Medbiotech Journal

MBTJ, 2(1): 124-131, 2018

Research Paper

Clinical, Biochemical and Immunological Profiles of HIV Patients Developing Immune Reconstitution Inflammatory Syndrome (IRIS)

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Received: 04 January 2018 Accepted: 14 February 2018 Published: 24 March 2018

Abstract

Cross sectional study was carried out in 32 cases of HIV infected patients on ART developing IRIS and attending Centre of Excellence(COE) RIMS and who were admitted in Medicine ward, RIMS Hospital. Duration of study was from October 2014 to September 2016. The study showed that IRIS was found mainly in the age group of 30-40 years and more common among patients with BMI of below 18.5 kg/m2 and paradoxical IRIS was more common than unmasking type of IRIS. Mean duration of development of IRIS was 87 days and the most common ART regimen in the study group was Tenofovir+Lamivudine+Efavirenz. Tuberculosis was the most common opportunistic infection and the mean baseline CD4 count at the time of initiation of ART was 167.5 cells/ µl. At the time of IRIS detection, the mean increase in CD4 cell count from the time of ART initiation was 86.66 cells/µl (Mean SD± 61.12cells/ µl. Tuberculosis was the most common opportunistic infection and paradoxical type of IRIS was more common than unmasking type.

Keywords: Antiretroviral therapy (ART); CD4 count; Human Immunodeficiency; Virus(HIV); Immune Reconstitution; Inflammatory; Syndrome (IRIS);

How to cite the article:

Z. Al Tariq, Clinical, Biochemical and Immunological Profiles of HIV Patients Developing Immune Reconstitution Inflammatory Syndrome (IRIS), Medbiotech J. 2018; 2(1): 124-131, DOI: 10.22034/mbt.2018.61528

1. Introduction

Antiretroviral therapy (ART) in HIV/AIDS patients leads to dramatic reductions in plasma viral load, improvement in CD4+ T cell counts and partial restoration of overall immune function. These immunological changes correlate with reduction in the frequency of opportunistic infections (OI) and prolonged survival. However, a subgroup of patients experience a clinical deterioration as a consequence of rapid and dysregulated restoration of antigen specific immune responses during the treatment. This was first noted following the introduction of Zidovudinemonotherapy in the early 1990s, when localized forms ofMycobacterium avium-intracellulare(MAI) infection were observed in association with the recovery rather than failure of cellular immune responses [1]. Over the past two decades, symptomatic deterioration in patients on antiretroviral therapy has been described in relation to a number of preexisting subclinical infections, inflammatory disorders and autoimmune diseases. Immune Reconstitution Inflammatory Syndrome (IRIS) is a widely recognised phenomenon that occurs in some patients initiating antiretroviral therapy (ART).

In India, the agreed practical definition of Immune Reconstitution Inflammatory Syndrome (IRIS) would be the "occurrence or manifestations of new opportunistic infections or existing opportunistic infections within six weeks to six months after initiating ART, with an increase in CD4 count" [2]. Typically, IRIS occurs within 2–12 weeks of the initiation of ART, although it may present later (usually between 6 weeks to 6 months) and has been reported in 1030% of patients initiating antiretroviral therapy (ART).In our country, the incidence of IRIS is estimated to be 10% among all patients in whom ART has been initiated; and up to 25% among those who have started ART and who have a CD4 cell count of below 50 cells/cu.mm.It is

most common in patients starting therapy with a CD4 +T cell count under 50/μL who experience a drop in viral load [3].

The IRIS may present in two different ways: ‘‘unmasking’’ IRIS, and “paradoxical” IRIS. In unmasking IRIS, the opportunistic infection (OI) is newly identified after initiation of ART. In paradoxical IRIS, the infection was previously treated but worsened clinically after ART initiation and the causative pathogens can be viable or non-viable [4]. The clinical spectrum is extremely diverse, and IRIS has been reported for at least 25 different infections, 2 tumours and 18 other non infectious conditions [5]. In the infectious category, most frequently reported cases are - Mycobacterium tuberculosis (TB), cryptococcal meningitis, varicella zoster, herpes viruses, CMV, Pneumocystis (carinii) jirovecipneumonia (PCP), hepatitis B and C etc. Other conditions like Mycobacterium aviumcomplex (MAC), latent cryptococcal infection are also reported. The non-infectious causes include rheumatoid arthritis, systemic lupus erythematosus (SLE), lupus like thyroid disease, Guillain-Barre syndrome, Reiter’s syndrome and Polymyositis [6-8]. Tuberculosis is the most common IRIS manifestation among HIV patients [9].

