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RESEARCH ARTICLE

Factors Associated with Immune Discordant Responses in Treated HIV-infected Omani Patients

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Abstract:

Background:

Despite sustained viral control by antiretroviral therapy (ART), some HIV-infected patients do not recover normal $CD4^+$ T cell counts. This Discordant Immune Response (DIR) increases the risk of opportunistic infections.

Objective:

To evaluate the factors associated with DIR in HIV-infected Omani patients attending public sector clinics.

Methods:

All HIV-infected patients receiving ART with regular follow-up visits were eligible for this study. The DIR group comprised patients on ART for at least two years with plasma HIV viral load < 50 copies/mL and helper $CD4^+$ T cell counts below 350 cells/µl. The Concordant Immune Responses (CIR) group was similar to DIR but with $CD4^+$ T cell counts above 350 cells/µl. Univariate and multivariate analyses using logistic regression models were used to assess the impact of demographic characteristics, clinical, immunological and virological parameters, type of ART regimens, tuberculosis and other opportunistic co-infections on DIR.

Results:

Among 153 enrolled participants, 28 and 76 patients were identified as having DIR and CIR, respectively. The multivariate analysis revealed that the only factors independently associated with DIR after adjustment were age (odds ratio [OR] 1.13; 95% confidence interval [CI] 1.04-1.23), baseline $CD4^+$ T cell count (OR: 0.98; CI: 0.97-0.99) and baseline $CD56^+$ cell count (OR: 0.97; CI: 0.96-0.99).

Conclusion:

Collectively, these findings suggest that a significant proportion of HIV-infected Omani patients develop DIR totaling 27%, and efforts should be made to improve early identification of these patients who tend to experience poor clinical outcomes.

Keywords: HIV, Predictors, Immune discordant, Antiretroviral therapy, Omanis, CD4.

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1. INTRODUCTION

Antiretroviral therapy (ART) is one of the greatest discoveries of the last century that decelerated the global epidemic of Human Immunodeficiency Virus (HIV). Clinicians usually assess the effectiveness of ART through the suppression of viral replication and the recovery of $CD4^+$ T cell count. The suppression of HIV replication by ART is often followed by a gradual increase in the number of circulating helper $CD4^+$ T cells, which in turn improve host immune functions [1]. This optimal response is referred to as concordant response. However, the direction of the virological and immunological responses to ART may not always be concordant. According to several studies, up to 30% of patients on ART might experience immune discordant responses to therapy [2 - 5]. A

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few studies have explored the risk factors for HIV-infected patients with discordant immune response and showed that older age and low baseline $CD4^+$ T cell count are important factors, which may delay the immunological recovery [3]. The latter is the key in the prevention of opportunistic infections, hence the increasing survival of HIV-infected patients.

At present the clinical management of treated HIV-infected patients with poor immunological recovery is controversial. Changing or intensifying ART regimen has not shown any effect on the $CD4^+$ T cell response, except in some patients whose regimen contains antiretroviral drugs that are associated with leucopenia [6]. Early forecasting of discordant immune response would avert unnecessary ART modification and would discourage the use of a drug that may have a potential effect on immunological recovery.

It has been shown that morbidity and mortality of HIV-infected patients occur mainly through acquiring or re-activation of opportunistic infections [7]. Therefore, the determining factors associated with poor immunological recovery are of great significance. To date, there is limited data about the risk factors associated with the development of discordant immune responses within the Gulf region, especially in the Sultanate of Oman. Hence, this study investigated predictors of immunological discordant responses in HIV-infected Omani patients who are taking ART for at least two years with a fully suppressed HIV viral load.

