoietin • Blunted response to erythropoietin	• RBC autoantibodies, hemophagocytic syndrome • Disseminated intravascular coagulation • Thrombotic thrombocytopenic purpura • Glucose 6-phophate dehdrogenase deficiency	• Folic acid deficiency caused by either dietary deficieny or jejunal deficiency • Vitamin B12 deficiency caused by malabsorption in the ileum • Pathology caused by array of infections • Conditions that affect the gastric mucosa in HIV-infected patients

SYMPTOMS OF ANEMIA

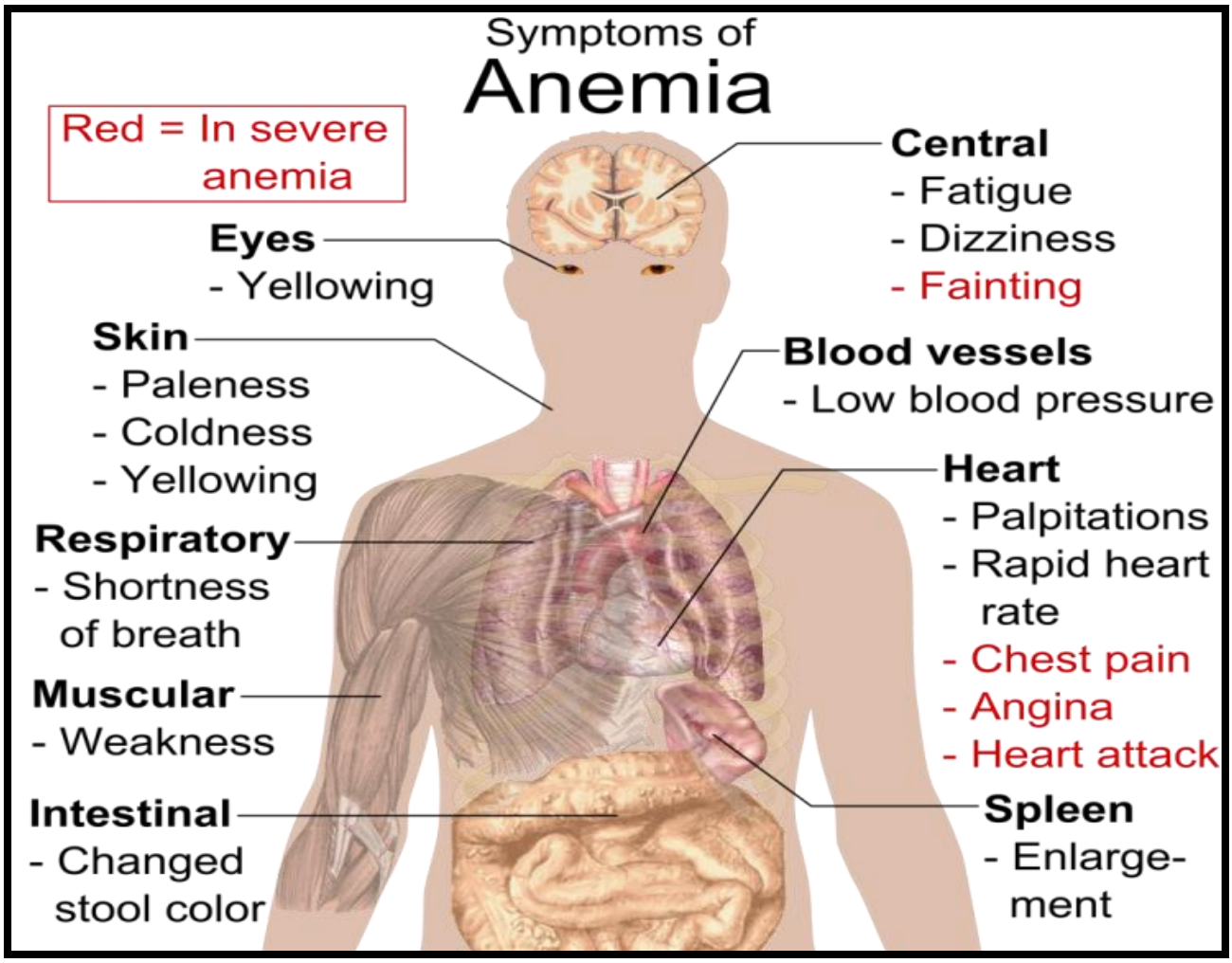


Fig 3: Symptoms of anemia

TUBERCULOSIS ASSOCIATED WITH AIDS [13]

Tuberculosis is the most common human immunodeficiency (HIV) virus-related opportunistic infection in India and caring for patients with both diseases is a major public health challenge. It is estimated that 60-70% of HIV-positive persons will develop tuberculosis in their lifetime. Approximately, 50% of adult Indian population is infected with *Mycobacterium tuberculosis*, and the spread of HIV infection could lead to a potentially explosive increase in the number of cases of tuberculosis. About 1.8 million new cases of tuberculosis are occurring annually in India. HIV infection is the most important known risk factor that favors progression to active TB from latent infection by suppressing the immune response against tuberculosis.

There are two types of tuberculosis infection, latent and active.

Table 3: Types of tuberculosis

Active TB	Latent TB
In case of active TB, due to the weak immune system, the germs multiply and cause symptoms.	In case of latent TB, the germs remain in the body and do not cause symptoms.

Active disease is more likely associated with HIV; especially if CD4 count is less than 200.Active tuberculosis can happen no matter what the CD4 level is. If infected with both HIV and TB, atleast 10 times the person is more likely to develop active TB than someone without HIV.

COMMON COMPLAINTS OF TB ASSOCIATED WITH AIDS

- A cough that lasts for more than two to three weeks
- Coughing up phlegm or blood
- Chest pain
- Weakness or fatigue
- Weight loss
- Lack of appetite
- Fever or chills
- Night sweats

A CO-EPIDEMIC [14-16]

HIV and tuberculosis (TB) are so closely connected that their relationship is often described as a co-epidemic. The two diseases are a deadly combination; they are far more destructive together than either disease alone. In developing countries many people infected with HIV contract TB as the first sign of AIDS. At least one-third of the 38.6 million HIV-positive people in the world is also infected with TB and is at greatly increased risk of developing TB disease (the active and contagious form of TB).

Tuberculosis (TB) and HIV have been closely linked since the emergence of AIDS. Worldwide, TB is the most common opportunistic infection affecting HIV-seropositive individuals, and it remains the most common cause of death in patients with AIDS.

By producing a progressive decline in cell-mediated immunity, HIV alters the pathogenesis of TB, greatly increasing the risk of disease from TB in HIV-coinfected individuals and leading to more frequent extra pulmonary involvement, atypical radiographic manifestations, and paucibacillary disease, which can impede timely diagnosis. Although HIV-related TB is both treatable and preventable, incidence continues to climb in developing nations.

SYMPTOMS OF TUBERCULOSIS IN AIDS PATIENTS

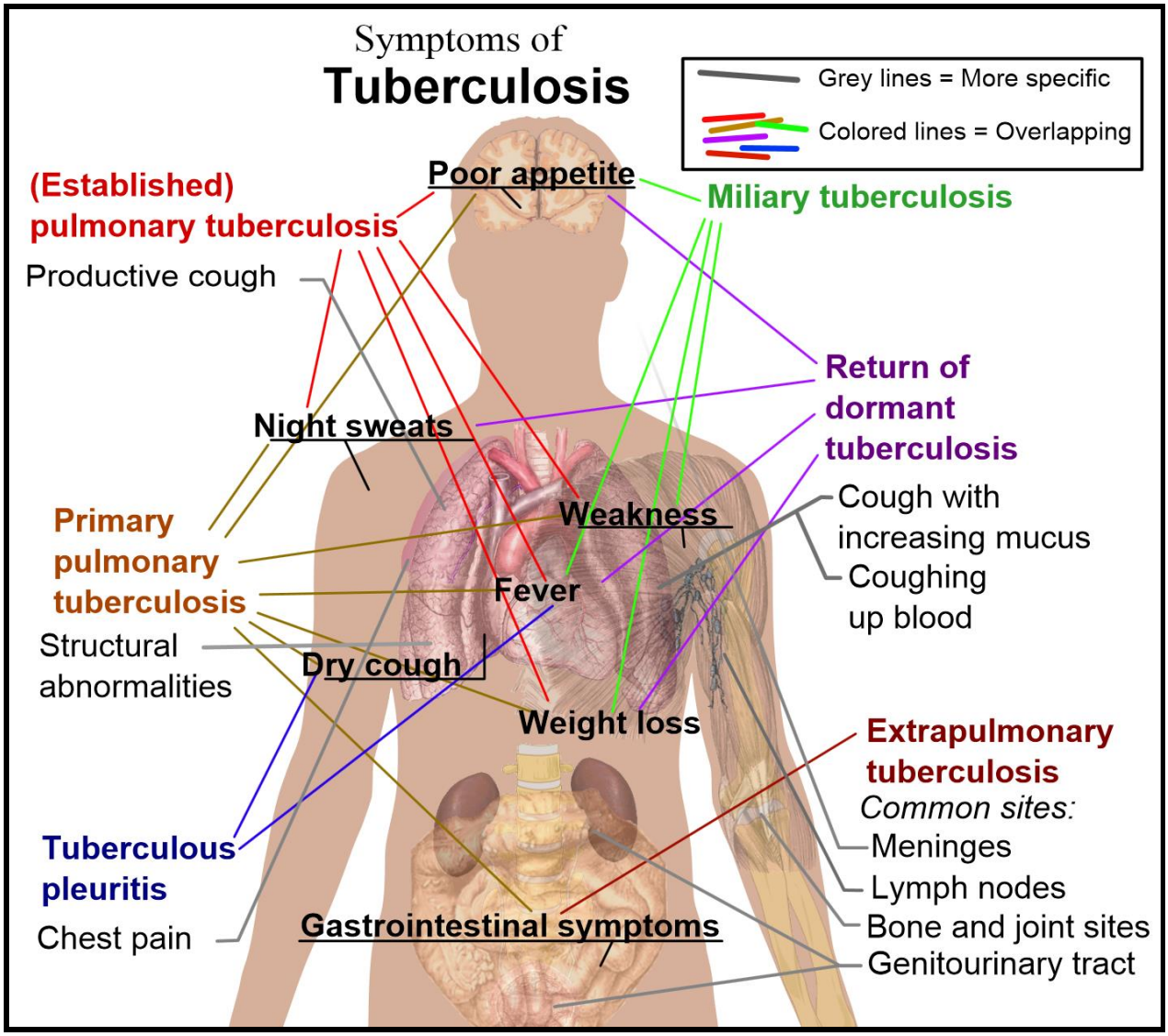


Fig 4: Symptoms of Tuberculosis in AIDS patients

2. REVIEW OF LITERATURE

1. Mohsen Meidani *et al*. (2012)[17] studied Prevalence, severity, and related factors of anemia in HIV/AIDS patients and have reported that anemia is slightly more common in women than men.

