ORIGINAL ARTICLE

Prevalence, Clinical Manifestations and Predictors of Immune Reconstitution Inflammatory Syndrome among HIV-Infected Patients in Malaysia Infectious Disease Centre: A Retrospective Study

Nurul Suhaili Kamarudin[1,2], Niazlin Mohd Taib[1], Adilahtul Bushro Zaini[2], Hasni Mahayidin[3]

[1] Department of Medical Microbiology and Parasitology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
[2] Microbiology Unit, Department of Pathology, Hospital Sungai Buloh, Jalan Hospital, 47000 Sungai Buloh, Selangor, Ministry of Health, Malaysia.
[3] Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.

ABSTRACT

Introduction: Immune reconstitution inflammatory syndrome (IRIS) is paradoxical clinical deterioration experienced by some HIV-infected patients in response to antiretroviral therapy (ART). There is still limited published data on IRIS from this region including Malaysia. This study aimed to determine IRIS prevalence, clinical manifestations and possible predictors among HIV-infected patients in an infectious disease centre in Peninsular Malaysia. **Method:** This retrospective study was conducted in Hospital Sungai Buloh involving secondary data of 256 HIV-infected patients who were initiated on ART in the year 2017. Medical record of each patient was reviewed for up to 12 months following ART initiation to identify IRIS diagnosis which was made by the treating physician. Relevant clinical and laboratory information were retrieved from hospital electronic database. **Results:** IRIS has occurred in 17.6% of patients. Infections by *Mycobacterium tuberculosis* (53.3%), *Pneumocystis jirovecii* (11.1%) and *Talaromyces marneffei* (6.6%) were the commonest three aetiologies of IRIS. Subacute lupus erythematosus was the only non-infectious IRIS identified. Baseline HIV viral load, CD4+ T-cell count and haemoglobin level between IRIS and non-IRIS patients were significantly different. Risk of developing IRIS was increased seven times in patients with CD4+ T-cell count < 100 cells/μL and four times in patients with HIV RNA viral load > 5.5 $\log_{10}$ copies/ml prior to ART initiation. **Conclusion:** *Mycobacterium tuberculosis* infections were the highest IRIS manifestation. Although rare, non-infectious IRIS does occur and should be part of the differential diagnosis. Patients with positive predictors should be appropriately monitored for possible IRIS development once initiated on ART.

Keywords: Immune reconstitution inflammatory syndrome (IRIS), Antiretroviral therapy (ART), Human Immunodeficiency Virus (HIV), Acquired Immune Deficiency Syndrome (AIDS)

Corresponding Author:
Hasni Mahayidin, MPath
Email: hasni_m@upm.edu.my
Tel: +603-97692390

INTRODUCTION

Antiretroviral therapy (ART) became available in the mid-1990s. The number of patients with access to ART increased following the introduction of a strategy by UNAIDS (Joint United Nations Programme on HIV/AIDS) which was known as 90-90-90 target (1). ART is known to have a major impact in reducing the mortality and morbidities associated with HIV as it can effectively restore CD4+ T-cell count and control viral replication. However, several patients receiving ART subsequently experienced clinical deterioration. This syndrome is called immune reconstitution inflammatory syndrome (IRIS) and is due to dysregulation of the immune response following ART initiation (2). IRIS is described as either paradoxical worsening of a condition has already been diagnosed, or emergence of a new condition previously subclinical (unmasking) as CD4+ T-cell count and immune function improve after ART commencement (3). IRIS which was first reported in a non-HIV patient is now a widely recognised phenomenon with estimated cases reported in 10-25% of HIV patients initiated on ART (4–6).

Although majority of IRIS are self-limiting with low overall mortality rate, the morbidities related to IRIS place a significant burden on the healthcare system. Some form

of opportunistic infections particularly involving the central nervous system in IRIS are associated with high mortality rate, particularly cryptococcal meningitis (7). Unfortunately, there is no single laboratory test which is specific enough to identify IRIS, making establishing its diagnosis difficult and complicated, thus halting appropriate management.

