Characteristics and Determinants of Discordant Virological and Immunological Responses to Antiretroviral Therapy in ART naïve patients in Korean HIV infected patients

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- ABSTRACT -

Characteristics and Determinants of Discordant Virological and Immunological Responses to Antiretroviral Therapy in ART naïve patients in Korean HIV infected patients

Background: The ultimate goal of HAART (highly active antiretroviral therapy) is suppression of viral replication and restoration of immune system. Despite sufficient viral response, some patients go through failure of immune restoration and poor immune restoration related to increased morbidity and mortality.

Objective: The objectives of this analysis are: (1) to identify the proportion of individuals who experience virological response and immunological response after 12, 36 and 60 months of suppressive antiretroviral therapy, respectively, and (2) to identify factors that are associated with discordant virological and immunological response to antiviral therapy despite sufficient decreased plasma viral load (pVL) in Korean HIV infected patients. Also, we would like to provide preliminary data about morbidity and mortality of these discordant populations for further researchs.

Patients and Methods: We included 610 patients who initiated their first HAART regimen between october 1997 and october 2011. Virological response (VR) was defined as HIV viral load <75copies/ml after initiation of HAART. Immunological response (IR) was defined as a rise in CD4 T cell count of at least 100cells/μl per year or a CD4 T cell count

more than 350cells/μl at 12 and 36months. At 60 months after ART, IR was defined as CD4 T cell count more than 500cells/μl.

Results: Discordant virological and immunological responses at 12, 36, and 60 months were 17.3%, 18.1% and 13.6% respectively. Low nadir CD4 T cell count was risk factor at 12 and 36months, Concurrent hepatitis B and or TB co-infection was clinically significant risk factor of virological and immunological responses at 36months. Initial HAART regimen containing NNRTI and low pre HAART BMI was associated with higher risk of VR/IR discordance at 60 months after HAART. However, unlike previous reports, old age, baseline anemia and co-infection of hepatitis C virus were not risk factors for VR/IR discordance. Also, discordant proportion of patients was not significant differences in each period.

Conclusion: Discordant virological and immunological responses are independently associated with concurrent TB co-infection at 36 months, low nadir CD4 T cell count at 12 and 36months and Initial ART regimen containing NNRTI and low preHAART body mass index (BMI) at 60months after HAART initiation.

Keyword: viral suppression, immune restoration, discordant response, low nadir CD4 T cell count, concurrent TB co-infection, hepatitis B co-infection, Initial ART regimen containing NNRTI, low body mass index (BMI)

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

I. INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) into clinical practice had led to dramatic reductions in morbidity and mortality of human immunodeficiency virus (HIV) patients [6-8]. Theoretically, HIV-1 RNA plasma level is decreased and CD4 cell count is increased after starting HAART regimen in HIV infected patients [1-3]. However, according to recent reports, about 40% to 60% of patients appear reductions in HIV viral load (VL) and increases in CD4 cell counts and about 12% to 23% have neither of these responses [4-7]. A considerable percentage of patients demonstrate incompatibility of immunologic and virologic outcome. Despite consistent treatment and an adequate virologic response, it has been observed that a significant proportion of patients do not attain CD4 cell restoration. We called this 'immunologic non responder' or 'discordant virologic and immunologic response', while the HIV-1 RNA plasma level is below the limit of detection in laboratory, but the immunologic reconstitution is absent or blunted. It is reported that discordant immune response following ART initiation was associated with older age, lower CD4 cell count at baseline, baseline HIV RNA load <100,000 copies/mL, the use lamivudine (3TC)/zidovudine (ZDV), baseline anemia, co-infection of Mycobacterium tuberculosis, co-infection of hepatitis C virus, first year after HAART initiation, poor adherence to therapy and delayed pre-HAART period [8-14]. It is known that those with accordant responses have generally favorable outcomes and that those with discordant responses have much worse outcomes, the prognostic significance of discordant responses is common concern over problems of morbidity and mortality of HIV infected patents. Although determinants affecting CD4 cell recovery have been studied in Western, European, African cohorts it is

uncertain to what extent these findings are applicable to HAART naïve HIV infected Korean patients [9, 15-22]. Also, factors appearing previous study could not explain sufficiently of failure of immune reconstitution in non-immune responder in HIV infected Korean patients. These days there are many immunologic approaches for investigate of failure of immune reconstitution in discordant population, not only clinical practice but also experimental practice. Therefore it is necessary to study of factors associated with discordant virologic and immunological responses in Korean HIV infected patients.