2. Akinsegun Akinbami *et al*. (2010)[18] evaluated Hematologic Abnormalities in Treatment-Naïve HIV Patients and have concluded that about one-fifth of HIV treatment-naïve patients were cytopenic at enrollment and the degree of cytopenia was directly related to the degree of immunosupression. It is necessary to investigate various causes of cytopenia in these patients so as to administer a specific intervention.

3. Anuja Balakrishnan *et al*. (2010)[19] reported Zidovudine- induced reversible pure red cell aplasia and have studied the first case of Zidovudine induced PRCA reported from the Indian subcontinent.

4. José A Mata-Marín et al. (2010)[20] studied factors and correlates for anemia in HIV treatment-naïve infected patients and have concluded that Anemia is a common manifestation in the Mexican population without antiretroviral therapy. In HIV naïve patients, a CD4+ Cell Count <200 cells/mm3 was associated with an increased risk of anemia. There is a positive correlation between hemoglobin and CD4+ cell count.

5. Dipti Agarwal *et al.* (2010)[21] studied high incidence of zidovudine induced anemia in HIV infected patients in eastern India and have concluded that out of 16.2% patients, 7.9% patients developed severe anemia and that females were more prone to develop anaemia.

6. Sara jam MD et *al.* (2009)[22] reported A Cross-Sectional Study of Anemia in Human Immunodeficiency Virus-Infected Patients in Iran and have stated that AZT-based highly active antiretroviral therapy (HAART) had a greater negative impact on hematologic parameters compared with the d4Tbased regimens.

7. Melanie-anne A *et al*. (2008)[23] reported Lamivudine-induced red cell aplasia and have indicated that the onset appears to be variable and occurs at any CD4+ count, but rapid improvement after cessation of drug administration appears to be a consistent feature.

8. Yulistiani *et al*. (2007)[24] reported the 'drug utilization profile in HIV/aids patients and have concluded that the drug profile used in HIV/AIDS patients are the first line ARV consisted of NRTIs (3TC, AZT) and NNRTIs (NVP, EFV); antimicrobial treatment including antibiotics and antifungal agents; and others to prevent or to treat opportunistic infections. ADRs occurred in 21% patients receiving ARV therapy.

9.Rochelle Chodock et al.(1999)[25] reported Survival of a human immunodeficiency patient with nucleoside-induced lactic acidosis-role of haemodialysis treatment and have concluded that life threatening lactic acidosis is an unusual but significant complication of antiretroviral treatment with nucleoside analogues and that discontinuation of the nucleoside analogue, intensive supportive care and high dose intravenous bicarbonate may not be sufficient therapy.Hemodialysis may confer benefits and improve survival.

10. Patrick S Sullivanet al. (1998)[26] studied the Epidemiology of Anemia in Human Immunodeficiency Virus (HIV) - Persons: Results From the Multistate Adult and Adolescent Spectrum of Infected HIV Disease Surveillance Project and have indicated that Anemia in HIV-infected patients, if persistent, is associated with substantially decreased survival and consideration should be given to evaluating the effects of treating anemia in a prospective study design. If recovery from anemia is shown to directly increase survival, screening for anemia should be aggressive and patients with anemia should be treated.

11. Ragni MV *et al.* (1995)[27] reported Randomized study of didanosine monotherapy and combination therapy with zidovudine in hemophilic and non hemophilic subjects with asymptomatic human immunodeficiency virus-1 infection. AIDS Clinical Trial Groups and have stated that the correlation observed between CD4 and quantitative viral titer suggests that reduction in viral load is accompanied by an increase in CD4. Given the imprecision of CD4 as a surrogate marker for clinical HIV disease progression, and it is possible that viral load quantitation, either alone or together with CD4, may provide a more predictive marker of disease progression and antiviral response and also summarized that didanosine monotherapy and combination therapy are well tolerated in asymptomatic HIV infection and result in significant CD4 increases and viral load reduction.

12. Raoul Moh et al. (1995)[28] have studied the Haematological changes in adults receiving a zidovudine-containing HAART regimen in combination with cotrimoxazole in Côte d'Ivoire and have concluded that cotrimoxazole and AZT are two important first-line HIV drugs with potential haematotoxic effects. Our data suggest that in patients receiving both drugs, severe neutropenia may be more frequent in sub-Saharan Africa than in industrialized countries. Administering both drugs to individuals similar to those who participated in our study requires close monitoring of the absolute neutrophil count and the discontinuation of cotrimoxazole in cases of severe neutropenia.

13. Merigan TC et al. (1991)[29] studied the Placebo-controlled trial to evaluate zidovudine in treatment of human immunodeficiency virus infection in asymptomatic patients with hemophilia.

14. Robert E *et al*. (1988)[30] investigated the anemia and erythropoiesis in patients with the acquired immune deficiency syndrome (AIDS) and Kaposi sarcoma treated with zidovudine and have concluded that the anemia associated with zidovudine therapy is due to red cell hypoplasia or aplasia.

3. AIM AND OBJECTIVE OF THE STUDY

RATIONALE OF THE STUDY

There are about 33 million people in the world suffering from AIDS ("a dying weigh of life) which foreshadows its explosion to various opportunistic diseases and has reached epidemic proportions globally with at least 2 million people dying each year.

AIM AND OBJECTIVE

The present study was to evaluate the basic hematological parameters of the persons developing anemia due to zidovudine and to understand the effect of zidovudine on haematogenesis and to explore alternate possible medications.

The purpose of this study was to analyze the drug profile in related to laboratory test and clinical data to determine when starting ARV therapy, stopping or changing therapy because of either side-effect/toxicity or treatment failure.

4. PLAN OF WORK

Fig 5: Plan of work

5. METHODOLOGY [19, 21, 23]

PATIENTS AND METHODS

The study method used was cohort which used observational method with descriptive analysis. The subjects observed were hospitalized HIV/AIDS patients at Catherine Booth hospital, Nagercoil. All the patients under this study were receiving anti-retroviral therapy and were determined by enzyme linked immuno sorbent assay (**ELISA**) and were confirmed by **Western blot assay**.

The important Hemoglobin parameter was assessed by **Sahli-Adams (tube) method**.

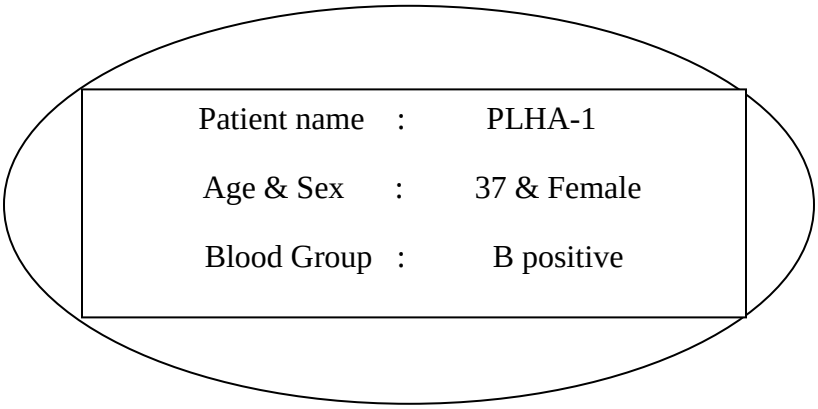
CRITERIA FOR INCLUSION:

- Age between 18-65
- HIV positive
- Zidovudine treatment

CRITERIA FOR EXCLUSION:

- Patients on other medications
- Defaulters

CASE 1



We report a 37 year old female diagnosed with HIV infection who was referred to hospital for initiation of Highly Active Anti-Retroviral Therapy (HAART).Baseline investigations revealed hemoglobin 12.8 g, WBC count 5400 cells/mm^3 and a platelet count of 132000 cells/mm^3. Urine examination, renal parameters and liver functions were within normal limits.

She was started on ZLN therapy daily on 25.06.2013. After 3 weeks, blood picture was revealed hemoglobin 11.9 g, WBC count 5200 cells/mm^3 and a platelet count of 189000 cells/mm^3.

After 3 months, she presented symptoms of tiredness, palpitation, swelling of both legs which she suffered for past 2 weeks. Analysis was made. Her blood pressure was found to be 90/60 mm/Hg and the pulse rate was 120/min. Hemoglobin was 3.3, WBC count was 4700 cells/mm^3 and the platelet count was 192000 cells/mm^3.

In urine, renal, liver parameters estimation, all was within normal levels except SGPT which showed 127 IU/L which was highly abnormal. Erythrocyte sedimentation rate was also high showing 40 mm/hr.

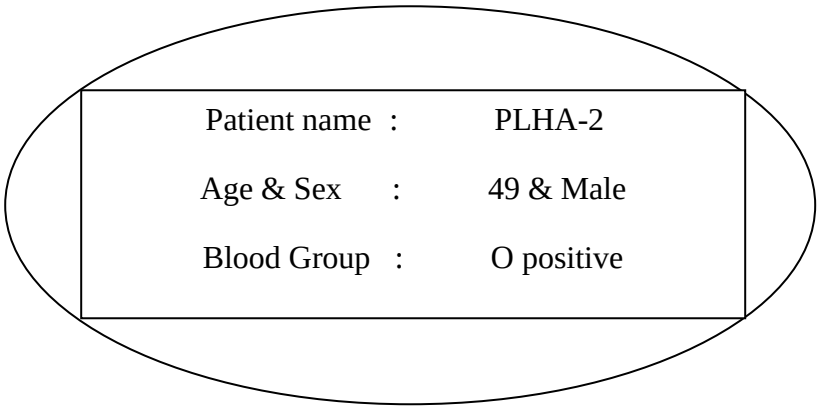
Hematological investigations confirmed the presence of macrocytic anemia .Treatment was given to treat anemia and antiviral therapy was changed to SLN. After 2 weeks and 6 weeks hematological changes were recorded.

TREATMENT:

Table 4: Treatment given in case 1

	DRUG	**STRENGTH**	**FREQUENCY**	**ROUTE**
1 st day 2 nd day 3 rd day	T.livogen		1 BD	Oral
	T.rantac	(150 mg)	BD	Oral
	T.mebex	(100 mg)	BD	Oral
	Inj.lasix	(20 mg)	OD	i.v
	T.liv 52		2 BD	Oral
	T.limarin	(140 mg)	BD	Oral
	Tranfusion	1 pint		i.v
4 th day	Inj.febrinil	1 amp		i.v (PRN)
	Tranfusion	1 pint		i.v
5 th day	Tranfusion	1 pint		i.v
	Inj.lasix	20 mg		i.v
	Inj.avil	1 amp		i.v
Discharge Medicines × 5 days	T.livogen		1 BD	Oral
	T.rantac		1 BD	Oral
	T.liv 52		2 BD	Oral
	T.limarin	140 mg	BD	Oral

CASE 2



Here we report a 49 year old male who was considered HIV positive before 5 months and was taking ZLN antiretroviral therapy for the past 2 months. At the start of the therapy (ie. On 01 .03.2013) his Hb was 11.8 g, WBC was 6000 cells/mm^3, other parameters like total bilirubin, direct bilirubin, calcium, potassium, SGOT, SGPT were normal. Suddenly he complained that he suffered from breathlessness on exute, fatigue.