There are several risk factors and predictors identified in IRIS development. Baseline results of low CD4+ T-cell count and high HIV RNA viral load, presence of a disseminated opportunistic infection prior to ART and initiation of ART too soon following antimicrobial therapy for opportunistic infections are some of the important risk factors for IRIS (5,8). Other risk factors include age as well as genetic predisposition (9). Identifying risk factors and predictors for IRIS may help clinicians to closely monitor HIV patients at risk of developing IRIS. Information on the opportunistic infection and its underlying burden in a specific population, diagnosis and treatment response prior to starting ART is important for identifying paradoxical IRIS. Establishing the diagnosis of unmasking IRIS is usually more challenging as proving the presence of a subclinical infection or disease process, as well as that the increased inflammatory process is due to immune restoration are not easy (10).

In Malaysia, the number of HIV-infected patients receiving ART is increasing in accordance with the strategy developed by National Strategic Plan for Ending AIDS 2016-2030, Ministry of Health Malaysia (11). However, there is lack of reports on the incidence as well as risk factors and predictors of IRIS in Southeast Asia including Malaysia. Most studies examined IRIS according to different aetiology and separated entity such as mycobacterial infections paradoxical IRIS in HIV-infected patients (12). Therefore, this study was conducted in order to determine the prevalence of IRIS in HIV-infected patients initiated on ART as well as to observe any association between demographic features and baseline laboratory parameters with IRIS. The study was also carried out to determine the aetiologies of IRIS in the local population. The data will increase awareness among clinicians to detect early IRIS presentations among HIV patients and will provide a baseline information regarding IRIS in Malaysia.

MATERIALS AND METHODS

This study retrospectively obtained secondary data of confirmed HIV cases in Hospital Sungai Buloh. Hospital Sungai Buloh is an infectious disease centre located in Selangor, Peninsular Malaysia. HIV-infected patients who were started on ART of any regimen in 2017 (1 January - 31 December) were included in this study. Medical record of each patient up to 12 months following ART initiation was reviewed. Relevant demographic characteristics (age, gender and ethnicity) and baseline laboratory parameters (CD4+ T-cell count, HIV RNA viral load and haemoglobin level prior to ART initiation) were retrieved from electronic Hospital Information System (eHIS) and Laboratory Information System (LIS), respectively. IRIS events and its clinical manifestation as diagnosed by the treating infectious disease physician were identified from eHIS. Cases with incomplete medical records and relevant laboratory parameters were excluded.

IRIS clinical manifestations were classified into infectious and non-infectious aetiologies. Infectious IRIS was further subdivided into specific causative organisms while for non-infectious IRIS, specific syndrome or condition was recorded. The baseline laboratory parameters were categorised as follow: (i) CD4+ T-cell count (≥ 100 vs < 100 cells/ μL); based on a bivariate analysis of risk factors for IRIS development by Ratnam et al., 2006 (5) (ii) HIV RNA viral load (> 5.5 vs ≤ 5.5 log10 copies/ml) and (iii) haemoglobin level (≥ 10 vs < 10 g/dL); both were based on a multivariable analysis of significant risk factors for paradoxical opportunistic infection-IRIS by Haddow et al., 2012 (14). Data analysis was carried out using SPSS (version 25.0). Significance level was set at p value of less than 0.05. Associations between demographic factors and baseline laboratory parameters with IRIS in HIV-infected patients initiated on ART were analysed using Chi-square test. Additionally, predictors of IRIS were determined by using multiple logistic regression. Approval of this study was obtained from the Medical Review & Ethics Committee (MREC), Ministry of Health Malaysia [NMRR-17-3144-38798 (IIR)].

RESULTS

A total of 256 patients who fulfilled the inclusion and exclusion criteria were selected into this study. Distribution of patients based on their demographic characteristics and baseline laboratory parameters is shown in Table I. The youngest patient was 17 years old and the oldest was 62 years old. Majority of patients were between 26-50 years old [n=188 (73.4%)] and male [n=236 (92.2%)]. Malay ethnicity [n=137 (53.5%)] was the majority followed by Chinese, Indian and other races comprised of Bumiputra from Sabah and Sarawak, as well as foreigners. Majority of patients had baseline HIV RNA viral load of ≤ 5.5 log10 copies/ml [n=227 (88.7%)]. 184 of 256 patients (71.9%) had baseline CD+4 T-cell count of ≥ 100 cells/μL. Haemoglobin level of ≥ 10 g/dL were seen in majority [n=217 (84.8%)] of cases.