2. MATERIALS AND METHODS

2.1. Study Population

This study was a single-center prospective cohort conducted in outpatient HIV clinics at the Sultan Qaboos University Hospital (SQUH), Sultanate of Oman. The SQUH provides free of charge medical care and ART for all Omani HIV-infected patients. Treated HIV patients above 18-year-old who have a known ART start date, and regular follow-up visits were eligible for inclusion. The enrolled patients should have been on ART for at least two years and their plasma HIV viral RNA was <50 copies/mL. Standardized case-report forms were used to collect demographic characteristics, clinical and laboratory data, duration of ART and ART regimens. In addition to this, data on previous infections with mycobacterium tuberculosis, *Pneumocystis jiroveci* and Hepatitis C Virus (HCV) were collected. Eligible patients were classified according to their immunological and virological responses to ART. The Discordant Immune Response (DIR) group comprised patients who have been on ART for at least two years with plasma HIV viral load <50 copies/mL and helper $CD4^+$ T cell count below 350 cells/µl. The Concordant Immune Response (CIR) group comprised patients who have been on ART for at least two years with plasma HIV viral load <50 copies/mL and helper $CD4^+$ T cell count above 350 cells/µl. The study was approved by the local ethics committee and all patients signed a consent form.

2.2. Phenotypic Analysis of Lymphocyte Subsets

Lymphocyte subsets were determined on fresh blood samples at the time of HIV diagnosis, and subsequently at three months apart during follow-up visits [8]. Two sets of four-color monoclonal antibody combinations were used (Cyto-Stat TetraChrome, Beckman Coulter, USA). The first set consisted of anti-CD45-fluorescein isothiocyanate (FITC), anti-CD3-phycoerythrin-cyanine 5 (PC5), anti-CD4-phycoerythrin (RD1) and anti-CD8-phycoerythrin-Texas-Red (ECD), while the second set comprised anti-CD45-FITC, anti-CD3-PC5, anti-CD19-ECD and anti-CD56-RD1. Fifty microliter of peripheral blood was incubated with 10 µl of each monoclonal antibody combination for 15 minutes at room temperature. After incubation red blood cells were lysed by TQ-Prep and 100 µl of flow-count fluorospheres was added to each tube (Beckman Coulter, USA). The samples were then analyzed by FC500 flow cytometer equipped with the CXP and tetraCXP System software (Beckman Coulter, USA). Lymphocytes were first gated on $CD45^{high}$ and side scatter ^{low} and T helper cells, T suppressor cells, B cells and Natural Killer (NK) cells were identified as $CD3^+CD4^+$, $CD3^+CD8^+$, $CD3^-CD19^+$ and $CD3^-CD56^+$, respectively. The absolute value of each lymphocyte subset was then determined.

2.3. Viral Load Determination

Plasma HIV viral load was measured by COBAS TaqMan 48 (Roche, France) [8].

2.4. Statistical Analysis

Data were summarized using median and interquartile values for continuous variables, while categorical variables were described by number and percentage. Fisher's exact test and student's t test were used for comparative analyses. Univariate and multivariate logistic regression models were constructed to identify baseline predictors of response. All variables with P values less than 0.25 in univariate analysis were included into the logistic regression models. All analyses were performed using Stata software (USA) and a P value less than 0.05 was considered as statistically significant.

3. RESULTS

3.1. Demographic and Therapy Regimens

By the end of December 2016, a total of 153 treated HIV patients remained under HIV clinic follow up for at least two years. Of those 49 patients were excluded as they did not fulfill the study inclusion criteria. Three patients were not taking ART and the rest of patients (n=46) were excluded since their most recent plasma HIV viral load was > 50 copies/mL. The remaining patients (n=104) were classified as DIR (n=28) and CIR (n=76) and their clinical and demographic characteristics at the time of starting ART are summarized in Table **1**. Compared to the CIR group, DIR group was older ($p = 0.03$), had significantly lower $CD4^+$ T cell count ($p = 0.001$) and lower $CD56^+$ cell (NK T cell) counts ($p = 0.002$). Other immunological and virological determinants were balanced between the two groups. There were no differences between the two groups in the hemoglobin levels, $CD8^+$ T cell counts, and $CD19^+$ cell counts. Also, there was no significant difference for tuberculosis co-infection between DIR and CIR groups (10% *versus* 8%, respectively, $P = 0.65$). Similarly, pneumocystis

Table 1. Baseline characteristics of study participants.