Hematological and other parameters was assessed .Hb was 2.5 g, Liver function tests were normal ,white blood cells were within normal limits, renal parameters like total bilirubin, direct bilirubin, sodium ,potassium levels also represented normal values.

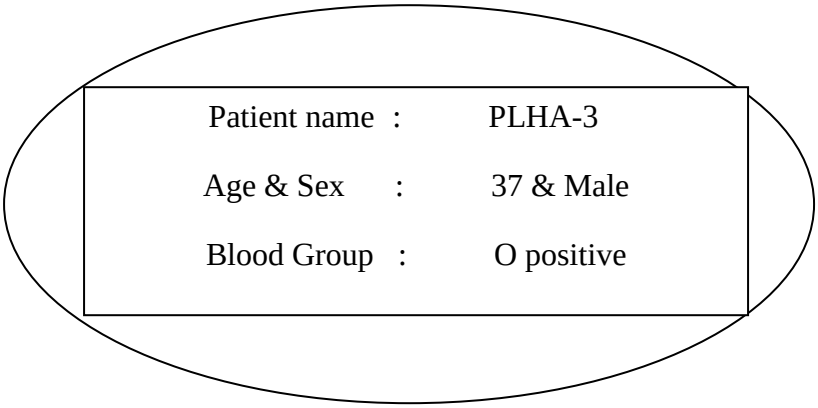
Anemia was confirmed and treatment was given and after 2 weeks all blood and other parameters was assessed.

TREATMENT

Table 5: Treatment given in case 2

	DRUG	STRENGTH	FREQUENCY	ROUTE
1 st day	T.tenolam		1 -0-0	Oral
	T.nevirapine		1-0-1	Oral
	T.livogen		1 BD	Oral
	Inj.lasix	(20 mg)	OD	i.v
	T.sepmax		2 BD	Oral
	Syr. ambrodiol	10 ml	TDS	Oral
2 nd day	Inj.deriphylline	1 amp		i.v Q 8 H
	Inj.lasix	20 mg		i.v stat
	Inj.avil	1 amp		i.v stat
	Transfusion	1 pint		
	Ipravent nebulization			Q 6 H
3 rd day	Tranfusion	1 pint		
	Inj.lasix	20 mg		i.v
	Inj.avil	1 amp		i.v stat
	Inj.dexa	4 mg		i.v stat
4 th day	Tranfusion Inj lasix	1 pint 20 mg		 i.v stat
	Inj avil	1 amp		i.v stat
5 th day	T rantac	150 mg	BD	Oral
	Tranfusion	1 pint		
	T infiniar		HS	Oral
	Inj. oframax	1 gm	BD	i.v
6 th day	Tranfusion	1 pint		
	Inj.lasix	20 mg		i.v PRN
	Inj.avil	1 amp		i.m PRN
7 th day	Tranfusion	1 pint		
	Inj.lasix	20 mg		i.v PRN
	Inj avil	1 amp		i.v stat
	Ipravent nebulization		BD	
	Inj.deriphylline	1 amp		i.v stat

CASE 3



A 37 year old male who was confirmed HIV positive in the month of May was given ZLN therapy .After 3 months he was admitted as he was suffering from symptoms like difficulty in walking, irrelevant talk, fever since morning, cough. He had no complaints of vomiting, loose stools and dissuria. Examination findings reported a pulse rate of 120/min, blood pressure was 100/50 mm/Hg and also he was reported to have spleenomegaly.

Hemoglobin was 2.1 g and the WBC count was 2000 cells/mm^3 (Neutrophils-67%, Lymphocytes-30%, Eosinophils-0.3%.Platelet count was 66,0000 cells/mm^3.SGPT, SGOT, serum creatinine, serum amylase were within normal limits 40 IU/L, 46 IU/L, 1.3 mg%, 77 IU/L respectively.

The diagnosed value indicates clearly that the patient was suffering from anemia and also neutropenia which is characterized by decreased white blood cells.

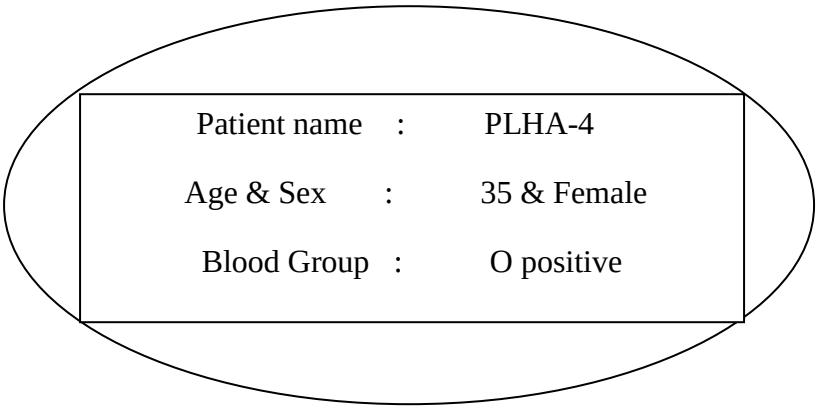
Treatment was given based on his exhibited complications.

TREATMENT

Table 6: Treatment given in case 3

	DRUG	**STRENGTH**	**FREQUENCY**	**ROUTE**
1 st day	Inj.oframax	1 gm		i.v Q 8 H
	Inj.rantac	50 mg	BD	i.v
	Inj.lasix	(20 mg)		i.v stat
	T.livogen		1 BD	Oral
	Inj.febrinil	1 amp		i.v stat PRN
	Inj.emeset	4 mg		i.v PRN
	T.sepmax	1 HS		Oral
	T.dolo	650 mg		PRN
	T.antican-O	150 mg	OD	Oral
	Transfusion	20 pint		
	T.SLN		1-0-1	Oral
	Inj.avil	1 amp		i.m stat
2 nd day 3 rd day	Transfusion	1 pint		
	Inj.lasix	20 mg		i.v stat
	Inj.avil	1 amp		i.v stat
	Inj.oframax	1 gm		i.v Q 8 H
	T.sep max		1 HS	Oral
4 th day	Inj.oframax	1 gm		i.v Q 8 H
	T.sep max		1 HS	Oral
5 th day	Tranfusion	1 pint		
	Inj avil	1 amp		i.v stat
	Inj.lasix	20 mg		i.v stat
	T.livogen		1 BD	Oral
6 th day	Transfusion	10 pints		
	Inj.lasix	20 mg		i.v stat
	Inj.avil	1 amp		i.v stat

CASE 4



We report a 35 year old patient of blood group O positive who was admitted in hospital due to various complaints like fever for 1 week, giddiness, fatigue and vomiting for a day who was on the treatment with anti-retroviral therapy for the past 3 months as she was confirmed with HIV with ELISA and western blot assay.

Various blood parameters and other organ function tests were carried out and was found that the Hb was only 3.9 g % which reduced from 12.4 g at the time of initiation of Antiretroviral therapy. All other levels were within normal limits.

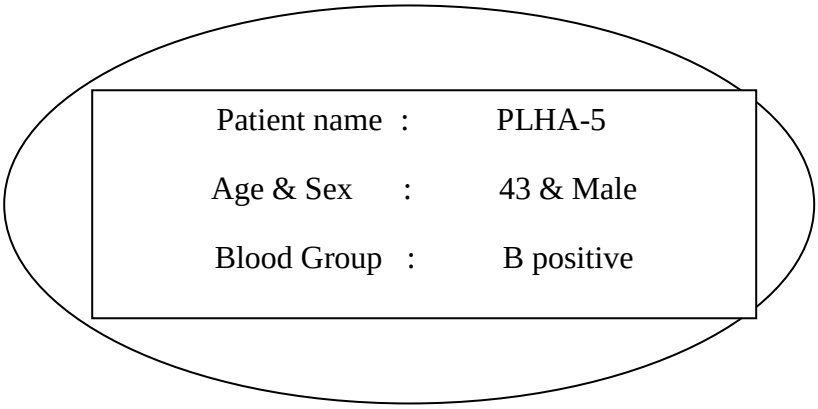
This indicated that Anemia was the keen cause for the symptoms and corresponding treatment was given.

TREATMENT

Table 7: Treatment given in case 4

	DRUG	**STRENGTH**	**FREQUENCY**	**ROUTE**
1 st day	Transfusion	1 pint		
	Inj.lasix	20 mg		i.v stat
	Inj.avil	1 amp		i.v stat
	Inj.emeset	4 mg	TDS	i.v
	T.sepmax		HS	Oral
	C.becosules		1 OD	i.v stat
	T.livogen		1 BD	Oral
	T.tenolam		1 HS	Oral
	T.efavirenz		1 HS	Oral
	T.liv 52	600 mg	2 BD	Oral
	T.limarin	140 mg	BD	Oral
	Transfusion	1 pint	Over 5-6 hrs	
	Inj.mol	1 amp		i.m stat
	T.alprax	0.5 mg		Stat
2 nd day	Transfusion	1 pint	Over 6 hrs	
	Inj.lasix	20 mg		i.v stat
	Inj.avil	1 amp		i.v stat
3 rd day	Tranfusion	1 pint		
	Inj.lasix	20 mg		i.v
	Inj.avil	1 amp		i.v stat
	Inj.perinom			i.v stat
	T.perinom	10 mg	TDS	Oral
Discharge medicines	T.emeset	4 mg	TDS× 3 days	Oral
	T.sepmax		1 HS×5 days	i.v stat
	T.liv 52		2 BD×5 days	Oral
	T.livogen		1 BD×5 days	Oral
	T.alprax	0.25 mg	HS-OD×5 days	Oral
	C.omez	20 mg	BD ½ hr before meals	Oral

CASE 5:



Here we present a case study of a HIV patient associated with TB infection of age 43 years old .He was considered HIV positive after the ELISA test and confirmation with western blot test in the month Jan 2013.He was prescribed with Anti-retroviral therapy.

In the month of April 2013, this patient had complaints of certain symptoms of fever for 4 days, swelling of both legs, he had regular hiccups, reduced intake, ulcers in mouth, coughing up phlegm and blood, fatigue, chest pain for past 2 weeks. He was diagnosed and the examination findings showed that is blood pressure was 110/60 mm/Hg, pulse rate of 120/min, CD_4 count was only 93 cells/mm^3.

He was also evaluated for certain renal, liver parameters and the SGPT was 90 IU/L, SGOT-184 IU/L. Sodium, potassium levels, serum creatinine was within normal limits.ESR was found to be 116 and the WBC count was 2200 cells/mm^3.Platelet count was 72000 cells/mm^3.RBC count was 5.8 g Sputum culture test was also performed which showed positive result indicating mycobacterium.