Among 256 HIV-infected patients receiving ART, 45 (17.6%) patients developed IRIS. Infectious IRIS that was commonly encountered comprised of Mycobacterium tuberculosis infection (53.3%), Pneumocystis jirovecii infection (11.1%), Talaromyces marneffei infection (6.6%), cytomegalovirus infection, herpes zoster and Toxoplasma gondii infection. There was only one case

of non-infectious IRIS in this study which was subacute lupus erythematosus as shown in Table II.

There were no significant differences in the demographic characteristics studied (gender, age and ethnicity) between IRIS and non-IRIS patients. However, significant differences were seen in HIV RNA viral load, CD4+ T-cell count and haemoglobin level prior to starting ART between the two groups (Table III). High HIV RNA viral load and low CD4+ T-cell count were shown to be associated with IRIS by multiple logistic regression analysis. Patients with HIV RNA viral load of > 5.5 log10 copies/ml prior to ART initiation were four times more likely to develop IRIS compared to patients with HIV RNA viral load of ≤ 5.5 log10 copies/ml (OR = 3.56, 95% CI = 1.39-9.14, p= 0.008). On the other hand, patients with CD4+ T-cell count of < 100 cells/μL were seven times more likely to develop IRIS than patients with baseline CD4+ T-cell count of ≥ 100 cell/μL (OR=7.15, 95% CI =3.28-15.59, p<0.001) (Table IV).

Table I : Demographic characteristics and baseline laboratory parameters of HIV-infected patients in Hospital Sungai Buloh initiated on ART in 2017

Criteria	Frequency (n) n=256	Percentage (%)
Demographic characteristics		
Age (years)		
< 19	3	1.2
19-25	36	14.1
26-50	188	73.4
> 50	29	11.3
Gender		
Male	236	92.2
Female	20	7.8
Ethnicity		
Malay	137	53.5
Chinese	84	32.8
Indian	24	9.4
Others	11	4.3
Baseline laboratory parameters		
HIV RNA viral load (log_{10} copies/ml)		
> 5.5	29	11.3
≤ 5.5	227	88.7
CD4+ T-cell (cells/μL)		
≥ 100	184	71.9
< 100	72	28.1
Haemoglobin level (g/dL)		
≥ 10	217	84.8
< 10	39	15.2

Table II : Clinical manifestations of IRIS among HIV-infected patients in Hospital Sungai Buloh initiated on ART in 2017

IRIS manifestations	Frequency (n) n=46	Percentage (%)
Infectious		
Bacterial		
Mycobacterium tuberculosis	24	53.3
Rhodococcus sp.	1	2.2
Treponema pallidum	1	2.2
Salmonella sp.	2	4.4
Viral		
Cytomegalovirus	2	4.4
Herpes zoster	2	4.4
Pox virus	1	2.2
Fungal		
Cryptococcus neoformans	1	2.2
Talaromyces marneffei	3	6.6
Pneumocystis jirovecii	5	11.1
Parasitic		
Toxoplasma gondii	2	4.4
Non-infectious		
Subacute lupus erythematosus	1	2.2

Table III: Association between demographic factors and baseline laboratory parameters with IRIS in HIV-infected patients initiated on ART

Criteria	n (%)		*df*	X^2	*p*-value
	IRIS	Non-IRIS			
Demographic factors					
Age (years)					
< 19	1 (33.3)	2 (66.7)	3	6.860	0.077
19-25	1 (2.8)	35 (97.2)			
26-50	38 (20.2)	150 (79.8)			
> 50	5 (17.2)	24 (82.8)			
Gender					
Male	37 (15.7)	199 (84.3)	1	7.528	0.12
Female	8 (40)	12 (60)			
Ethnicity					
Malay	23 (16.8)	114 (83.2)	3	4.515	0.211
Chinese	19 (22.6)	65 (77.4)			
Indian	1 (4.2)	23 (95.8)			
Others	2 (18.2)	9 (81.8)			
Baseline laboratory parameters					
HIV RNA viral load (log_{10} copies/ml)					
> 5.5	15 (51.7)	14 (48.3)	1	26.319	*<0.001
≤ 5.5	30 (13.2)	197 (86.8)			
CD 4 count (cells/μL)					
≥ 100	13 (7.1)	171 (92.9)	1	49.906	*<0.001
< 100	32(44.4)	40 (55.6)			
Haemoglobin level (g/dL)					
≥ 10	29 (13.4)	188 (86.6)	1	17.459	*<0.001
< 10	16 (41)	23 (59)			