Characteristics	Immune Discordant Response Patients (n=28)	Immune Concordant Response Patients (n=76)	P values
Age (years) Mean (SD) Median (IQR)	52 ± 14 (30-80) 49 (40-59)	45 ±12 (18-71) 44 (36-52)	0.03
Male [n (%)]	17 (60)	42 (55)	0.66
Hemoglobin (g/dL) Mean (SD) Median (IQR)	12.1 ± 2.3 (8-16) 12 (10-14)	12.4 ± 2.1 (9-17) 12.5 (10.5-14)	0.76
Platelet count ($x10^9$/L) Mean (SD) Median (IQR)	265 ± 91 (140-490) 234 (197-317)	256 ± 101 (170-686) 253 (202-299)	0.68
$CD4^+$ T cell count (cells/μL) Mean (SD) Median (IQR)	10 6 ± 107 (30-343) 89 (13-164)	350 ± 277 (90-1177) 271 (75-444)	0.001
$CD8^+$ T cell count (cells/μL) Mean (SD) Median (IQR)	740 ± 674 (77-2780) 459 (347-923)	996 ± 972 (78-7703) 849 (492-1120)	0.19
CD4/CD8 ratio mean (SD) Median (IQR)	0.31 ± 0.2 (0.07-0.7) 0.1 (0.04-0.25)	0.46 ± 0.3 (0.1-1.19) 0.27 (0.12-0.51)	0.04
$CD19^+$ cell count (cells/μL) Mean (SD) Median (IQR)	141 ± 138 (14-479) 95 (51-188)	194 ± 184 (19-1042) 147 (66-257)	0.17
$CD56^+$ cell count (cells/μL) Mean (SD) Median (IQR)	89 ± 73 (14-256) 67(32-119)	185 ± 157 (10-996) 160(78-255)	0.002
Co-infection with HCV [n (%)]	5 (18)	9 (12)	0.42
HIV viral load (log_{10} copies/mL) Mean (SD) Median (IQR)	4.2 ± 0.98 (2.6-6) 4.42 (3.5-4.8)	4.1 ± 1.3 (2.6-6.9) 4.3 (2.6-5.1)	0.35
Duration on ART (year) Mean (SD) Median (IQR)	8 ± 3 (5-11) 8 (5-13)	7.8 ± 3 (4-11) 8 (4-14)	0.97
Efavirenz-based regimen [n (%)]	22 (78)	56 (73)	0.79
AZT-3TC-based regimen [n (%)]	16 (57)	62 (81)	0.02
Tuberculosis co-infection [n (%)]	3 (10)	6 (7)	0.69

Results are shown as mean, median, Standard Deviation (SD) and Interquartile Range (IQR). HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; ART: Antiretroviral Therapy. AZT: Zidovudine; 3TC: Lamivudine.

monia was found in 15% of patients in DIR group compared to 14% in ICR group ($P = 0.88$).

All patients were taking ART that consisted of two Nucleotide Reverse Transcriptase Inhibitors (NRTI) and one protease inhibitor (PI) or one non-nucleotide reverse transcriptase inhibitors (NNRTI). Two patients (2%) received integrase inhibitors. Due to intolerance, drug interaction or drug resistance approximately (15%) of the patients had one or more ART drugs modified during the study period. A total of 74 (71%) patients were exposed to Zidovudine, 78 (75%) to Lamivudine, 38 (36%) to Abacavir, 22 (21%) to Stavudine, and 38 (36%) to Tenofovir. No patients received Didanosine. At the time of the analysis 53 (51%) were on first line therapy with Atripla (Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate) while 51 (49%) were on second or third line therapy. Regarding the components of ART regimen, there were no statistically significant differences in the number of NNRTI, NRTI or PI between CIR and DIR patients. However, a significant difference was observed for Zidovudine-lamivudine-based regimens between CIR and DIR patients ($p = 0.02$).