In this article, we analyzed the degree of virologic suppression and immunologic recovery and investigate of factors affecting suboptimal CD 4 cell restoration in HAART naïve HIV infected Korean patients who appeared complete virologic suppression after 12, 36 and 60 months of antiretroviral therapy.

II. PATIENTS AND METHODS

We enrolled 610 HIV infected Korean patients ≥18 years of age from October 1997 to October 2011 in Yeonsei University Hospital, Ajou University Hospital, Wonju Severance Christian Hospital and Seoul Medical Center, 324, 166, 98 and 22 participants respectively. All the patients initiated their first HAART regimen in 1997 to 2011. Patients who have at least 2 consecutive plasma HIV RNA levels over 1000copies or follow up loss over 6 months were excluded. Virologic response (VR) was defined as HIV viral load <75copies/ml after initiation of HAART. Immunological response (IR) was defined as a rise in CD4 T cell count of at least 100cells/μl per year or a CD4 T cell count more than 350cells/μl at 12 and 36 months. At 60 months after ART, IR was defined as CD4 T cell count more than 500cells/μl. HAART was defined as treatment with ≥3 antiretroviral drugs, including two nucleoside reverse-transcriptase inhibitors plus a non-nucleoside reverse-transcriptase inhibitor or a protease inhibitor [9].

Patients characteristics including gender and age, CD4 cell counts (nadir and at 12, 36 and 60 months after HAART initiation), HIV plasma RNA levels (at 12, 36 and 60 months after HAART initiation), body-mass-index (BMI), hemoglobin (Hgb) level at time of treatment initiation, antiretroviral treatment information, smoking history, hepatitis B virus co-infection, hepatitis C virus co-infection, Tbc co-infection and previous history of opportunistic infection were collected from patient charts and computerized medical records.

Statistical analysis

The primary end point of the study was to identify the proportion of individuals who experience virological response and immunological response after 12, 36 and 60 months of suppressive antiretroviral therapy, respectively. Multivariate analysis using logistic regression was employed to assess potential factors simultaneously that are associated with discordant virological and immunological response to antiviral therapy in Korean HIV infected patients. A 2-sided *P* value 0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS, version 14.0 (SPSS).

III. RESULTS

A total of 610 antiretroviral-naive Korean HIV infected patients aged 18 years or older initiated triple combination therapy consisting of 2 nucleosides plus a PI, an NNRTI or other medication in the study. Of these, 107 were excluded because they were missing a plasma viral load (pVL) and or CD4 cell measurement within the study period. Also, 98 were excluded because of they were not have proper plasma viral response. Excluded subjects did not differ with including subjects respect to gender, age, nadir CD4 T cell count and initial HAART medication.

The baseline characteristics of participants were presented on the table 1. Over 90 percent were male and the median age was 47 years (range 21−86 years) (table 1). Median CD4 cell count at baseline was 160 (range 0-591). The percent of injection drug users was very smaller in our study. Gender, age, Nadir CD4 T cell count and initial HAART regimen were not different among each analysis period. Participants who treated with PI based regimen were more frequent than NNRTI based regimen. Participants with NNRTI based regimen was 35.0 %(214), from among these, 178 patients mainly combined with Zidovudine(ZDV), Lamivudine(3-TC) and Efavirenz. Participants with PI based regimen was 61.3%(375), from among these, 181 patients mainly combined with Zidovudine(ZDV), Lamivudine(3-TC) and Azatanavir, 110 patients combined with ZDV, 3-TC and Indinavir or Ritonavir. The rest of 21 participants were prescribed regimen combined with Stavudine, didanosine or integrase inhibitor. Initially, 60.2 %(368) of the patients were relevant Centers for disease control and prevention (CDC) category A, 10.5 %(64) were CDC category B, 23.1%(141) were CDC category C and remaining participants demonstrate limited data. There were no significant

differences with proportion of CDC HIV-1 disease category C among each analysis groups. The proportion of patients with Mycobacterium tuberculosis complex under CDC HIV-1 category C was 6 % (37), Pneumocystis jirovecii pneumonia was 5.9 % (36) and esophageal candidiasis was 4.7 % (29). Cytomegalovirus infection corresponding CDC HIV-1 category C was account for 2.7 % (17), 2.6 % (16) of the parcitipants presented with chronic diarrhea, >10% of unexpected weight loss and fatigue. Patients accompanied with Kaposi's sarcoma, Toxoplasma gondii infection, progressive multifocal leukoencephalopathy, HIV encephalopathy and non-tuberculosis mycobacterial disease were found in less than 1% of patients at study entry.