* Significant at p < 0.05

Table IV : Predictors of IRIS in HIV-infected patients initiated on ART

Variables	Coefficient	Standard error	Odds ratio	p-value	95% CI for Odds ratio	
					Lower bound	Upper bound
HIV RNA viral load (log_{10} copies/ml)						
[≤ 5.5]						
> 5.5	1.26	0.481	3.558	*0.008	1.386	9.136
CD4+ T-cell count (cell/μL)						
[≥ 100]						
< 100	1.967	0.398	7.148	*< 0.001	3.278	15.589
Haemoglobin level (g/dL)						
[< 10]						
≥ 10	0.720	0.450	2.054	0.110	0.850	4.963

[ ] Reference group for Odds Ratio (OR)

* Significant at $p < 0.05$

DISCUSSION

Acquiring data on IRIS epidemiology is challenging, due to its broad and increasing spectrum of clinical manifestations apart from varying incidence of the underlying opportunistic infections and capacity of diagnostic testing at different localities (10). The reported IRIS prevalence varied according to study, depending on several factors such as the study location whereby different country has different developmental and healthcare background, IRIS definition used and enrolment criteria (9). Our study appears to be the first to report on the prevalence of IRIS in Malaysia. We found that IRIS developed in 17.6% of HIV-infected patients started on ART of any regimen at this centre. This figure was similar to several studies conducted in South Africa, United States of America and China which had reported that IRIS prevalence was around 10-25% (4,13–17). Local data and reports on IRIS are scarce. To our knowledge, there is only one study reported in 2014 by Tan and colleagues who determined the prevalence and risk factors for TB-IRIS in Malaysia (18). The incidence of IRIS in HIV-infected patients varies according to the pre-existing condition, either it has been recognised or unrecognised (subclinical) (13,19). Among the aetiologies of IRIS are infections particularly opportunistic, autoimmune diseases and malignancies. A higher incidence rate of IRIS of 45.0% among HIV-infected patients initiated on ART was reported in those with underlying opportunistic infections (20).

Clinical manifestations of IRIS vary according to different aetiologies and patient pre-morbid condition. Mycobacterium tuberculosis was the most common aetiology of IRIS identified in this study. Tuberculosis is endemic in this region and is the commonest opportunistic infection in HIV-infected patients (Malaysia 2019 Country Progress Report on HIV/AIDS- Anita Suleiman) (21). A systematic review of HIV/AIDS Research in Malaysia published in 2014 reported that tuberculosis (48%) topped the four main AIDS-defining diseases, followed by pneumocystis pneumonia, toxoplasma encephalitis and cryptococcal meningitis (22). Incidence of TB-IRIS in HIV-infected individuals in developing countries ranges from 11-43% (23). According to a previous study among 106 TB-HIV coinfected patients in Malaysia, 9.4% developed paradoxical TB-IRIS while 8.1% presented with unmasking TB-IRIS, giving a total of up to 17.5% of cases (18).

Many patients demonstrated inflammatory response upon receiving antibiotic treatment for Pneumocystis jirovecii infection. However, deteriorating pulmonary disease with evidence of immune function restoration following ART should raise the suspicion of pneumocystis pneumonia paradoxical IRIS (10). A review on published cases in 2014 has found that pneumocystis pneumonia IRIS tends to develop as early as 15 days following ART (24). Pneumocystis pneumonia was reported to be the highest manifestation (28%) among 196 patients with AIDS-defining opportunistic infections in a study conducted in the United States of America (19). In our study, pneumocystis pneumonia IRIS was the second most common clinical manifestation which was identified in 5 of 45 IRIS patients.

The other less frequent clinical manifestations of infectious IRIS in our study included other fungal (Talaromyces marneffei and Cryptococcus neoformans), viral (cytomegalovirus, pox virus and herpes zoster), parasitic (Toxoplasma gondii) and bacterial infections. These findings were in agreement with a review in 2014, which reported that cryptococcal meningitis was among the top five most common opportunistic infections among HIV-infected patients in Malaysia (22).