Blood calcium level was 11.7 mg/dl. Microscopic examination in spleen and liver was done as a result coarse nodule is seen in spleen, minimal ascitis was observed. Uric acid crystals and few epithelial cells were also observed.

This analysis indicates that the patient is associated with Disseminated TB, Hepatospleenomegaly, Hypercalcemia due to TB, Anemia, Neutropenia, Thrombocytopenia. Fever evaluation confirmed the fever as Dengue.

Treatment was given to improve the patient from the symptoms he was suffering.

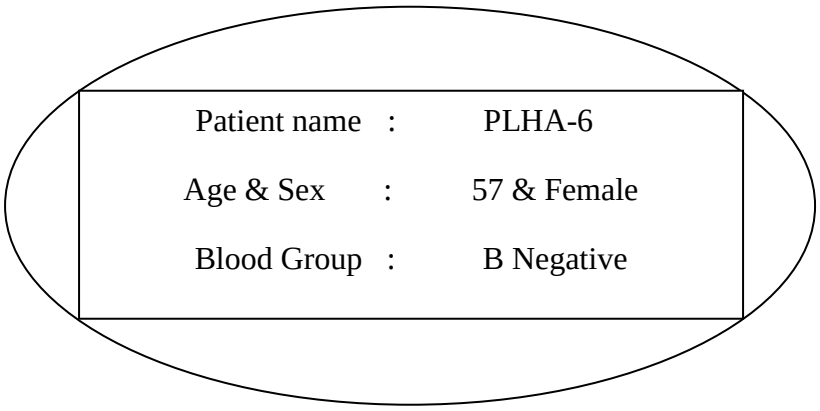
TREATMENT

Table 8: Treatment given in case 5

1 st day	**DRUG**	**STRENGTH**	**FREQUENCY**	**ROUTE**
	T.largatil	25 mg	BD	Oral
	IVF.RL	2.0 RL	stat	i.v
	T.livogen		1 BD	Oral
2 nd day	IVF.RL	1.0 RL	Over 6 hrs	i.v
	IVF.RL	1.0 RL		i.v
3 rd day	DNS	1.0		i.v
	Inj .pantoprazole	40 mg		i.v
4 th day	T.aciloc RD		1-0-1	Oral
	T.largatil	25 mg	BD	Oral
	T.lasix	20 mg		Oral
	Transfusion	1 pint		
	T.largatil	25 mg	BD	Oral
5 th day	Tranfusion	1 pint		
	T.lasix	20 mg		Oral
	Inj. Avil	1 amp		i.v stat
	DNS	10	Over 6 hrs	i.v
	Inj.oframax	1 gm	BD	i.v
	Inj.rantac	50 mg	BD	i.v
6 th day	Inj. Amikacin O	150 mg	OD	i.v
	T.Sepmax			Oral
	T.Alcin	500 mg	OD	Oral
	T.Liv 52		2 BD	Oral
	T.Livopill B		1 BD	Oral

	T.Aciloc RD		1 BD	Oral
	T.Ethambutol	800 mg	OD	Oral
	T.Microdox	100 mg	BD	Oral
	T.Perinom	10 mg	BD	Oral
	Inj.Avil	1 ampoule		i.v stat
	Inj. Mol	1 ampoule		i.v stat
7 th day	Inj.Pantoprazole	40 mg	BD	i.v
	Transfusion	10 pints		
	Inj.Avil	1 ampoule		i.v stat
	Inj. Lasix	20 mg		i.v stat
	T. Inderal	20 mg	BD	Oral
	T.Alprax	0.25-0-0.5 mg		Oral
8 th day	T.Dolo	650 mg		Stat
	T.perinom	10 mg	TDS	Stat
9 th day	T.largatil	25 mg	TDS	Oral
	Inj.Oframax			i.v
	Inj.Amikacin			i.v
	T.INH	150 mg	OD	Oral
Discharge Medicines	T.INH	300 mg	OD	Oral
	T.Ethambutol	800 mg	OD	Oral
	T.Levofloxacin	500 mg	OD	Oral
	T.aciloc RD		1-0-1	Oral
	T.Sepmax		1 HS	Oral
	T.Antican O	150 mg	OD	Oral
	T.largatil	25 mg	TDS	Oral
	T.Inderal	20 mg	BD	Oral
	T.Alprax	0.25-0-0.5 mg		Oral
	T.Limarin	140 mg	BD	Oral
	T.B6	40 mg	OD	Oral
	T.Ativan	1 mg-HS	OD	Oral

CASE 6:



We report a 57 year old female diagnosed with HIV infection who was referred to hospital for initiation of Highly Active Anti-Retroviral Therapy (HAART).Baseline investigations revealed hemoglobin 12.4 g, WBC count 6000 cells/mm^3 and a platelet count of 321000 cells/mm^3. Urine examination, renal parameters and liver functions were within normal limits.

She was started on ZLN therapy daily on 13.10. 2013. After 2 weeks, blood picture was revealed hemoglobin 3.9 g, WBC count 5900 cells/mm^3 and a platelet count of 320000 cells/mm^3 as she presented with symptoms of tiredness and swelling of both legs.

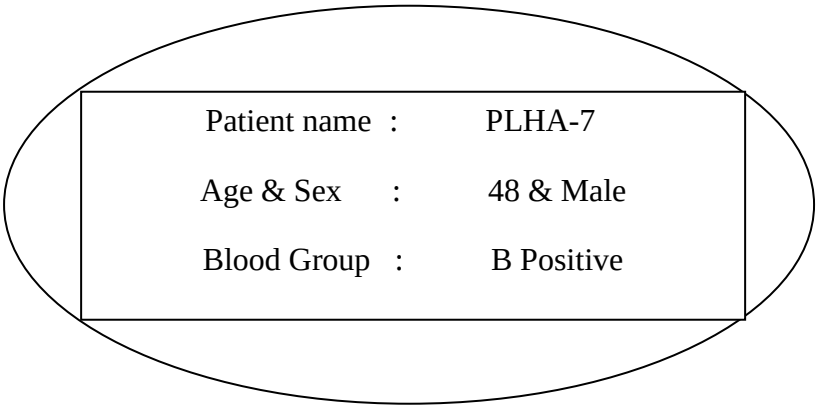
Analysis confirmed the presence of red cell aplasia as there was no abnormality in the white blood cell count .Treatment was given to treat aplasia.

TREATMENT:

Table 9: Treatment given in case 6

	DRUG	STRENGTH	FREQUENCY	ROUTE
1 st day 2 nd day 3 rd day	T.livogen		1 BD	Oral
	T.rantac	(150 mg)	BD	Oral
	T.mebex	(100 mg)	BD	Oral
	Inj.lasix	(20 mg)		i.v
	Inj.avil	1 amp		i.v
	T.liv 52		2 BD	Oral
	Tranfusion	1 pint		
4 th day	Inj.febrinil	1 amp		i.v (PRN)
	Inj. Dolonex	1 amp		i.m stat.
	T.deriphylline	(150 mg)	BD	Oral
	Tranfusion	1 pint		
5 th day	Tranfusion	1 pint		
	Inj.lasix	20 mg		i.v
	Inj.avil	1 amp		i.v
Discharge Medicines × 7 days	T.livogen		1 BD	Oral
	T.rantac		1 BD	Oral
	T.deriphylline	150 mg	BD	Oral
	T.liv 52		2 BD	Oral
	T.limarin	140 mg	BD	Oral

CASE 7



A 48 year old male patient who was confirmed HIV positive in the month of July was given ZLN therapy .After 2 weeks he was admitted as he was suffering from symptoms like difficulty in walking, irrelevant talk, fever since morning and tiredness.

He had no complaints of vomiting, loose stools and dissuria. Examination findings showed that his hemoglobin was 4.0 g and the WBC count was 2100 cells/mm^3.Platelet count were 251000 cells/mm^3. SGPT was 95 and SGOT was 65.All the other assessed parameters were within limits.

The diagnosed value indicates clearly that the patient was suffering from anemia and also neutropenia.

TREATMENT

Table 10: Treatment given in case 7

1 st day	Inj.oframax	1 gm		i.v Q 8 H
	Inj.rantac	50 mg	BD	i.v
	Inj.lasix	(20 mg)		i.v stat
	Inj.febrinil	1 amp		i.v stat PRN
	Inj.emeset	4 mg		i.v PRN
	T.sepmax	1 HS		Oral
	T.dolo	650 mg		PRN
	T.antican-O	150 mg	OD	Oral
	Transfusion	2 pints		
	T.SLN		1-0-1	Oral
	T.livogen		1 BD	Oral
	Inj.avil	1 amp		i.m stat
2 nd day 3 rd day	Transfusion	1 pint		
	Inj.lasix	20 mg		i.v stat
	Inj.avil	1 amp		i.v stat
	Inj.oframax	1 gm		i.v Q 8 H
	T.sep max		1 HS	oral
4 th day	Inj.oframax	1 gm		i.v Q 8 H
	T.sep max		1 HS	Oral
5 th day	Tranfusion	1 pint		
	Inj avil	1 amp		i.v stat
	Inj.lasix	20 mg		i.v stat
	T.livogen		1 BD	Oral
6 th day	Transfusion	1 pint		
	Inj.lasix	20 mg		i.v stat
	Inj.avil	1 amp		i.v stat

6. RESULTS AND DISCUSSION

All the patients under this study had a history of Zidovudine Antiretroviral therapy treatment. The existence of anemia out of 7 cases studied was in all. Haemoglobin levels were much deviating from the normal limit in all patients after 2-3 weeks of Anti-retroviral therapy. Certain patients also showed abnormal liver enzyme levels, white blood cells, platelet count which was accompanied by anemia.