Table 1

Clinical data of the patients included in this study

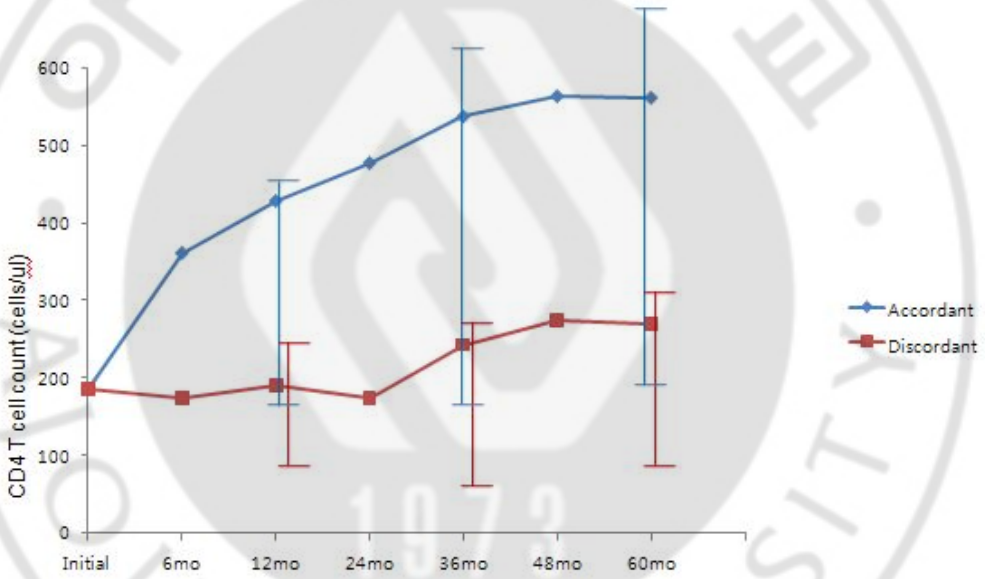
Characteristics	Initial	HAART 12m	HAART 36m	HAART 60m
Age (years)				
<40	160 (26.2)	115 (26.6)	79 (23.9)	34 (17.9)
≥40	450 (73.8)	318 (73.4)	252 (76.1)	156 (82.1)
Gender				
Male	562 (92.1)	405 (93.5)	307 (92.7)	173 (91.1)
Female	48 (7.9)	28 (6.5)	24 (7.3)	17 (8.9)
CDC category				
A	368(60.2)			
B	64 (10.5)			
C	141(23.1)			
Body mass index (BMI)(kg/m^2)				
<18.5	44 (10.1)	29 (9.0)	20 (8.3)	10 (7.8)
18.5~25	316 (51.7)	235 (54.2)	174 (52.5)	94 (49.4)

≥25	74 (12.1)	60 (13.8)	48 (14.5)	24 (12.6)
Smoking history				
Absent	147 (39.3)	99 (37.4)	77 (38.5)	46 (42.6)
Present	227 (60.7)	166 (62.6)	123 (61.5)	62 (57.4)
Nadir CD4 cell count				
<50	144 (24.6)	93 (21.8)	83 (25.3)	52 (27.5)
≥50	442 (75.4)	334 (78.2)	245 (74.7)	137 (72.5)
Initial HAART regimen				
NNRTI based regime	214 (35.0)	158 (36.4)	129 (38.9)	66 (34.5)
PI based regimen	375 (61.3)	248 (57.2)	182 (54.9)	110 (57.5)
Others	21(3.7)	27 (6.4)	20 (6.2)	15(8.0)
Hepatitis B				
Absent	522 (95.2)	405 (95.3)	315 (96.0)	179 (95.2)
Present	28 (4.8)	20 (4.7)	13 (4.0)	9 (4.8)
Hepatitis C				
Absent	566 (98.6)	419 (99.1)	319 (98.5)	181 (99.5)
Present	8 (1.4)	4 (0.9)	5 (1.5)	1 (0.5)
Diagnosis of active tuberculosis				
Absent	515 (85.0)	386 (89.6)	280 (84.6)	156 (82.1)
Present	91 (15.0)	45 (10.4)	51 (15.4)	34 (17.9)

Totally, 415 patients showed complete viral suppression at 6months after treatment initiation. Virologic response at 12, 36 and 60 months after ART initiation were 84.2%, 91.1% and 88.9%. Among these, 17.3%, 18.1% and 13.6% showed discordant virological and immunological responses at at 12, 36 and 60 months, respectively.