Although rare, IRIS may arise from non-infectious aetiologies such as autoimmune diseases, other inflammatory conditions and malignancies (2,3). Despite frequent association with several autoimmune diseases, the co-existence of HIV infection and SLE is uncommon. Differential diagnosis of IRIS should be considered in HIV-infected patients who developed an unusually accelerated disease or atypical SLE presentations following ART initiation. Clinical and laboratory evidence of immune restoration must also be present in order to conclude that the autoimmunity is caused by IRIS phenomenon rather than a mere

coincidence (2,25). In our study, the only non-infectious IRIS identified was subcutaneous lupus erythematosus. To date, the publications on SLE-IRIS are only limited to case reports.

In present study, none of the demographic factors which included age, gender and ethnicity showed significant associations with IRIS. Our findings were in consistent with a study by He et al., 2013 who concluded similar findings on gender and age between HIV-infected IRIS and non-IRIS groups (26). Two studies in Peru and Gambia also concluded similar findings (27,28). The youngest patient in this study cohort was 17 years old. In our setting, all HIV-infected paediatric patients were managed in other referral centre. These patients will only be referred to Hospital Sungai Buloh for continuation of management after reaching 16 years old. According to several limited studies of IRIS in paediatric patients, the prevalence was reported to be around 20% (27,29).

There was significant association between baseline CD4+ T-cell count and IRIS in this study. This finding was consistent with several previous studies (15,17,26). Lower baseline CD4+ T-cell count indicates a more advanced degree of immunodeficiency which increases the susceptibility of immune dysregulation during immune restoration following ART initiation (4). The pathogenesis of IRIS is believed to be associated with rapidly increasing CD4+ T-cell count. This response is seen in as early as 28 days after ART initiation, reflecting the release of residual CD4+ T-memory cells from recovering lymphoid tissue (30). Patients with lower CD4+ T-cell count are at risk of severe immune dysregulation following inability to maintain effector and regulatory T-cells homeostasis, as well as Th1/Th2 cytokine balance. The levels of Th1 cytokines such as IL-1, IL-6 and IFN-ɣ decreased, while levels of Th2 cytokines such as IL-4 and ILN-10 increased in HIV/AIDS patients. These cytokine imbalances are corrected in response to CD4+ T-cell count restoration following ART. The unregulated production of Th1 proinflammatory cytokines, however, may drive the development of IRIS. The Th1 cytokine levels were found to increase higher and more rapid in IRIS than non-IRIS AIDS patients who received ART (31). A study among 238 HIV-infected patients in 2013 concluded that the risk of IRIS doubles when CD4+ T-cell count was < 100 cells/μL prior to ART initiation (26). Low CD4+ T-cell count usually indicates a more advanced stage of HIV infection and higher susceptibility to opportunistic infections, which is one of the significant factors associated with IRIS occurrence (32). At this level of immunosuppression, they are also at a higher risk of having undiagnosed opportunistic infections.

In our study, baseline HIV RNA viral load was shown to be significantly associated with IRIS. The risk of IRIS increased with higher HIV RNA viral load. This finding is consistent with results from the following studies. Development of IRIS was found to be significantly associated with baseline viral load of ≥ 4 log10 copies/ml in a study by Novak et al., 2012 (17). Another study on HIV-infected patients also reported that high HIV RNA viral load was an independent risk factor for paradoxical TB-IRIS (33). Univariate analysis of a study conducted among HIV-infected infants in South Africa also concluded that children with IRIS had higher HIV RNA prior to ART initiation (15). Higher baseline HIV RNA viral load is associated with a more severe CD4+ T-cell count depletion. Published data suggest that high-level HIV viraemia impaired CD4+ T-cell proliferation because of decreased IL-2 levels (34,35). This subsequently increased the susceptibility for opportunistic infections, either clinically manifested or subclinical (13). Increased antigenic burden of opportunistic infection which associated with greater degree of immune suppression is a known risk for IRIS (36). Some studies have also concluded that a rapid decline in HIV RNA viral load was associated with an increased risk of developing IRIS (8,16,32). Theoretically, patients with higher amount of HIV RNA have higher chance of experiencing a more significant drop in viral load following ART. However, in this recent study, the degree of viral suppression was not within the scope of analysis.

