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STUDY OF INCIDENCE & RISK FACTORS FOR IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) IN ADULT HIV PATIENTS IN NAGPUR REGION

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ABSTRACT: BACKGROUND & OBJECTIVES: It is estimated that 10-25% of patients who are started on HAART, experience Immune Reconstitution Inflammatory Syndrome (IRIS). This clinical deterioration is a result of an exuberant inflammatory response towards previously diagnosed or incubating opportunistic pathogens as well as response towards undefined antigens. Thus study was carried out with objectives to determine incidence, clinical spectrum & the risk factors of IRIS in HIV patients initiating HAART, registered in ART clinic. **METHODS:** Prospective study of 118 HIV positive patients (all HIV-1) attending ART clinic between Nov. 2006 & Aug. 2007 was carried out at Government medical college, Nagpur. Patients were investigated as per standard protocol. CD4 cell counts were performed on the blood samples (FACS calibur, Becton- Dickinson, Immunocytometry system). Clinical follow up was done every 15 days as per the NACO guidelines. Base line & follow up values of CD4 counts were compared to assess the IRIS events. The patients presented with opportunistic infections, they were first treated for opportunistic infections & subsequently HAART was initiated as per NACO guidelines. **RESULTS:** Out of 118 HIV positive patients, 112 patients were started on HAART. Out of Fifty nine patients who came for the regular clinical follow up when followed over a period of 10 months, 8 patients (13.56%) experienced IRIS infections. Mean+SEM of baseline CD4 count in IRIS was 85.75+20.84/ μ l at the time of initiation of HAART while for patients without IRIS was 151.7+12.45 cells/ μ l (Significant 'p' value 0.0480). Mean+SEM of increase in CD4 count after HAART in IRIS patients was 76.88 + 29.13/ μ l while for patients without IRIS after HAART initiation was found to be 181.8+18.92/ μ l (Significant 'p' value 0.0379). Mean duration of development of IRIS in 8 cases after HAART was about 47.25 days. Infections in 8 IRIS patients were extra-pulmonary Mycobacterium tuberculosis, Cryptococcal meningitis, Herpes Zoster, Cytomegalovirus retinitis & oral candidiasis as single or in mixed form. Six IRIS cases experienced reactivation of dormant infection & 2 cases showed new infections. **INTERPRETATION & CONCLUSION:** In present study, high incidence of IRIS was found with male preponderance mostly with reactivation of occult infections. Risk factor for development of IRIS was found to be baseline CD4 cell count less than 100/ μ l. So, we suggest that occurrence of IRIS infections can be prevented or reduced by initiating HAART before CD4 cell count drops below 100 cells/ μ l.

KEYWORDS: Immune Reconstitution Inflammatory Syndrome, Highly Active Antiretroviral Therapy, AIDS.

INTRODUCTION: After introduction of highly active antiretroviral therapy (HAART) in 1995, it took three years to recognize the new syndrome of Lipodystrophy as a long-term complication of HAART. It was found to be a direct toxic consequence of the various drugs used in combination regimen.

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Another two years later, an additional syndrome was described in patients who recently initiated HAART i.e. the Immune Reconstitution Inflammatory Syndrome (IRIS). Although already recognized in pre HIV era, in patients with treatment for tuberculosis & leprosy; it became substantially more frequent in HIV infected patients on HAART.¹

The immune reconstitution inflammatory syndrome is characterized by worsening in clinical, laboratory or radiological findings despite improvements in the HIV RNA levels & CD4 counts after the introduction of antiretroviral therapy & it is due to restoration of pathogen specific responses. IRIS may occur during or shortly after treatment of an opportunistic infection (OI) or as a new clinical syndrome resulting from previously unrecognized occult infection.¹

The term IRIS describes a collection of different inflammatory disorders, which are associated with paradoxical deterioration of various preexisting infectious processes following commencement of HAART in HIV, infected patients. These preexisting infections in individuals with IRIS may have been previously diagnosed & treated or may have been symptomless & later revealed by the patient's improved capacity to mount an inflammatory response.¹

It is estimated that 10-25% patients who start HAART experience immune reconstitution inflammatory syndrome.² Various studies have reported infections with Mycobacteria (M. tuberculosis & atypical, both), Cryptococcus neoformans, Skin infections with Herpes virus, Cytomegalovirus retinitis, Pneumocystis jirovecii pneumonia, Candida & Molluscum contagiosum etc. in IRIS cases.^{2,3} Since, the data on IRIS from our region is not available so study was undertaken with the objectives to study the incidence, predictors & clinical spectrum of IRIS in HIV-1 positive cases attending ART clinic.¹

MATERIAL & METHODS: Prospective study of 118 HIV positive patients attending ART clinic between Nov. 2006 & Aug. 2007 was carried out at Government medical college, Nagpur. Patients were investigated as per their presenting symptoms. Different samples as per their complaints along with specimen of blood were collected. Samples were processed as per conventional techniques⁴ in the laboratory. CD4 cell counts were performed on the blood samples as per manufacturer's instructions (Facs calibur, Becton- Dickinson, Immunocytometry system). Clinical follow up was done every 15 days as per the NACO guidelines.