CASE 1

Table 11: Hematological assessment in case 1

DATE	Hb (g)	WBC cells/mm^3	Platelets Cells/mm^3	SGPT (IU/L)	HAART
25 JUN 2013	12.8	5400	132000	45	ZLN
18 JUL 2013	11.9	5200	189000	90	ZLN
20 OCT 2013	**3.3**	4700	192000	**127**	ZLN
05 NOV 2013	4.5	4700	191000	112	SLN
18 DEC 2013	7.3	4800	190000	99	SLN

Z-Zidovudine L-Lamivudine N-Nevirapine S-Stavudine

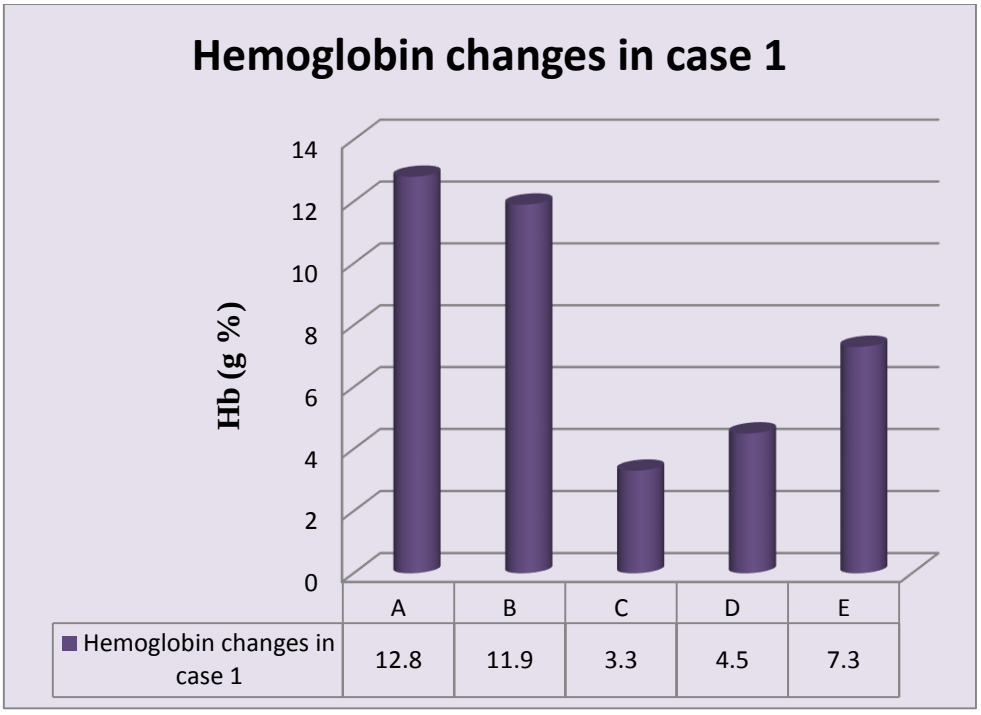


Fig 6: Hemoglobin changes in case 1

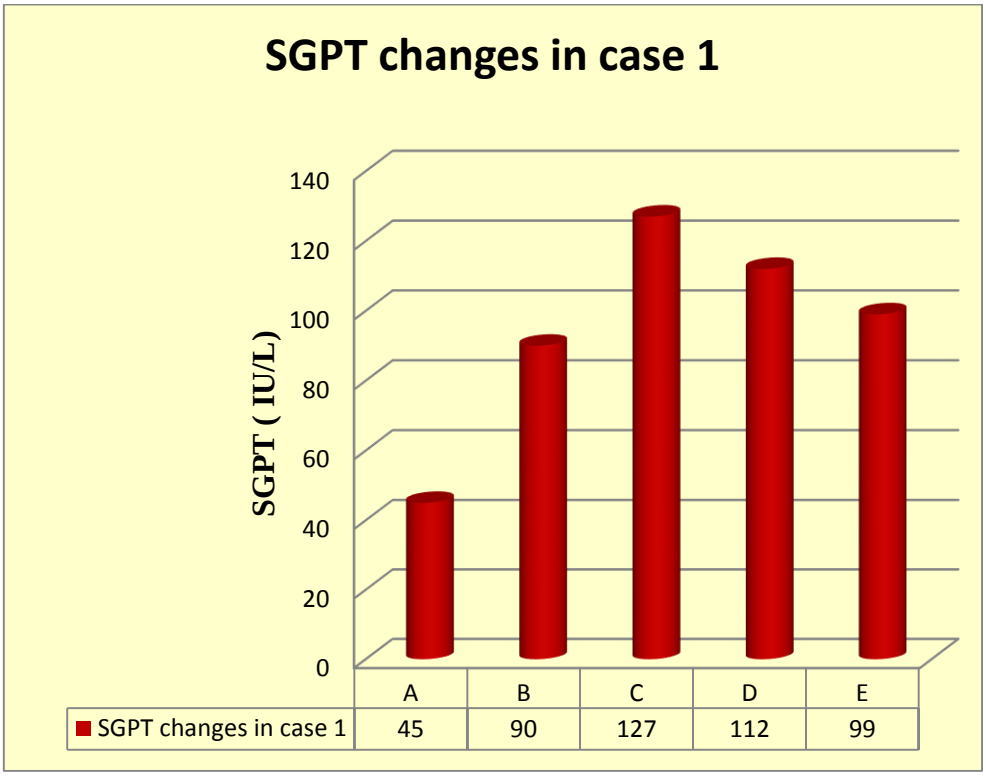


Fig 7: SGPT changes in case 1

After 2 weeks of change of drug regimen from ZLN to SLN, Hb was increased from 3.3 to 4.5 and SGPT was from 127 to 92 and after 6 weeks the Hb was 9.7 and SGPT was 64.These changes in hematological parameters clearly indicates that the anemia caused was induced by Zidovudine.

CASE 2

Table 12: Hematological assessment in case 2

DATE	Hb (g)	WBC cells/mm^3	SGPT (IU/L)	SGOT (IU/L)	Total Bilirubin (mg/dl)	Direct Bilirubin (mg/dl)	Na (mEq/L)	K (mEq/L)	HAART
1MAR 2013	11.8	6000	17	22	0.9	0.5	130	4	ZLN
18 MAY 2013	**2.5**	5200	17	23	0.9	0.2	140	4.4	ZLN
10 JUN 2013	5.8	5000	18	23	1.2	0.2	135	4.4	TLN
05 JUL 2013	7.3	5200	18	22	1.1	0.3	134	4.3	TLN

Z-Zidovudine L-Lamivudine N-Nevirapine T-Tenofovir

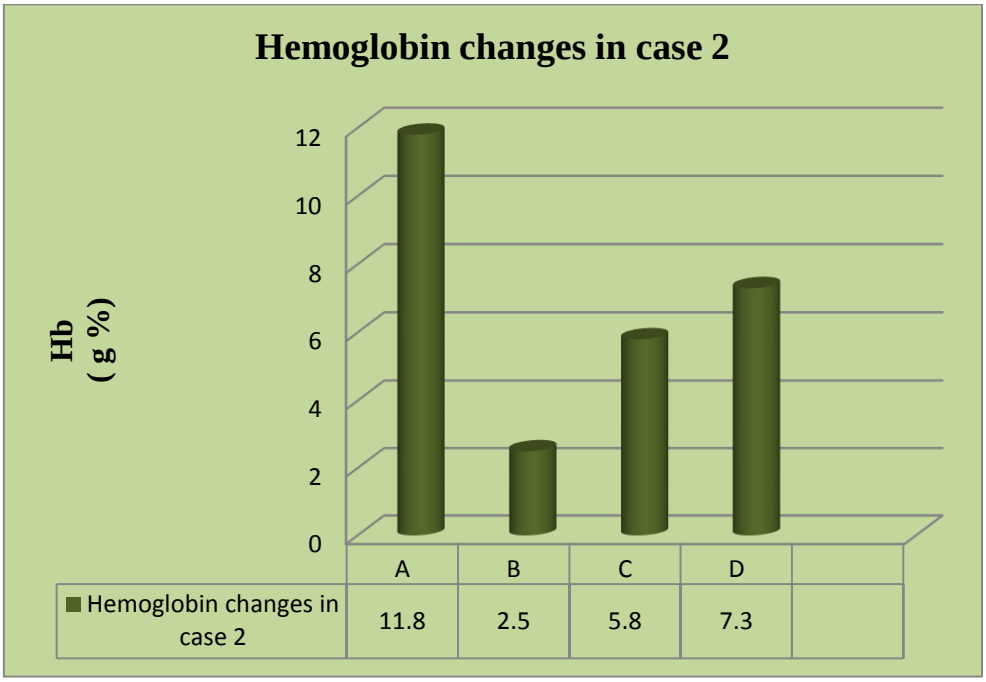


Fig 8: Hemoglobin changes in case 2

Out of all the assessed parameters ,only Hb drastically reduced from 11.8 to 2.5.After change from ZLN to TLN there was a increase in Hb from 2.5 to 5.8 and this anemia was drug induced that was caused by Zidovudine.

CASE 3

Table 13: Hematological assessment in case 3

DATE	Hb (g)	WBC cells/mm^3	SGPT (IU/L)	SGOT (IU/L)	HAART
30 MAY 2013	10.7	5000	35	44	ZLN
06 AUG 2013	**2.1**	**2000**	40	46	ZLN
21 AUG 2013	4.8	3200	39	46	SLN
15 SEP 2013	5.8	3450	41	46	SLN