In our study, baseline haemoglobin level was shown to be associated with IRIS development. This agrees with the result of a randomised controlled trial in Chennai, India which revealed that significant association between baseline haemoglobin and the development of paradoxical TB-IRIS (37). A prospective international study published in 2019 concluded that HIV-infected patients with baseline anaemia were at a higher risk of developing IRIS, with level of < 8.5 g/dL identified to be highly predictive. Anaemia with haemoglobin level of < 10.0 g/dL was reported to be one of the risk factors for unmasking opportunistic infections in IRIS (32). Anaemia is one of the most frequent haematologic findings in HIV-infected patients which correlates with HIV/AIDS advance clinical progression and poor prognosis (38). There are multiple factors that potentiate anaemia in HIV patients. The direct effects of the virus itself on haematopoietic progenitor cells and erythropoietin responsiveness can lead to anaemia. Opportunistic infections or malignancies to which HIV patients are susceptible to, can also result in anaemia (38). However, the exact mechanism of how anaemia contributed to IRIS development is still unclear.

Higher risk of developing IRIS was identified in HIV-infected patients with lower baseline CD4-T cell count and haemoglobin, as well as higher HIV RNA viral load prior to starting ART indicating a more advanced

disease stage. These patients are prone to present with disseminated opportunistic infections and a higher pathogen load, contributing to a higher tendency of generating an excessive inflammatory response once their immune system started to improve following ART commencement (39).

As there is no specific test available for diagnosing IRIS, it is crucial to be attentive of the IRIS predictors. We have identified two laboratory parameters which are able predict the likelihood of developing IRIS following ART initiation. HIV-infected patients with baseline CD4+ T-cell count of < 100 cells/μL have 7 times higher risk of developing IRIS. Patients with baseline HIV RNA viral load of > 5.5 log10 copies/ml on the other hand, have 4 times chances of developing IRIS. These two predictors can be used to identify patients at a higher risk of developing IRIS, where closer monitoring is indicated.

There are several limitations in our study. Due to several constrains, this study only included HIV-infected patients who were started on ART in 2017. A longer duration of study with higher number of patient enrolment will better reflect on IRIS scenario in Malaysia. IRIS studies are hampered by lack of internationally accepted IRIS definition as well as confirmatory diagnostic test. The general definitions available do not identify different forms of IRIS. There was also a possibility that some IRIS cases were missed to be recognised due to the high variation of clinical manifestations and lack of standard clinical case definitions for each condition. Risk factors and predictors for IRIS would be different according to different IRIS-subtypes. We also examined the epidemiology and predictors for both paradoxical and unmasking IRIS as one entity rather than categorising them into paradoxical IRIS and unmasking IRIS. Our current study also did not analyse the duration between the commencement of treatment for opportunistic infections and ART initiation, degree of CD4+ T-cell restoration and viral suppression. The outcomes of IRIS and its contribution to hospitalisation and death were also beyond the scope of this study.

CONCLUSION

With the expanding availability and accessibility of ART in Malaysia, the awareness of IRIS is important as its associated morbidities place significant burden to healthcare system. Clinical manifestations of IRIS vary according to different aetiologies and the patients' pre-morbid conditions. Patients with advanced HIV infection are at a higher risk of developing IRIS than those at the initial disease stage. To date, there is not a single laboratory investigation specific enough to diagnose IRIS. Therefore, identifying IRIS predictors prior to initiating ART will enable close monitoring of those at a higher risk.

ACKNOWLEDGEMENT

We would like to thank the Director General of Health, Ministry of Health, Malaysia for permission to publish this paper. We also would like to thank the staff from the Microbiology Unit, Department of Pathology, Hospital Sungai Buloh, Malaysia for their kind assistance in completing this work.