3.2. Logistic Regression Analysis

In order to identify the factors that may predict DIR to ART, a logistic regression analysis adjusting for several factors simultaneously was performed. All variables showing a *P* value less than 0.25 in univariate analysis were tested in the logistic regression models. As shown in Table **2**, age at the diagnosis, baseline $CD4^+$ T cell and $CD3^-CD56^+$ cell counts, but not Zidovudine-lamivudine-based regimens, were all associated with DIR. Other patients' characteristics, including baseline hemoglobin, platelets and other demographic parameters were not associated with DIR (data not shown). In addition, no significant associations were found between *Mycobacterium tuberculosis, Pneumocystis jirovecii*, or HCV infections and DIR.

Table 2. Factors affecting immunological discordant response in HIV-infected Omani patients.

Characteristics	Univariate Analysis		Multivariate Analysis	
	Odd Ratio (95% confidence interval)	P values	Odd Ratio (95% confidence interval)	P values
Age (years)	1.04 (1.06-1.08)	0.017	1.13 (1.04-1.23)	0.002
Increase of baseline $CD4^+$ T cell counts by 50 cells (cell/μL)	0.75 (0.63-0.89)	0.001	0.78 (0.64-0.94)	0.0001
Baseline $CD56^+$ cell counts (cell/μL)	0.99 (0.985-0.996)	0.002	0.97 (0.96-0.99)	0.001
Zidovudine-lamivudine-based regimen	0.3 (0.11-0.77)	0.013	0.73 (0.22-2.35)	0.60

4. DISCUSSION

Although most patients in this study responded favorably to ART by showing a concordant $CD4^+$ cell recovery, a total of 27% of patients failed to achieve an adequate immune response after two years of the initiation of ART. This result is in line with other findings of cohort studies conducted in developed countries, where the prevalence of DIR was reported to be 20-30% after six months to two years from starting therapy [5, 9 - 12].

This study revealed that older age at the diagnosis is associated with DIR. Early studies have shown that $CD4^+$ cell recovery is associated with thymus activity, which decreases with aging [13]. To date, debate still exists about the effect of age on immune restoration in HIV-infected patients. While some studies reported that increasing aging was linked with lower chance to increase $CD4^+$ T cells [5], other studies, however, demonstrated that age had no significant impact on $CD4^+$ cell recovery in HIV-infected patients [14]. Using a pooled analysis of data from nineteen prospective North American cohort studies, Althoff *et al* reported that immunologic responses decreased with increasing age regardless of initial ART regimen [15]. Our results are consistent with those findings, although the demographics and epidemiological characteristics of the study populations were distinct.

So far, published data on the predictive values of $CD4^+$ T cells and viral loads at baseline in patients with DIR have yielded conflicting results. Some studies revealed that $CD4^+$ T cell and viral load before starting ART were significantly associated with DIR, while other studies showed the opposite or no association [4, 16 - 20]. In this study significant effects of $CD4^+$ T cell counts, but not viral load, on DIR were observed. These findings could be explained in part by the lack of a clear definition of DIR, which varied significantly among published studies [20]. Another explanation could be the fact that $CD4^+$ T cell measurements were subjected to a large individual variability and a considerable variation across different laboratories [22]. In this study, T-cell subsets were performed in the morning from only fasting patients.