Z-Zidovudine L-Lamivudine N-Nevirapine S-Stavudine

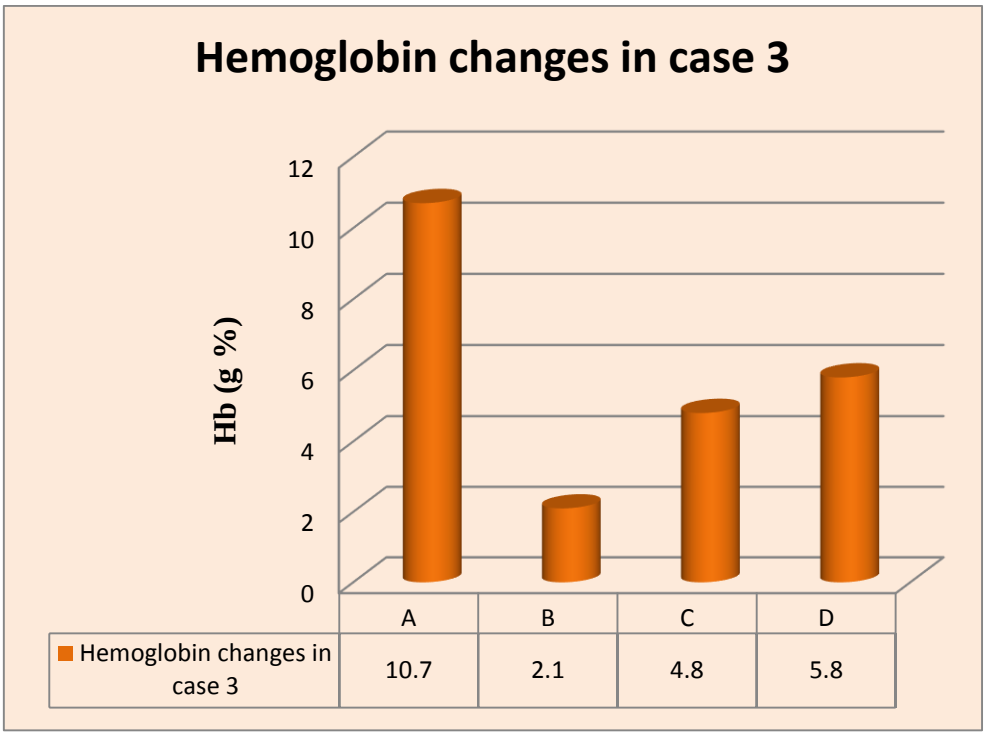


Fig 9: Hemoglobin changes in case 3

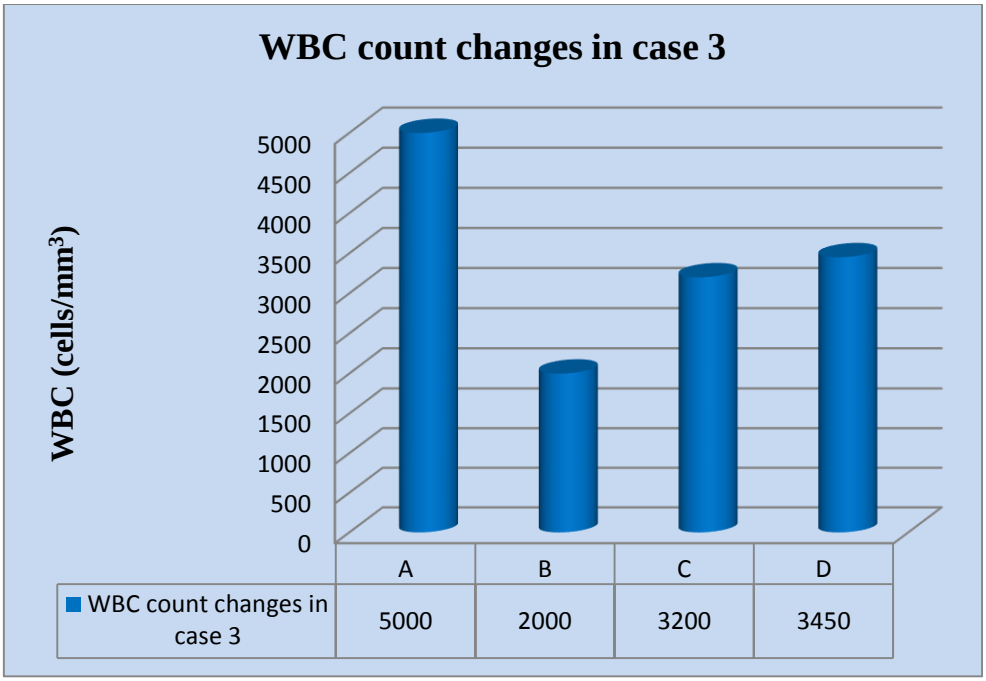


Fig 10: WBC count changes in case 3

After a change from Zidovudine to Stavudine, the hemoglobin value increased from 2.1 to 4.8 g %.Also there was an increase in white blood cells. This drastic reduction in hemoglobin value was due to Zidovudine induced anemia.

CASE 4

Table 14: Haematological assessment in case 4

DATE	Hb (g)	WBC cells/mm^3	Platelets Cells/mm^3	HAART
14 AUG 2013	12.4	6000	312000	ZLN
29 AUG 2013	**3.9**	5900	320000	ZLN
13 SEP 2013	7.1	5900	192000	SLN
05 OCT 2013	10.2	6000	191000	SLN

Z-Zidovudine L-Lamivudine N-Nevirapine S-Stavudine

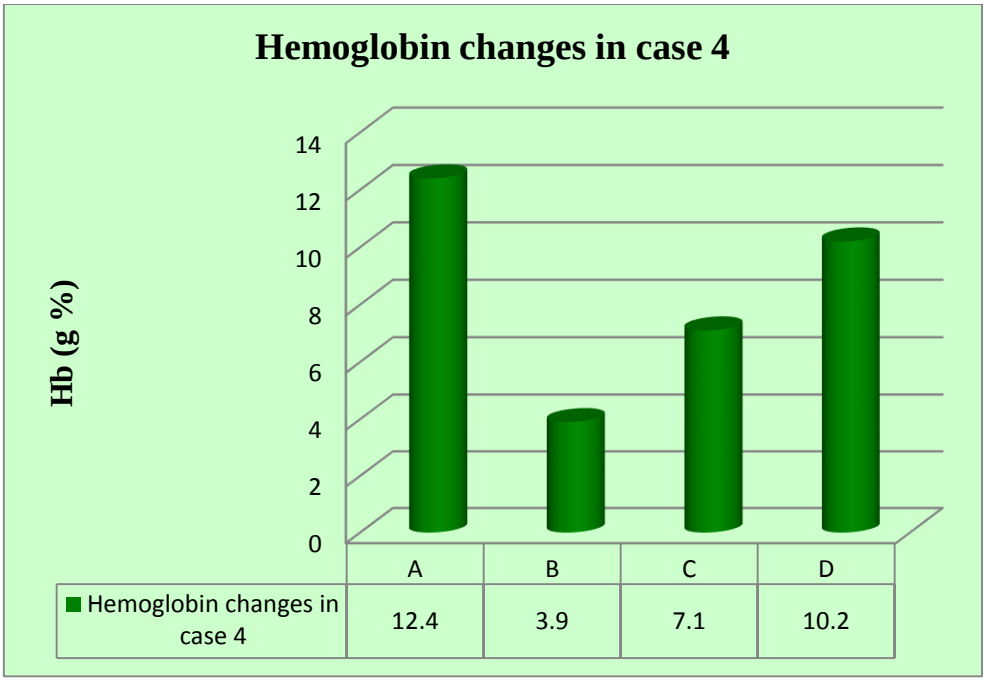


Fig 11: Hemoglobin changes in case 4

The change of ZLN therapy to SLN therapy brought up the drastic reduction of Hb from 3.9 to 7.1 and further after six weeks to 10.2 g %.

CASE 5

Table 15: Haematological assessment in case 5

Date	RBC (g)	WBC (cells/ mm^3)	Platelet (cells/ mm^3)	CD4 (cells/ mm^3)	SGOT (IU/L)	SGPT (IU/L)	Ca (mg/ dl)	Na (mEq/L)	K (mEq/ L)	HAART
10 JAN 2013	11.5	5600	110000	234	32	26	9.1	136	4.5	ZLE
02 APR 2013	**5.8**	2200	60000	93	**184**	**90**	11.7	132	4.2	ZLE
21 APR 2013	7.2	2800	62000	132	76	73	10.9	132	4.3	SLE
15 May 2013	7.6	2860	64000	163	70	67	10.1	130	3.8	SLE
10 JUN 2013	8.5	3050	64000	171	70	68	10.1	131	4.1	SLE

Z-Zidovudine L-Lamivudine E-Efavirenz S-Stavudine

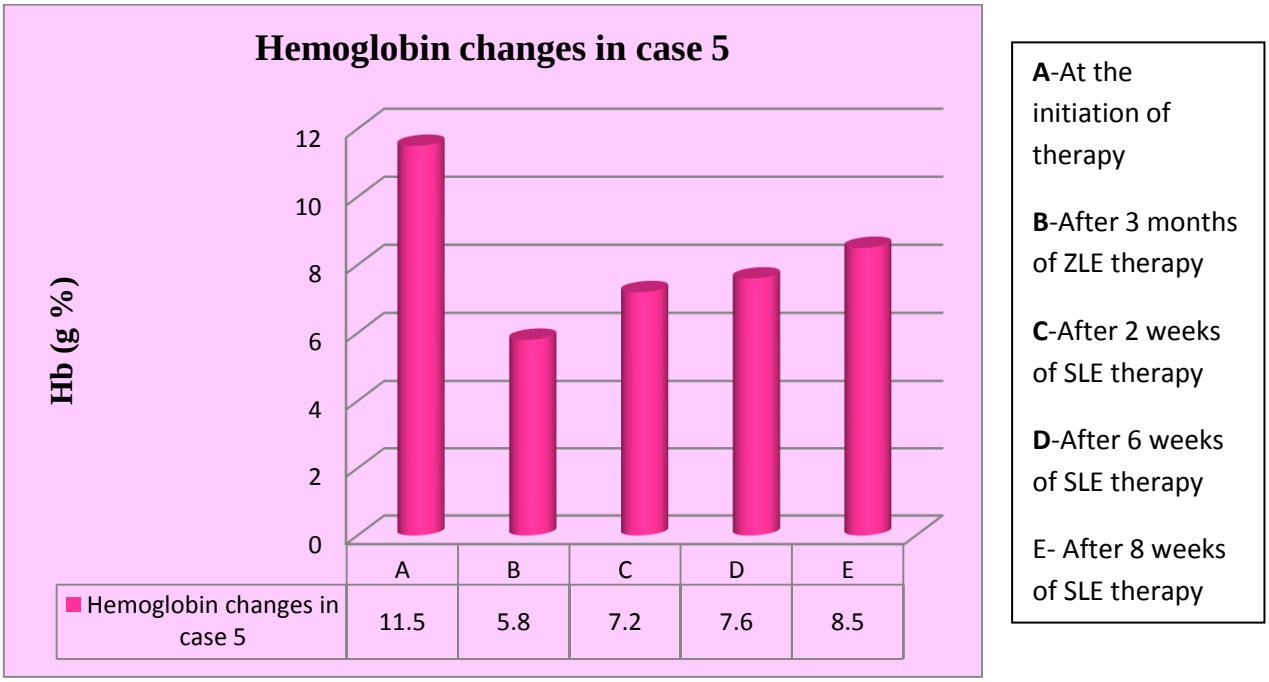
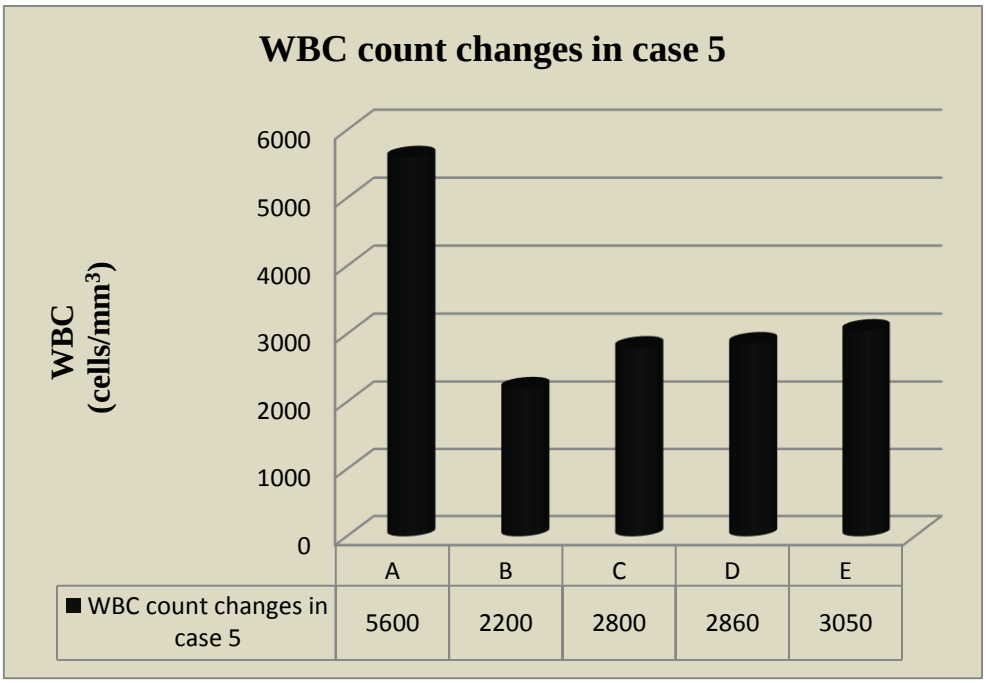