REFERENCES

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). 90-90-90 An ambitious treatment target to help end the AIDS epidemic [Internet]. Joint United Nations Programme on HIV/AIDS (UNAIDS); 2014. Available from: https://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf
2. Sharma SK, Soneja M. HIV & immune reconstitution inflammatory syndrome (IRIS). Indian J Med Res. 2011 Dec;134(6):866–77.
3. Bosamiya SS. The immune reconstitution inflammatory syndrome. Indian J Dermatol. 2011 Oct;56(5):476–9.
4. Ratnam I, Chiu C, Kandala N-B, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. Clin Infect Dis. 2006 Feb 1;42(3):418–27.
5. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis. 2010 Apr;10(4):251–61.
6. Jevtović DJ, Salemović D, Ranin J, Pesić I, Zerjav S, Djurković-Djaković O. The prevalence and risk of immune restoration disease in HIV-infected patients treated with highly active antiretroviral therapy. HIV Med. 2005 Mar;6(2):140–3.
7. Murthy AR, Marulappa R, Hegde U, Kappadi D, Ambikathanaya UK, Nair P. Treatment guidelines and prognosis of immune reconstitution inflammatory syndrome patients: a review. J Int Oral Health. 2015 Apr;7(4):92–5.
8. Sereti I. Immune reconstruction inflammatory syndrome in HIV infection: beyond what meets the eye. Top Antivir Med. 2020 Jan;27(4):106–11.
9. Manzardo C, Guardo AC, Letang E, Plana M, Gatell JM, Miro JM. Opportunistic infections and immune reconstitution inflammatory syndrome in HIV-1-infected adults in the combined antiretroviral therapy era: a comprehensive review. Expert Rev Anti Infect Ther. 2015 Jun;13(6):751–67.
10. Gopal R, Rapaka RR, Kolls JK. Immune reconstitution inflammatory syndrome associated with pulmonary pathogens. Eur Respir Rev. 2017 Jan;26(143).
11. HIV/STI Section of Ministry of Health Malaysia.

National Strategic Plan for Ending AIDS 2016 - 2030 [Internet]. Ministry of Health Malaysia; 2015. Available from: https://aidsdatahub.org/sites/default/files/publication/Malaysia_National_strategic_plan_2016-2030.pdf
12. Angkasekwinai N, Chareesil C, Weerarak P. Incidence and Outcomes of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome (IRIS) After Antiretroviral Therapy in Human Immunodeficiency Virus (HIV)-Infected Patients. Open Forum Infectious Diseases. 2016 Dec 1;3(suppl_1):565.
13. Haddow LJ, Moosa M-YS, Mosam A, Moodley P, Parboosing R, Easterbrook PJ. Incidence, clinical spectrum, risk factors and impact of HIV-associated immune reconstitution inflammatory syndrome in South Africa. PLoS ONE. 2012;7(11):e40623.
14. Murdoch DM, Venter WDF, Feldman C, Van Rie A. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. AIDS. 2008 Mar 12;22(5):601–10.
15. Smith K, Kuhn L, Coovadia A, Meyers T, Hu C-C, Reitz C, et al. Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. AIDS. 2009 Jun 1;23(9):1097–107.
16. Manabe YC, Campbell JD, Sydnor E, Moore RD. Immune reconstitution inflammatory syndrome: risk factors and treatment implications. J Acquir Immune Defic Syndr. 2007 Dec 1;46(4):456–62.
17. Novak RM, Richardson JT, Buchacz K, Chmiel JS, Durham MD, Palella FJ, et al. Immune reconstitution inflammatory syndrome: incidence and implications for mortality. AIDS. 2012 Mar 27;26(6):721–30.
18. Tan HY, Yong YK, Lim SH, Ponnampalavanar S, Omar SFS, Pang YK, et al. Tuberculosis (TB)-associated immune reconstitution inflammatory syndrome in TB-HIV co-infected patients in Malaysia: prevalence, risk factors, and treatment outcomes. Sex Health. 2014 Dec;11(6):532–9.
19. Achenbach CJ, Harrington RD, Dhanireddy S, Crane HM, Casper C, Kitahata MM. Paradoxical immune reconstitution inflammatory syndrome in HIV-infected patients treated with combination antiretroviral therapy after AIDS-defining opportunistic infection. Clin Infect Dis. 2012 Feb 1;54(3):424–33.
20. Shelburne SA, Montes M, Hamill RJ. Immune reconstitution inflammatory syndrome: more answers, more questions. J Antimicrob Chemother. 2006 Feb;57(2):167–70.
21. Anita Suleiman, Chai PT, editors. Country Progress Report On HIV/AIDS 2019 Malaysia [Internet]. Ministry of Health Malaysia; Available from: http://www.moh.gov.my/moh/resources/Penerbitan/Laporan/Umum/Report_GAM_2019_(Final).pdf
22. Koh KC. A Review of HIV/AIDS Research in Malaysia. Med J Malaysia. 2014 Aug;69 Suppl A:68–81.
23. Dibyendu D, Sarkar RN, Phaujdar S, Bhattacharyya K, Pal HK. Incidence and risk factors of immune reconstitution inflammatory syndrome in HIV-TB coinfected patients. Braz J Infect Dis. 2011 Dec;15(6):553–9.
24. Mok HP, Hart E, Venkatesan P. Early development of immune reconstitution inflammatory syndrome related to Pneumocystis pneumonia after antiretroviral therapy. Int J STD AIDS. 2014 Apr;25(5):373–7.
25. Belgaumkar VA, Chavan RB, Suryataley PR, Salunke AS, Patil PP, Borade SM. Systemic lupus erythematosus in HIV: An insight into clinical implications and management. Indian J Sex Transm Dis AIDS. 2019 Jun;40(1):64–6.
26. He B, Zheng Y, Liu M, Zhou G, Chen X, Mamadou D, et al. Identifying risk factors of immune reconstitution inflammatory syndrome in AIDS patients receiving highly active anti-retroviral therapy. Braz J Infect Dis. 2013 Apr;17(2):170–3.
27. Wang ME, Castillo ME, Montano SM, Zunt JR. Immune reconstitution inflammatory syndrome in human immunodeficiency virus-infected children in Peru. Pediatr Infect Dis J. 2009 Oct;28(10):900–3.
28. Zaidi I, Peterson K, Jeffries D, Whittle H, de Silva T, Rowland-Jones S, et al. Immune reconstitution inflammatory syndrome and the influence of T regulatory cells: a cohort study in The Gambia. PLoS ONE. 2012;7(6):e39213.
29. Puthanakit T, Oberdorfer P, Punjaisee S, Wannarit P, Sirisanthana T, Sirisanthana V. Immune reconstitution syndrome due to bacillus Calmette-Guérin after initiation of antiretroviral therapy in children with HIV infection. Clin Infect Dis. 2005 Oct 1;41(7):1049–52.
30. Martin-Blondel G, Mars LT, Liblau RS. Pathogenesis of the immune reconstitution inflammatory syndrome in HIV-infected patients. Curr Opin Infect Dis. 2012 Jun;25(3):312–20.
31. Zheng Y, Zhou H, He Y, Chen Z, He B, He M. The immune pathogenesis of immune reconstitution inflammatory syndrome associated with highly active antiretroviral therapy in AIDS. AIDS Res Hum Retroviruses. 2014 Dec;30(12):1197–202.
32. Sereti I, Sheikh V, Shaffer D, Phanuphak N, Gabriel E, Wang J, et al. Prospective international study of incidence and predictors of immune reconstitution inflammatory syndrome and death in people with HIV and severe lymphopenia. Clin Infect Dis. 2019 Sep 5;
33. Bonnet M, Baudin E, Jani IV, Nunes E, Verhoustraten F, Calmy A, et al. Incidence of paradoxical