Several studies have shown that NK cells are key player in HIV infection. Using *ex-vivo* experiments, Kuri-Cervantes *et al*., reported that NK cell activation was significantly increased in chronic progressors compared to elite controllers, and it was positively correlated with HIV disease progression [23]. Likewise, in a recent study, Luo *et al*., demonstrated that NK cell activation were associated with $CD4^+$ T cell recovery, independently of age, gender and T cell activation in immunologic non-responder HIV patients [24]. In the current study, associations were evidenced between NK cells, as phenotypically defined by $CD3^-CD56^+$ and DIR. Given that this is the first study to document NK cell predictive effect in patients with DIR, further investigation is needed to explore this association deeper. In line with the previous reports, this study did not find that TB co-infection before starting ART was associated with DIR, but caution should be taken when generalizing these findings as a few patients had tuberculosis when starting ART in our study.

The current study also investigated the effect of ART on DIR. It has been shown that NNRTI-based regimens were associated with a lower increase of $CD4^+$ T cells after two years of ART [25]. In the current study, ART regimens were not found to be associated with DIR, although a significant association with Zidovudine-lamivudine-based regimens was evidenced, but did not remain significant thereafter when adjusted in the multivariable logistic regression models.

This analysis is subjected to several limitations. Firstly, the sample size was relatively small, which may have impacted the statistical power to discriminate the effects of tested predictors between the analyzed groups. However, these findings reflect the routine care and HIV prevalence in our clinical setting. According to the World Health Organization (WHO), the Sultanate of Oman has a low prevalence of HIV. An average of one hundred and twenty new cases are reported annually. In 2014, a total of 2506 HIV cases were documented among Omanis. Of those, 908 cases received ART. Regardless of their helper $CD4^+$ T cell count, all HIV-infected Omani patients are eligible for ART, as recommended by the HIV Management Guideline in 2015 [26]. Secondly, this study relied on $CD4^+$ T cell count measurements performed approximately three months apart to classify study participants. It is therefore possible that this may have affected the classification given the fluctuation of CD4+ T cell measurements. Thirdly, ART regimen modification, as a result of the availability of new drugs over the study period may be regarded as a limitation. Nevertheless, in Oman, the first-line standard regimen is Emtricitabine plus Tenofovir preferably with Efavirenz or alternatively with boosted Atazanavir. Zidovudine plus Lamivudine either with Efavirenz or boosted Atazanavir is considered as an alternative ART [26]. The impact of the current HIV practice on patients' outcomes was carefully considered in this analysis. Lastly, adherence to ART was not assessed in this study, knowing that poor adherence could lead to a discordant response. Nevertheless, repeated measures of viral load were used as a practical tool to follow patients and

also to distinguish between viral suppression due to suboptimal adherence or to appearance of drug resistant strains.

In conclusion the current study demonstrated that a significant proportion of HIV-infected Omani patients attending the clinics fail to recover $CD4^+$ T cell counts despite sustained viral control with ART for at least two years. The main important risk factors independently associated with DIR were older age, lower baseline $CD4^+$ T cell count and $CD56^+$ cell counts. Further studies are needed to evaluate these factors for early identification of patients who could most likely develop DIR after ART.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Sultan Qaboos University, Oman.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Written informed consent was obtained from all the participants prior to the study.

AVAILABILITY OF DATA AND MATERIALS

The data-sets generated and/or analyzed during the present study are not publicly available due to SQU regulations, but are available from the corresponding author on reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Battegay M, Nüesch R, Hirschel B, Kaufmann GR. Immunological recovery and antiretroviral therapy in HIV-1 infection. Lancet Infect Dis 2006; 6(5): 280-7. [http://dx.doi.org/10.1016/S1473-3099(06)70463-7] [PMID: 16631548]

[2] Gazzola L, Tincati C, Bellistrì GM, Monforte Ad, Marchetti G. The absence of CD4+ T cell count recovery despite receipt of virologically suppressive highly active antiretroviral therapy: clinical risk, immunological gaps, and therapeutic options. Clin Infect Dis 2009; 48(3): 328-37. [http://dx.doi.org/10.1086/695852] [PMID: 19123868]

[3] Kaufmann GR, Furrer H, Ledergerber B, *et al.* Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. Clin Infect Dis 2005; 41(3): 361-72. [http://dx.doi.org/10.1086/431484] [PMID: 16007534]