The underlying mechanism appears to be related to a phenomenon similar to type IV Hypersensitivity reaction and reflects the immediate improvements in immune function that occur at levels of HIV RNA drop and the immunosuppressive effects of HIV infection are controlled. In severe cases, the use of immunosuppressive drugs such as glucocorticoids may be required to blunt the inflammatory component of these reactions while specific antimicrobial therapy takes effect [10].

The differential diagnosis for IRIS includes active opportunistic infections, ARV drug failure, ARV drug toxicity or failure of antimicrobial therapy if the patient is already on the treatment. Culturing the microorganism in body fluids may provide clues to an active opportunistic infections, which would warrant antimicrobial therapy.

Previous reports of IRIS have primarily been published in the developed world. There is so far very little study in Manipur about the profiles of HIV patients with IRIS. Therefore this study was taken to assess clinical, biochemical and immunological profiles of HIV patients developing Immune Reconstitution Inflammatory Syndrome.

2. Materials and Methods

This cross sectional study was carried out in 32 cases of HIV infected patients on ART developing IRIS and attending Centre of Excellence(COE) RIMS and who were admitted in Medicine ward, RIMS Hospital. The duration of study was from October 2014 to September 2016.

All the patients were subjected to detailed history taking, clinical examination and relevant laboratory investigations were monitored at regular intervals as per NACO guidelines. The observations of the study were recorded in a data based program and collected data were checked for completeness and consistency. Descriptive and inferential statistical analysis was carried out in the present study. . Results on continuous measurements are presented on Mean SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Analysis of variance (ANOVA) was used to find the significance of study parameters between three or more groups of patients, Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. P value <0.05 was taken as significant. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Study variables were age,gender, religion,BMI,previous opportunistic infections,ART regimens, duration of ART, main presenting complaints.WHO clinical staging for HIV/AIDS opportunistic infection at the time of presentation, type of IRIS, Random Blood Sugar level(RBS), serum Proteins, SGOT and SGPT, serum Sodium and Potassium level and CD4 count.

2.1 Inclusion Criteria

Age above 15 years

HIV positive patients fulfilling Criteria for diagnosis of IRIS :

Increase in CD4 count(>25 cell/cu.mm)

New active infection or worsening of infection after initiating ART.

Occurrence or manifestations within 6 weeksto 6 months after initiation of ART.

New lymph node enlargement.

New radiological appearance and signs after initiation of ART. Patients willing to participate in this study.

2.2 Exclusion Criteria

Patients with drug toxicity, and treatment failure.

Patients who were unwilling for the study.

Patients who were likely to migrate and be transferred out to othercentres. Patients with decreasing CD4 count.

CD4 count was done by flow cytometry (FACS Count) - baseline and at the time of IRIS detection. Specific investigations was also done to rule out or confirm OIs, depending on the clinical need.
The diagnosis of IRIS was made as defined in NACO guidelines [2]:
Increase in CD4 count(>25 cell/cu.mm)
New active infection or worsening of infection after initiating ART.
Occurrence or manifestations within 6 weeks to 6 monthsafter initiation of ART
New lymph node enlargement
New radiological appearance and signs after initiation of ART

Approval for conducting the study was obtained from the institutional Ethics Committee, RIMS. Informed written consent was taken from all patients who fulfilled the inclusion criteria and did not have any exclusion criteria. Patients were explained about the purpose and procedure of the study in their native language. Name of the participants were not disclosed. Confidentiality was maintained.

3. Results

Between October 2014 to September 2016, 32 patients developed immune reconstitution inflammatory syndrome and were taken up for the study. There were 20 males which comprised 62.50 % of the study group. Females were less and comprised 12(37.50 %) of the study population.Fig. 2 shows that 40.62% of the study subjects were in the age group of 31-40 followed by 41-50 age group comprising of 28.12%.Only 3.13% of patients were below 20 years of age, 6.25% between 21-30 years and 12.50% of patients were above 60 years. The mean age of the patients was 42.75 years with standard deviation of 13.03 years. Majority of the patients were Hindu (59.4%) followed by Christian (34.4%) and Muslim (6.3%).Body Mass Index(BMI) of 59.5% were below 18.5 followed by 40.6% of patients having 18.5 to 25. None of the patients had BMI above 25.