tuberculosis-associated immune reconstitution inflammatory syndrome and impact on patient outcome. PLoS ONE. 2013;8(12):e84585.
34. McNeil AC, Shupert WL, Iyasere CA, Hallahan CW, Mican JA, Davey RT, et al. High-level HIV-1 viremia suppresses viral antigen-specific CD4(+) T cell proliferation. Proc Natl Acad Sci USA. 2001 Nov 20;98(24):13878–83.
35. Iyasere C, Tilton JC, Johnson AJ, Younes S, Yassine-Diab B, Sekaly R-P, et al. Diminished proliferation of human immunodeficiency virus-specific CD4+ T cells is associated with diminished interleukin-2 (IL-2) production and is recovered by exogenous IL-2. J Virol. 2003 Oct;77(20):10900–9.
36. Beishuizen SJE, Geerlings SE. Immune reconstitution inflammatory syndrome: immunopathogenesis, risk factors, diagnosis, treatment and prevention. Neth J Med. 2009 Nov;67(10):327–31.
37. Narendran G, Andrade BB, Porter BO, Chandrasekhar C, Venkatesan P, Menon PA, et al. Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. PLoS ONE. 2013;8(5):e63541.
38. Volberding PA, Levine AM, Dieterich D, Mildvan D, Mitsuyasu R, Saag M, et al. Anemia in HIV Infection: Clinical Impact and Evidence-Based Management Strategies. Clinical Infectious Diseases. 2004 May 15;38(10):1454–63.
39. Walker NF, Scriven J, Meintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. HIV AIDS (Auckl). 2015;7:49–64.