[4] Moore DM, Hogg RS, Yip B, *et al.* Discordant immunologic and virologic responses to highly active antiretroviral therapy are associated with increased mortality and poor adherence to therapy. J Acquir Immune Defic Syndr 2005; 40(3): 288-93. [http://dx.doi.org/10.1097/01.qai.0000182847.38098.d1] [PMID: 16249702]

[5] Falster K, Petoumenos K, Chuah J, *et al.* Poor baseline immune function predicts an incomplete immune response to combination antiretroviral treatment despite sustained viral suppression. J Acquir Immune Defic Syndr 2009; 50(3): 307-13. [http://dx.doi.org/10.1097/QAI.0b013e3181945ed4] [PMID: 19194311]

[6] Bowen LN, Smith B, Reich D, Quezado M, Nath A. HIV-associated opportunistic CNS infections: Pathophysiology, diagnosis and treatment. Nat Rev Neurol 2016; 12(11): 662-74. [http://dx.doi.org/10.1038/nrneurol.2016.149] [PMID: 27786246]

[7] Balkhair AA, Al-Muharrmi ZK, Ganguly S, Al-Jabri AA. Spectrum of AIDS defining opportunistic infections in a series of 77 hospitalised HIV-infected omani patients. Sultan Qaboos Univ Med J 2012; 12(4): 442-8. [http://dx.doi.org/10.12816/0003169] [PMID: 23275840]

[8] Boulassel MR, Mercier F, Gilmore N, Routy JP. Immunophenotypic patterns of CD8+ T cell subsets expressing CD8alphaalpha and IL-7Ralpha in viremic, aviremic and slow progressor HIV-1-infected subjects. Clin Immunol 2007; 124(2): 149-57. [http://dx.doi.org/10.1016/j.clim.2007.05.005] [PMID: 17560832]

[9] Schechter M, Tuboi SH. Discordant immunological and virological responses to antiretroviral therapy. J Antimicrob Chemother 2006; 58(3): 506-10. [http://dx.doi.org/10.1093/jac/dkl263] [PMID: 16854959]

[10] Kayigamba FR, Franke MF, Bakker MI, *et al.* Discordant treatment responses to combination antiretroviral therapy in rwanda: A prospective cohort study. PLoS One 2016; 11(7)e0159446 [http://dx.doi.org/10.1371/journal.pone.0159446] [PMID: 27438000]

[11] Grabar S, Le Moing V, Goujard C, *et al.* Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. Ann Intern Med 2000; 133(6): 401-10. [http://dx.doi.org/10.7326/0003-4819-133-6-200009190-00007] [PMID: 10975957]

[12] Piketty C, Weiss L, Thomas F, Mohamed AS, Belec L, Kazatchkine MD. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. J Infect Dis 2001; 183(9): 1328-35. [http://dx.doi.org/10.1086/319861] [PMID: 11294663]

[13] Mackall CL, Fleisher TA, Brown MR, *et al.* Age, thymopoiesis, and CD4+ T-lymphocyte regeneration after intensive chemotherapy. N Engl J Med 1995; 332(3): 143-9. [http://dx.doi.org/10.1056/NEJM199501193320303] [PMID: 7800006]

[14] Ribeiro RM, de Boer RJ. The contribution of the thymus to the recovery of peripheral naive T-cell numbers during antiretroviral treatment for HIV infection. J Acquir Immune Defic Syndr 2008; 49(1): 1-8. [http://dx.doi.org/10.1097/QAI.0b013e318184fb28] [PMID: 18667918]

[15] Althoff KN, Justice AC, Gange SJ, *et al.* North american AIDS cohorts collaboration on research, design (NA-ACCORD). Virologic and immunologic response to HAART, by age and regimen class. AIDS 2010; 24(16): 2469-79. [http://dx.doi.org/10.1097/QAD.0b013e32833e6d14] [PMID: 20829678]