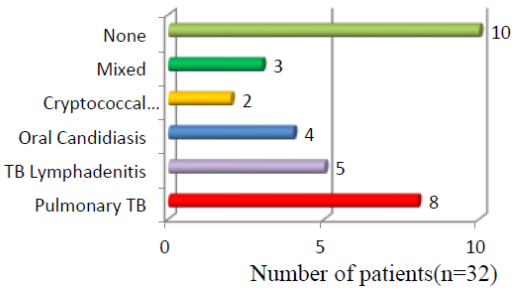

Figure 1. Pattern of previous Opportunistic Infections of respondents

Figure 1 shows that 10(31.3%) patients were having no detectable previous opportunistic infection. The most common previous opportunistic infections in IRIS was Pulmonary tuberculosis which was seen in 8(25%) patients followed by TB Lymphadenitis 5(15.6%). Oral candidiasis without any other opportunistic infection was seen in 4(12.5%) of the study patients.3(9.37%) of respondents had mixed infection of Pulmonary TB or extra Pulmonary TB with Oral candidiasis. 2(6.25%) patients had previous cryptococcal meningitis at the time of initiation of ART.
The majority of patients, 24(75%) were taking Antiretroviral Therapy(ART) regimen of Tenofovir(TDF), Lamivudine(3TC) and Efavirenz(EFV) followed by 7(22%) taking Zidovudine(ZDV), Lamivudine(3TC) andNevirapine(NVP). Only 1(3%) of respondents was takingZidovudine(ZDV), Lamivudine(3TC) and Efavirenz(EFV). All the respondents were on the first line of ART regimen.53.12% of the population under study had taken ART for 61-90 days, 18.75% had taken for 31-60 days and same percentage had taken for 91-120 days,
9.37% had taken for more than 120 days.Mean duration of treatment was 87 days with a Standard Deviation of
25.86 days.

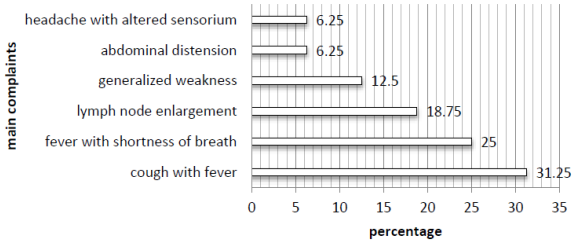

Figure 2. Main patient complaints at the time of presentation of IRIS

Figure 2 shows main presenting complaints of HIV patients with IRIS were cough with fever(31.25%) and fever associated with shortness of breath(25%). 18.5% of patients came to hospital with a complaint of enlargement of one or more group of cervical lymph node. Other complaints of the patient included generalized weakness(12.5%), abdominal distension(6.5%) and headache with altered sensorium(6.5%).
Majority (53.12%) of the respondents were having WHO clinical stage IV of HIV/AIDS and 46.87 were having clinical stage III. 20(twenty) patients were diagnosed as IRIS-Pulmonary TB according to the X-ray chest findings. Computerized Tomography(CT)

scan was used for the supportive diagnosis of 3(three) patients of Pulmonary TB,
4(four) patients of TB lymphadenitis, and 2(two) patients for Koch's abdomen. Ultrasound(USG) abdomen was used for diagnosis of 2(two) cases of Koch's abdomen with ascitic fluid analysis showing protein >3gms/dl and ADA >40 U/L. Sputum for AFB was positive in 5(five) cases of Pulmonary TB despite having increased CD4 count of >25cells/µL. Fine Needle Aspiration Cytology was used for diagnosis of 7(seven) cases of TB Lymphadenitis and 1(one) case of TB Orchits showing caseous necrosis or suppuration. 2(two) cases of cryptococcal meningitis of paradoxical IRIS were diagnosed according to cerebrospinal fluid(CSF) analysis showing positive Indian Ink preparation and cryptococcal antigen agglutination system(CALAS) test.
Unmasking subtype of IRIS(53.12%) was more common sub types of IRIS and Paradoxical IRIS event was found in46.87% among the respondents.