Fig 11: Hemoglobin changes in case 5



A-At the initiation of therapy

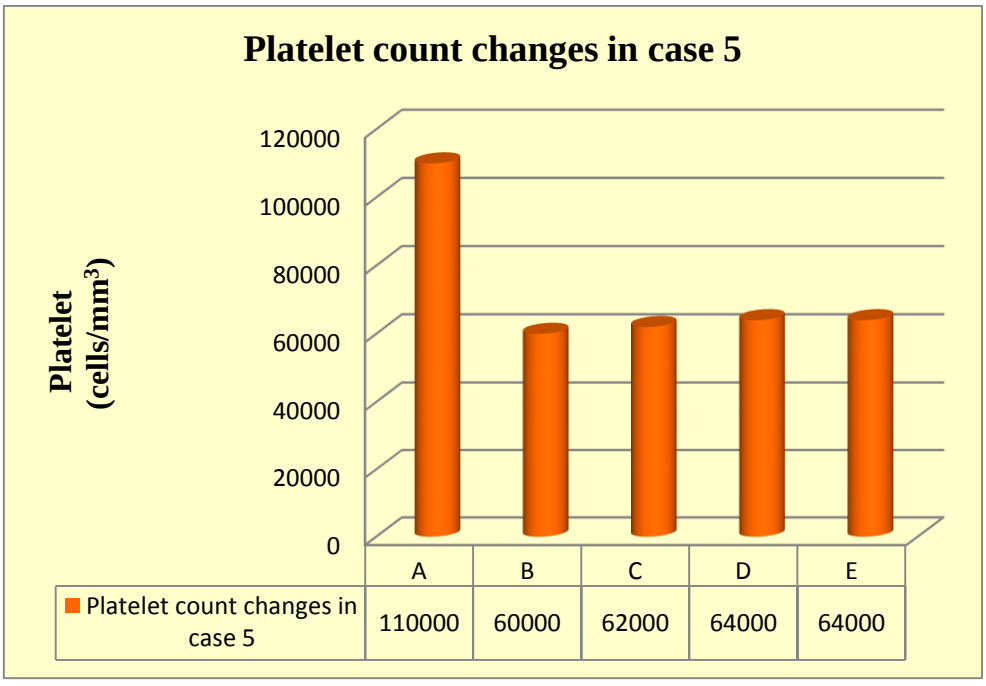
B-After 3 months of ZLE therapy

C-After 2 weeks of SLE therapy

D-After 6 weeks of SLE therapy

E- After 8 weeks of SLE therapy

Fig 13: WBC count changes in case 5



A-At the initiation of therapy

B-After 3 months of ZLE therapy

C-After 2 weeks of SLE therapy

D-After 6 weeks of SLE therapy

E- After 8 weeks of SLE therapy

Fig 14: Platelet count changes in case 5

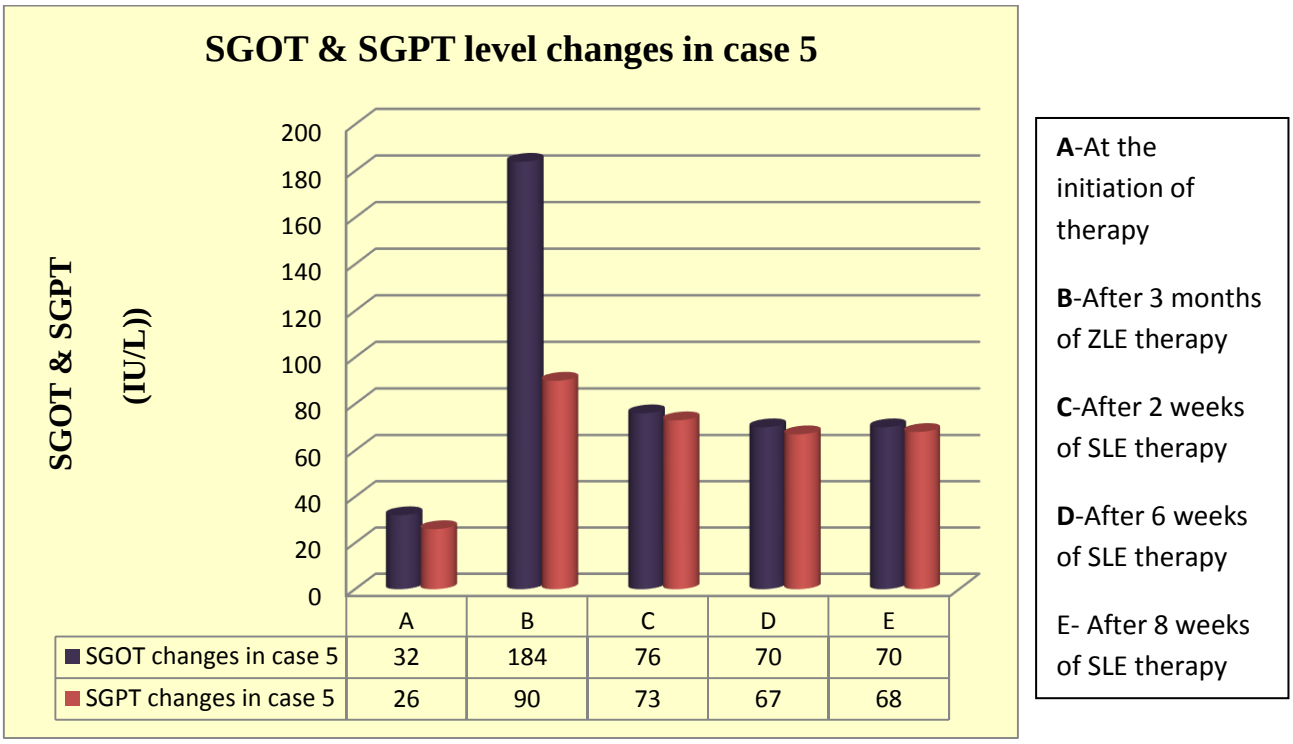


Fig 15: SGOT & SGPT level changes in case 5

From the table, it is concluded that from a Hb value of 11.5 g, a prominent decrease of 5.8 was observed 2 weeks later after Anti retroviral therapy consisting of Zidovudine .After a changeover of Zidovudine to Stavudine there was a slight increase in Hb of upto 8.5 gafter 8 weeks of treatment. Platelet count was also decreased from 110000 cells/mm^3 to 60000 which is much deviated from a normal value .Even after the changeover of drug, there was not a much increase in the platelet count.

This clearly indicates that the anemia caused was due to Zidovudine which was reversed after a change of drug from Zidovudine to Stavudine

CASE 6

Table 16: Hematological assessment in case 6

DATE	Hb (g)	WBC cells/mm^3	SGPT (IU/L)	SGOT(IU/L)	PLATELET (cells/mm^3)	HAART
13 OCT 2013	10.9	3800	58	40	251000	ZLN
28 OCT 2013	**4.0**	**2100**	95	65	250000	ZLN
12 NOV 2013	6.8	2200	87	59	249000	SLN
04 DEC 2013	7.9	3100	78	48	250000	SLN