Base line & follow up values of CD4 counts were compared to assess the IRIS events. When patients presented with opportunistic infections, they were first treated for opportunistic infections & subsequently HAART was initiated as per NACO guidelines. The plasma viral load could not be carried out due to non-availability of facility in the laboratory. No healthy controls were taken in this study.

RESULTS: In the present study, 118 patients were studied. All were HIV-1 positive. Out of that, 112 patients were started on HAART. Eighty five (75.9%) were males & 27 (24.1%) were females. Fifty nine patients came for the regular clinical follow up every 15 days in ART clinic and were investigated for evaluation of CD4 cell count every six months following HAART commencement. All patients were followed over a period of 10 months. Out of 59 patients, 8 patients experienced IRIS infections.

Two patients in non-IRIS group did not show increase in CD4 cell count rather showed decrease in CD4 cell count at the end of 6 months of HAART initiation. Eight patients (13.56%)

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experienced IRIS events. out of which 7(87.5%) were males & 1 (12.5%) was female. Mean+SEM of age of IRIS patient was 35.38+2.375years. Mean+SEM of baseline CD4 count in IRIS was 85.75+20.84/ μ l at the time of initiation of HAART. Mean + SEM of increase in CD4 count after HAART in IRIS patients was 76.88+29.13/ μ l. Among six symptomatic patients, Mean + SEM of duration between treatment of opportunistic infections & and the commencement of HAART was 47.38+23.29 days.

Two patients were asymptomatic at the time of recruitment for HAART. Mean duration of development of IRIS in 8 cases after HAART was about 47.25days. Infections in 8 IRIS patients were, Mycobacterium tuberculosis (Extra pulmonary) seen in 5 patients (62.5%), Cryptococcal meningitis in 3 patients (37.5%), Herpes Zoster in 2 patients (25%), oral candidiasis in 1 patient(12.5%) & Cytomegalovirus retinitis in 1 patient (12.5%).

These infections were seen as singly or in mixed form. Six IRIS cases experienced reactivation of dormant infection & two cases showed new infections (Table No. I). Mean + SEM of age of patients without IRIS was 35.84+1.029 years. 35 were males (68.63%) and 16(31.37%) were females. Mean+SEM of CD4 count in patients without IRIS was 151.7+12.45 cells/ μ l at the time of start of HAART.

Mean+SEM of increase in CD4 count in patients without IRIS after HAART initiation was found to be 181.8+18.92/ μ l. Mean+SEM of duration between treatment of opportunistic infections & and the commencement of HAART was 26.53+7.548 days (Table No. II).

DISCUSSION AND CONCLUSION: Numerous studies have shown that HAART corrects many of the immune defects caused by HIV infection.⁵⁻⁷ Restored pathogen specific immune responses may result in regression or prevention of OI's.⁶⁻⁹ However, the restoration of pathogen –specific immune responses may also cause inflammation of tissues infected by pathogen, known as Immune Restoration Disease (IRD).

Thus the major question in the setting of HAART – treated HIV disease is whether a clinical OI is immunodeficiency- related or an IRD, because the appearance of OI's among HIV infected patients on HAART always raises the concern of possible HAART failure. Attempts at solving this problem resulted in the first proposal of criteria for diagnosis of IRD⁵, which include, in addition to precise clinical findings, success of HAART, where virological success is considered a major criterion & an increased blood CD4 cell count a minor criterion.

In our patient series, 59 of 112 patients started on HAART came for regular follow up every 6 months for evaluation of CD4 cell count after HAART initiation over a study period of 10 months. Of them, all OI episodes in 8 patients fulfilled the above clinical & immunological criteria for the clinical OI to be defined as IRD while remaining 51 patients did not experience any kind of IRIS infection over a follow up period of 10 months, thus belonged to Non IRIS group.

Two patients in non- IRIS group did not show increase in CD4 cell count rather showed decrease in CD4 cell count at the end of 6 month of HAART initiation. These two patients could undergo immunological improvement in subsequent follow ups. This deterioration can be ascribed either to incomplete adherence to HAART or could be due to resistance to HAART.

Present Study showed male preponderance as described in other studies.^{2, 3, 10, 11}

As far as age is concerned, most of the IRIS patients (87.5%) belonged to age groups 23-30 and 31-40 years at HAART initiation. However, there was not much of statistical difference observed

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as regards to age group between IRIS group and Non- IRIS group of patients at the time of HAART initiation. Though, this is not in agreement with other studies, Initiation of HAART at younger age has been reported to be strong risk factor for development of IRIS infection.^{2,3,11}

Incidence of IRIS in our study was found to be 13.56%. This falls in line with 16.7% incidence value reported by other workers³. One Indian study by N. Kumarasamy et al found out the Incidence of immune reconstitution syndrome in patients co-infected with HIV/ tuberculosis to be 15.2%¹³. But high incidences of IRD i.e. 22.7% to 68% have also been reported by others^{2, 10, 11, 14}. One reason for the lower incidence in our study may be that this was a prospective study with a shorter period of ten months follow up and onset of IRIS continues for up to 2 years following initiation of HAART as described in previous studies.^{11, 15}