Table 1: Opportunistic infections(OI) among the respondents

Name of OI	Paradoxical	Unmasking	TOTAL	
	n	n	n	%
Pulmonary TB	15	5	20	62.5
TB Lymphadenitis	5	2	7	21.87
Cryptococcal meningitis	2	0	2	6.25
Koch's abdomen	0	2	2	6.25
TB Orchitis	0	1	1	3.125
	22	10	32	100

Table 1 shows that most common opportunistic infection was Pulmonary Tuberculosis 15 (46.88%) followed by TB Lymphadenitis10(31.25%). Other opportunistic infections were Koch's abdomen 4(12.5%), Cryptococcal meningitis 2(6.25% and TB Orchitis 1(3.12%).
Half of the respondents (50%) of IRIS patients had random blood sugar of less that 100mg/dl and 40.6% of patients had 100-120mg/dl followed by 9.4% patients having random blood sugar >120mg/dL(Mean ± SD: 102.19±19.89).Majority of the respondents(75%) were having normal total protein level of 6-8gms/dL with a Mean ± SD 7.09±0.99. While total protein was normal in majority of the patients, albumin level were 2.5-3.5gm/dL in half of the patients and 12.5% of the patients were having <2.5gm/dL. Only 37.5% of the patients had >3.5gm/dL of serum albumin(Mean ± SD 3.18±0.70). 53.1% of patients were having Serum Globulin level of 3.5-4.5gm/dL with a Mean ± SD 3.94±0.78.
Serum Glutamic Oxaloacetic Transaminase(SGOT) level was higher than 48 IU/L in 56.3% of the patients while 43.8% had 0-42IU/L (Mean ± SD 76.28±98.07). Serum Glutamic Pyruvic Transaminase(SGPT) level was 0-48 IU/L in majority of the patients(68.8%) while 31.3% had >48 IU/L(Mean ± SD 47.06±42.58.Table 16 and Figure 16a&b shows 87.5% of IRIS patients were having Serum Sodium level of <135 mmol/L and 12.5% had 135-146 mmol/L(Mean ± SD 130.50±5.07). Majority of patients(90.6%) were having Serum Potassium of 3.5-5.5 mmol/L (Mean ± SD 3.94±0.51).

Table 2: Biochemical profiles of IRIS patients

Name	No. of patients	%	Mean ± SD:
Random Blood Sugar(mg/dL)			
<100	16	50.0	102.19±19.89
100-120	13	40.6	
>120	3	9.4	
TOTAL PROTEIN(gm/dL)		%	Mean ± SD
<6	3	9.4	
6-8	24	75.0	7.09±0.99
>8	5	15.6	
ALBUMIN (gm/dL)			
<2.5	4	12.5	
2.5-3.5	16	50.0	3.18±0.70
>3.5	12	37.5	
GLOBULIN (gm/dL)			
<3.5	8	25.0	
3.5-4.5	17	53.1	3.94±0.78
>4.5	7	21.9	
SGOT (IU/L)			
0-42	14	43.8	
>42	18	56.3	
SGPT (IU/L)			
0-48	22	68.8	47.06±42.58
>48	10	31.3	
Sodium (mEq/l)			
<135	28	87.5	
135-146	4	12.5	130.50±5.07
>146	0	0.0	
Potassium (mEq/l)			
<3.5	3	9.4	
3.5-5.5	29	90.6	3.94±0.51
>5.5	0	0.0	

Table 3: CD4 count of IRIS patients
P value <0.001

CD4	No. of patients (n=32)	%	Mean ± SD
Initial CD4			
<100	10	31.3	
100-200	15	46.9	167.50±116.54
>200	7	21.9	
IRIS CD4			
<200	11	34.4	
200-400	18	56.3	254.22±130.35
>400	3	9.4	
Difference of CD4			
<50	12	37.5	
50-100	11	34.4	86.66±61.12
>100	9	28.1	

Table 3 shows that the initial CD4 was <100 cells/µl in 31.3% of the patients 100-200 cells/µl in 46.9% of the patients with Mean ± SD167.50±116.54. At the time of diagnosis of IRIS, more than half of the patients (56.5%) had CD4 count of 200-400cells/µl and 34.4% of patients had <200cells/µl. 9.4% of patients were having CD4 count of<400cells/µl at diagnosis of IRIS(Mean ± SD 254.22±130.35). We found statistically significant increase in CD4 count from the baseline to the time of diagnosis of IRIS (p value <0.001). There was mean increase in CD4 cell count of 86.66±61.12 from the time of initiation.37.5% had an increase of CD4 count <50 while 34.4% of patients were having 50-100 cells/µl. CD4 count increase >100 cells/µl was found in 28.1% of the patients.