Z-Zidovudine L-Lamivudine N-Nevirapine S-Stavudine

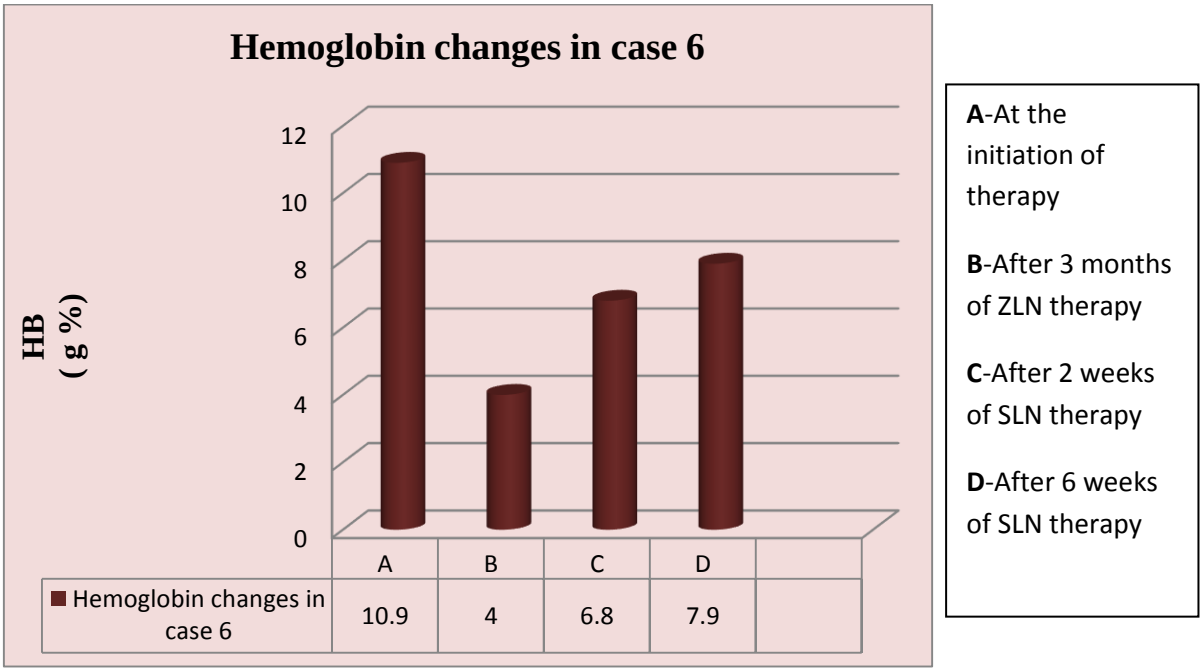


Fig 16: Hemoglobin changes in case 6

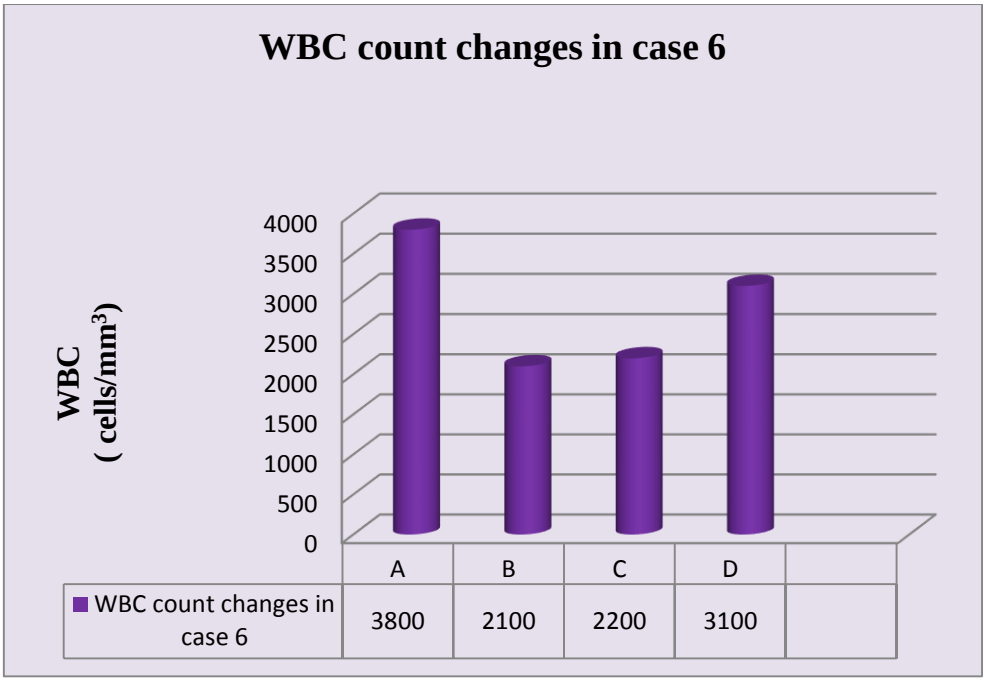


Fig 17: WBC count changes in case 6

After 2 weeks of change of drug regimen from ZLN to SLN, Hb was increased from 3.9 to 7.1 and after 3 weeks the Hb was 10.2.These changes in hematological parameters clearly indicates that the anemia caused was induced by Zidovudine and was reversed after a changeover of treatment to Stavudine.

CASE 7

Table 17: Haematological assessment in case 7

DATE	Hb (g)	WBC cells/mm^3	Platelets Cells/mm^3	SGOT (IU/L)	SGPT (IU/L)	HAART
19 JUL 2013	11.1	4700	450000	42	64	ZLN
21 SEP 2013	**2.3**	4500	460000	40	65	ZLN
07 OCT 2013	6.2	4500	460000	41	60	SLN
02 NOV 2013	8.0	4590	470000	40	62	SLN

Z-Zidovudine L-Lamivudine N-Nevirapine S-Stavudine

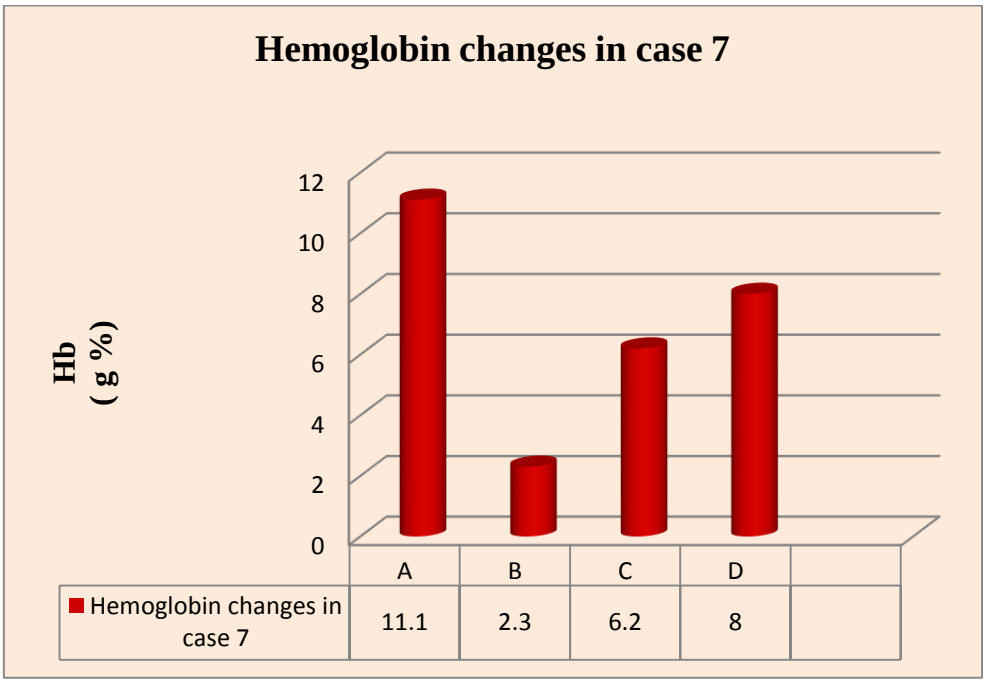
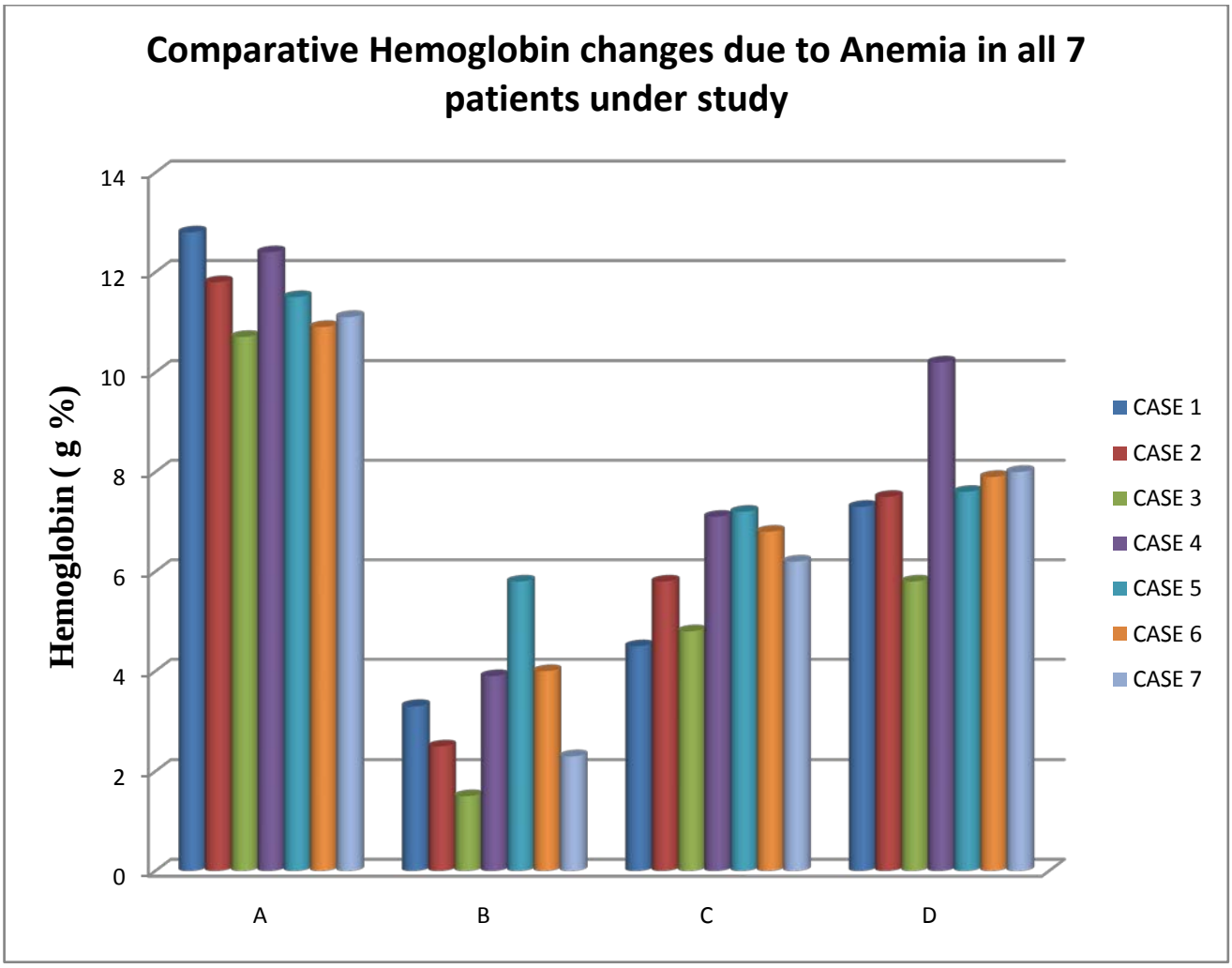


Fig 18: Hemoglobin changes in case 7

After a change from Zidovudine to Stavudine, the hemoglobin value increased from 4.0 to 6.8 and further to 7.9Also there was an increase in white blood cells from 2100 to 3100. This drastic reduction in hemoglobin value was due to Zidovudine induced anemia. An increased level of SGPT and SGOT also showed a decrease.

7. SUMMARY AND CONCLUSION

- Seven different patients were studied who were confirmed HIV positive by ELISA and Western blot assay.
- The literature review showed that works have been performed in AIDS patients, especially in other parts of India, this study have attempted in Tamilnadu.
- All the patients under this study were on Anti-retroviral therapy. After 3 months of treatment, they presented with different symptoms like fatigue, swelling of legs etc…,
- Various haematological analysis were performed and conditions like Anemia, Neutropenia, increase level of liver enzymes (SGOT & SGPT) and rarely thrombocytopenia was reported.
- Based on their reports they were given different treatments including blood transfusion and antiretroviral therapy was changed.
- After 2 weeks and 6 weeks, haematological parameters were analysed again and was found that there was improvement in haemoglobin and other parameters.
- The observations and findings clearly indicated that the improvement in haematological parameters was due to changeover of drug Zidovudine to Stavudine and confirmed that Anemia which existed in all patients studied was induced by Zidovudine.
- Out of 7 patients studied, Neutropenia, Thrombocytopenia, increased level of SGOT and SGPT was not found in all patients, but Anemia existed in all patients with a drastic reduction in Hemoglobin and was improved to an extent after changeover of antiretroviral drug regimen.



A-At the initiation of Anti-retroviral therapy

B-After 3 months of treatment containing Zidovudine

C-After 2 weeks of treatment changeover to Stavudine

D- After 6 weeks of treatment changeover to Stavudine

Fig 18: Comparative Hemoglobin changes due to anemia in all 7 patients under study

CONCLUSION

This study is concluded that Anemia is the most common hematologic abnormality associated with HIV infection. The incidence of anemia was found to be strongly associated with progression of HIV disease. People with anemia often suffer decreased quality of life as well as potential increased chance of mortality. While anemia may manifest as a mere laboratory abnormality in some individuals, others may experience typical symptoms (eg, fatigue, dyspnea, reduced exercise tolerance, diminished functional capacity) directly related to a reduction in hemoglobin concentration. It is important to remember that despite the potential side effects of these drugs, they may be essential for treatment of HIV infection or its complications, so they should not necessarily be avoided. Rather, people should be aware that side effects are a possibility and make efforts to identify and treat them.

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