[16] Zoufaly A, an der Heiden M, Kollan C, *et al.* Clinical outcome of HIV-infected patients with discordant virological and immunological response to antiretroviral therapy. J Infect Dis 2011; 203(3): 364-71. [http://dx.doi.org/10.1093/jinfdis/jiq055] [PMID: 21208929]

[17] Tuboi SH, Brinkhof MW, Egger M, *et al.* Discordant responses to potent antiretroviral treatment in previously naive HIV-1-infected adults initiating treatment in resource-constrained countries: The antiretroviral therapy in low-income countries (ART-LINC) collaboration. J Acquir Immune Defic Syndr 2007; 45(1): 52-9. [http://dx.doi.org/10.1097/QAI.0b013e318042e1c3] [PMID: 17460471]

[18] Gilson RJ, Man SL, Copas A, *et al.* Discordant responses on starting highly active antiretroviral therapy: Suboptimal CD4 increases despite early viral suppression in the UK Collaborative HIV Cohort (UK

CHIC) Study. HIV Med 2010; 11(2): 152-60.
[http://dx.doi.org/10.1111/j.1468-1293.2009.00755.x] [PMID: 19732175]

[19] Piketty C, Weiss L, Thomas F, Mohamed AS, Belec L, Kazatchkine MD. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. J Infect Dis 2001; 183(9): 1328-35.
[http://dx.doi.org/10.1086/319861] [PMID: 11294663]

[20] Tan R, Westfall AO, Willig JH, *et al.* Clinical outcome of HIV-infected antiretroviral-naive patients with discordant immunologic and virologic responses to highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2008; 47(5): 553-8.
[http://dx.doi.org/10.1097/QAI.0b013e31816856c5] [PMID: 18285713]

[21] Kelly C, Gaskell KM, Richardson M, Klein N, Garner P, MacPherson P. Discordant immune response with antiretroviral therapy in HIV-1: A systematic review of clinical outcomes. PLoS One 2016; 11(6)e0156099
[http://dx.doi.org/10.1371/journal.pone.0156099] [PMID: 27284683]

[22] Raboud JM, Haley L, Montaner JS, Murphy C, Januszewska M, Schechter MT. Quantification of the variation due to laboratory and physiologic sources in CD4 lymphocyte counts of clinically stable HIV-infected individuals. J Acquir Immune Defic Syndr Hum Retrovirol 1995; 10(Suppl. 2): S67-73.
[PMID: 7552516]

[23] Kuri-Cervantes L, de Oca GS, Avila-Ríos S, Hernández-Juan R, Reyes-Terán G. Activation of NK cells is associated with HIV-1 disease progression. J Leukoc Biol 2014; 96(1): 7-16.
[http://dx.doi.org/10.1189/jlb.0913514] [PMID: 24399837]

[24] Luo Z, Li Z, Martin L, *et al.* Increased Natural Killer Cell Activation in HIV-Infected Immunologic Non-Responders Correlates with CD4+ T Cell Recovery after Antiretroviral Therapy and Viral Suppression. PLoS One 2017; 12(1)e0167640
[http://dx.doi.org/10.1371/journal.pone.0167640] [PMID: 28076376]

[25] Dronda F, Moreno S, Moreno A, Casado JL, Pérez-Elías MJ, Antela A. Long-term outcomes among antiretroviral-naive human immunodeficiency virus-infected patients with small increases in CD4+ cell counts after successful virologic suppression. Clin Infect Dis 2002; 35(8): 1005-9.
[http://dx.doi.org/10.1086/342695] [PMID: 1235 53 89]

[26] Management HIV. Oman: A guide for health care workers National AIDS Program, Department of Communicable Diseases, Directorate General for Disease Surveillance and Control. 3rd ed. Oman: Ministry of Health 2015.https:// www. researchgate. net/ publication/ 299827458_HIV_Managment_In_Oman [Accessed September 2018]