IRIS events are usually experienced in patients with CD4 count less than 100/ μ l at HAART initiation. IRIS infections more commonly seen in 6/8(75%) of patients who had baseline CD4 cell count less than 100/ μ l as compared to those with baseline CD4 count more than 100/ μ l at the time of HAART initiation. The 8 patients who experienced IRIS events had Mean + SEM of baseline CD4 cell count 85.75+20.84/ μ l while Mean+SEM of baseline CD4 cell count in non-IRIS group was 151.7+12.45/ μ l. This difference in baseline CD4 counts was found to be statistically significant as has also been reported in studies by other workers.^{3, 10}

This study thus showed that low baseline CD4 cell count represents a risk factor for IRD. This data thus indicates the need for earlier HAART initiation. In our study, association between the risk of IRIS and the magnitude of increase in CD4 cell count over 6 months of HAART was observed, which indicates that the rate of immune reconstitution is an important factor in susceptibility to IRIS¹¹. As a whole, IRIS events were observed with- in four months of initiation of HAART but average duration of development of IRIS events after HAART initiation was found to be 47.25 days. Majority (75%) of the cases of IRIS occurred within the first 60 days of initiating HAART, which is in accord with prior individual reports and case series.^{10, 11, 14, 16-19}

Six out of Eight IRIS cases showed reactivation of old occult infections whereas remaining two cases experienced new infections. Reactivation was observed in the form of Mycobacterium tuberculosis, Cryptococcal meningitis and CMV retinitis infections. New infections were observed in the form of Herpes zoster infection and Mycobacterial cold abscess. Mycobacterial tuberculosis infections were extra pulmonary infections. These IRIS infections were also reported by other workers^{2, 3, 10, 11}. Most of the cases i.e. 6/8(75%) showed reactivation of old treated infections with increase in CD4 count with- in two months of HAART initiation while Only two cases i.e. 2/8(25%) showed new infections with improved immune response in more than 3 month period. This showed that reactivation of old occult or asymptomatic infection occurs earlier than the appearance of new infection.¹⁰

Incidence of IRIS infections in this study was found to be 13.56% which is quite high and alarming. IRIS group of patients presented with reactivation of old occult infections. Risk factor for development of IRIS infections was found to be CD4 cell count less than 100/ μ l at the time of HAART initiation. So, we suggest that occurrence of IRIS infections can be prevented or reduced by initiating HAART before CD4 cell count drops below 100 cells/ μ l.

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Case No	Age (Years)	Sex	Base Line CD4 count / μ l	CD4 count/ μ l at IRIS events	Duration between Opportunistic infection therapy & HAART (days)	Duration of development of IRIS after HAART (days)	IRIS events	Nature of IRIS events
1.	30	M	23	57	55	57	Cryptococcal meningitis	Reactivation
2.	38	M	64	88	19	28	Tuberculous meningitis	Reactivation
3.	34	M	85	145	191	32	Cryptococcal meningitis, Tuberculous meningitis	Reactivation
4.	30	M	136	190	18	12	Tuberculous lymphadenitis	Reactivation
5.	47	M	25	45	90	33	Pulmonary, Abdominal tuberculosis & CMV retinitis	Reactivation (all)
6.	39	M	58	81	0	10	Cryptococcal meningitis, Genital Herpes Zoster	Reactivation (both).
7.	26	F	96	349	0	114	Mycobacterial Cold abscess	New infection
8.	39	M	199	346	6	92	Herpes Zoster, oral candidiasis	New infection

TABLE 1: SHOWING DETAILS OF EIGHT CASES WITH IRIS EVENTS

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SL. No.	Characteristic	Patients with IRIS (8)	Patients without IRIS (51)	'p' value
1.	Male: female	7:1	2.18:1 (35 Males & 16 Females)	
2.	Age (years)	35.38 + 2.375	35.84 + 1.029	0.8662
3.	CD4 cell count, cells/ μ l at the time of initiation of HAART	85.75 + 20.84	151.7 + 12.45	0.0480*
4.	Average duration of development of IRIS events after HAART initiation (days)	47.25	Patients are under follow up.	
5.	Time from initiation of therapy for OI's to initiation of HAART (days)	47.38+23.29	26.53 + 7.548	0.3276
6.	Average increase in CD4 cell count (cells/ μ l) after HAART initiation at the time of development of IRIS events	76.88 + 29.13	181.8 + 18.92	0.0379*

TABLE 2: SHOWING ANALYSIS OF FACTORS (ASSOCIATED WITH THE OCCURRENCE OF IRIS) IN PATIENTS WITH IRIS & THOSE WITHOUT IRIS

* ---- 'p' value < 0.05 is considered as statistically significant.

'p' value was calculated by unpaired 't' test using Graph pad prism version 4 for statistical analysis.

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