4. Discussion

The study included 32 cases of HIV patients on ART developing immune reconstitution inflammatory syndrome(IRIS) who wereattending Centre of Excellence(COE) RIMS and who were admitted in Medicine ward, RIMS hospital from October 2014 to September 2016.The COE RIMS initiated ART to a total of 738 HIV positive patients in between October 2014 to September 2016. Out of 738 patients who were initiated on ART first line during the study period, only 32 patients were eligible for our study. Out of the total 32 patients, 20 were males
(62.5%) and 12 were females(37.5%). The higher incidence in males can be attributed to the high prevalence of intravenous drug abuse in Manipur.Higher incidence of male (62.5%) in the study population was almost similar with the study conducted by Achappa N et al11 where male comprised of 75% of the HIV patients developing IRIS in their study at KMC Hospital, Mangalore.

Maximum cases were in the age group of 30-40 years (40.62%). Mean age of the patients was 42.75±13.03 years. Our finding is higher than the study conducted by Kumarasamy N et al [12] where the mean age was 29 years in their study. This distribution of age can be explained by the declining trend in the prevalence among people with injection drug (PWID) use who reside in northeastern states. Since Hindu people are dominant in the study population society, majority of the study population were Hindus(65.6%) followed by Christians(28.1%). Majority of our study population(59.4%) were having Body Mass Index(BMI) of mean 18.22 with standard deviation of 2.56 which is comparable to the findings by Latang et al 13 and Grant PM et al [14] where they found mean BMI of 18.5 in their study.Low BMI(<18.5) is a marker for poor prognosis in patients with HIV and has also been associated with increased risk of TB and death [28].

In our study it was also observed that 10(31.3%) patients were having no other previously diagnosed infection apart from HIV infection. The most common previous opportunistic infections at the time of presentation of IRIS was Pulmonary tuberculosis which was seen in 25% patients followed by TB Lymphadenitis. Our findings was similar to study conducted by Huruy K et al15and Tieu HV et al [16] where Pulmanary tuberculosis was the most common preexisting opportunistic infections in their study.

All of the patients were taking first line ART and most common(75%) regimen being combination of Tenofovir (TDF), Lamivudine(3TC) and Efavirenz(EFV). This is due to high incidence of preexisting pulmonary and extra pulmonary tuberculosis in the study population, and majority of the patients were taking treatment for tuberculosis. Our finding was different from study conducted by Achappa B et al11 where 65% of patients developing IRIS were on Stavudine+Lamivudine+Nevirapine regimen.The average mean duration of ART before IRIS episodes was was 87 days with SD±25.86 days. Our finding was nearly similar with study findings of Huruy K et a l15 where mean duration of treatment before manifestations of IRIS was 80 days, but longer duration than findings of Kumarasamy N et al [12] and Porter B et al [17] where mean duration of treatment was42 days and 60 days respectively.

The main presenting complaints of HIV patients with IRIS at presentations were cough with fever(31.25%) and fever associated with shortness of breath(25%). 18.5% of patients presented with a complaint of enlargement of one or more group of cervical lymph node. Other complaints of the patient included generalized weakness(12.5%), abdominal distension(6.5%) and headache with altered sensorium(6.5%). Our findings were almost similar with study findings conducted by Tieu HV et al [15] in Thailand where 73% developed lymph node enlargement predominantly along the cervical chain, 59% had fever, 36% reported cough, and 18% had abdominal pain. It was also consistent with study findings by Dibyendu D et al [18] where fever was predominant involving 40% patients of IRIS followed by generalized lymphadenopathy (38%).

More than half (53.12%) of the respondents were having WHO clinical stage IV of HIV/AIDS and 46.87 were having clinical stage III. This findings was is comparable with other studies by Huruy K et al [15] at Addis Ababa, Ethiopia in 2006- 2007. This findings can be explained by the fact that majority of study population were having CD4 count

mean±SD254.22±130.35, the level where various opportunistic infections are common.

Diagnosis of IRIS was made according to NACO guideline. All the patients had temporal association between the commencement of ART within 6 months and the development of unusual clinical phenomena providing a strong clue to the diagnosis of IRIS. All the study subjects were clinically examined and all of them were having increase in CD4 count(>25 cells/µL after the initiation of ART thereby ruling out immunological failure. ART failure was also ruled out in the study subjects as at least 6 months of ART treatment is needed to considera ART failure.2 Relevant laboratory investigations were done to confirm the diagnosis of IRIS in our study subjects. Chest X ray was showing findings supportive of diagnosis of 20(twenty) cases ofpulmonary TB. Fine Needle Aspiration Cytology(FNAC) of lymph node was showing necrosis or suppuration in 7(seven) cases of TB Lymphadenitis and 1(one) case of TB Orchitis.

A majority (68.75%) had worsening of preexisting infections (paradoxical IRIS) and 31.25% of the study subjects had new opportunistic infections (unmasking IRIS). This finding is almost similar with study finding by Tieu HV et al15where paradoxical IRIS was found in 82% in their study, but different from study results by Haddow LJ et al 19 and Murdoch et al 20 wheremajority of IRIS episodes were unmasking type. The most common opportunistic infection associated with IRIS was pulmonary tuberculosis 20(62.5%) followed by tuberculous lymphadenitis 7(21.87%), other infections being abdominal Kochs 2(6.25%), paradoxical worsening of Cryptococcal meningitis 2(6.25% and unmasking of TB Orchitis 1(3.12%). These infections were manifested by worsening of pre-existing symptoms or appearance of new symptoms supported by new changes in imaging. Our study findings were consistent with the findings of Huruy K et al [15] and Manosuthi W et al [21] where tuberculosis was the most common opportunistic infections in their study.

In this study, 50% of IRIS patients had random blood sugar of less that 100mg/dl and 40.6% of patients had 100120mg/dl followed by 9.4% patients having >120mg/dL with mean ± SD: 102.19±19.89mg/dL. This finding can be explained by majority of study population having decreased oral intake at the time of presentation due to their illness like fever, cough, etc.

The majority of the this study population(75%) were having normal total protein level of 6-8gms/dL with a Mean ± SD 7.09±0.99gm/dL. While total protein was normal in majority of the patients, albumin level was low<3.5gm/dL) in majority of the patients(62.5%) with Mean ± SD 3.18±0.70). More than half of patients were having Serum Globulin level of > 3.5 gm/dL with a Mean ± SD 3.94±0.78.

There was mild increase in mean Serum Glutamic Oxaloacetic Transaminase(SGOT) level of 76.28 IU/L with standard deviation of 98.07 IU/L. Serum Glutamic Pyruvic Transaminase(SGPT) level was normal in majority of the patients.(Mean±SD 47.06±42.58). Our findings were lower and different from other study finding by Huruy K et al 15 where there was significant increase in mean SGPT(AST) and SGOT(ALT) level, 102 IU/L with a standard deviation of 119.4 IU/L and 86.5 with standard deviation of 109.6 respectively. More than two third of patients (87.5%) of were having low serum Sodium level of <135 mmol/L with Mean ± SD 130.50±5.07. Majority of the study population were having normal serum Potassium levels (Mean ± SD 3.94±0.51).

In our study, mean baseline CD4 count(at the time of initiation of ART) 167.5 cells/µl (Mean ± SD 116.54). CD4 count at the time of diagnosis of IRIS was 254.22 cells/µl (Mean ± SD 130.35 cells/µl). There was mean increase in CD4 cell count of 86.66 cells/µl with standard deviation of 61.12cells/mm from the time of initiation. Our study findings were nearly similar to other study findings in other parts of the country by Achappa B et al11 where initial mean CD4 count was 135 and CD4 count at development of IRIS was 239 cells/µ. l However, our findings were higher than findings of Agarwal SG et al [22] where the mean+SD of baseline CD4 count in IRIS was 85.75+20.84 cells/µl at the time of initiation of ART and Mean+SD of increase in CD4 count after diagnosis of

IRIS patients was 76.88 + 29.13/µl. Our study findings confirmed that IRIS is likely to develop if CD4 cells are <200 cells/µL prior to ART initiation [23].

5. Conclusion

The present study showed that IRIS was found mainly in the age group of 30-40 years. And IRIS was more common among patients with low BMI of below 18.5 kg/m2. Paradoxical IRIS was more common than unmasking type of IRIS. The mean duration of development of IRIS was 87 days and the most common ART regimen in the study group was Tenofovir + Lamivudine+Efavirenz.

Tuberculosis was the most common opportunistic infection found in the study. Serum albumin was low in half of the patients and globulin level was normal in majority of the study population. The mean baseline CD4 count at the time of initiation of ART was167.5 cells/ µl. At the time of IRIS detection, the

mean increase in CD4 cell count from the time of ART initiation was 86.66 cells/µl with standard deviation of 61.12cells/ µl. Timely recognition and management of IRIS is very important to reduce mortality and mobidity among ART patients. HIV infected patients who are initiated on ART should be followed up regularly in the first 6 months so as to diagnose development of IRIS at the earliest. Since low CD4 count at ART initiation also contributes to increase chance of development of IRIS, cheap and robust version of virologic monitoring is important.

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