We presented median value of CD4 T cell count (vertical axis) following time rogression(horizontal axis)(figure1). It appeared significant differences in each following group. Median value of CD4 T cell count was 187cells/μl(range 0-564) at HAART initiation and over half of the population (57%) have low nadir CD4 cell (below 200 cells/mm3).

Median value of CD 4 T cell count were 430cells/μl(range 0-564) at 12months, 539cells/μl(range 0-564) at 36months and 563cells/μl(range 0-564) at 60 months in accordant population. In discordant cases, median value were 189cells/μl(range 1-300) at 12months, 243cells/μl(range 0-232) at 36months and 271cells/μl(range 9-262) at 60 months. Poor CD4 T cell restoration is associated with low nadir CD4 T cell count (<50 cells/mm3) at 12 and 36 months.



The proportion of discordant population were similar among each follow up groups on our study in contrast with previous reports from Western country, Europe and South Africa which demonstrate increased discordant population [9].

Infection of hepatitis B virus and mycobacterium tuberculosis is associated with poor immunologic recovery at 36months (P=0.017 and 0.007). Interestingly, initial HAART regimen containing NNRTI and low pre HAART BMI was associated with higher risk of discordance at 60 months after HAART initiation. However, unlike previous reports, old age, baseline anemia and co-infection of hepatitis C virus were not risk factors for discordance of virologic and immunologic response in our study group.

Table 2. Occurrences of discordance according the factors at each follow up periods.

	Occurrence of discordance in 12 months			**Occurrence of discordance in 36 months**			**Occurrence of discordance in 60 months**		
	OR	**95% CI**	***p-value***	***OR***	**95% CI**	***p-value***	***OR***	**95% CI**	***p-value***
Age (<40 vs. ≥40 years)	1.127	0.511-2.484	0.767	1.710	0.618-4.729	0.302	2.014	0.456-8.890	0.355
Gender (Male vs. Female)	5.690	1.818-17.806	0.003	0.507	0.053-4.844	0.555	0.000	0.000	0.999
PreHAART BMI (<18.5 vs. ≥18.5)	0.543	0.161-1.828	0.324	1.262	0.379-4.204	0.704	5.215	1.093-24.876	0.038
Nadir CD4 cell count (≤50 vs. >50 cells/mm^3)	5.229	2.584-10.583	<0.001	8.549	3.759-19.443	<0.001	2.555	0.784-8.326	0.120
Initial HAART regimen (NNRTI vs. PI)	1.762	0.867-3.580	0.117	1.941	0.846-4.450	0.117	4.425	1.178-16.621	0.028
Hepatitis B (No vs. Yes)	0.717	0.143-3.603	0.686	6.297	1.397-28.392	0.017	4.449	0.622-31.818	0.137
Concomitant active tuberculosis (No vs. Yes)	1.366	0.492-3.797	0.549	3.735	1.422-9.809	0.007	1.403	0.315-6.258	0.657

IV. DISCUSSION

In this study, we analyzed the factors predicting poor immunologic restoration despite sufficient virologic suppression in ART naïve HIV infected Korean patients from 12months to 60months in four institutions after HAART initiation. The rate of discordant response was not significantly different among each follow up periods in our study.

The association between low baseline CD4 cell counts <50cells/mm3 and failure to restore CD4 cell count with HAART has been reported from some European cohorts [10, 18, 19, 25]. It has been shown in South African cohort that baseline CD4 T cell count under 50 cells/mm3 is related to increased morbidity and mortality [1].

We included active tuberculosis in factor analysis because of the prevalence of Tbc co infection in Korean HIV patients is much higher than in Korean general population, 0.35% and 8.4% respectively. Our study results revealed HIV patients who diagnosed with active tuberculosis defined by positive AFB smear, radiographic evidence or highly clinical suspicion are less likely to achieve immune restoration at 36 months after ART initiation.

Chronic hepatitis B virus carrier rate in our study is not significantly different in general population in Korea, 3.3% and 3.7%, respectively. Little is known about hepatitis B virus co infection with HIV, we included this factor in our analysis and the result is available in 36months after treatment.

Generally, nucleoside analogues have cytotoxic effects potentially; they were not associated with a poorer immunological outcome [4]. But interestingly, this study results

revealed initial HAART regimen containing NNRTI and low pre HAART BMI was associated with higher risk of discordance at 60 months after HAART. On the other hand PI treatment was associated with a better immunological outcome in this study.

Poor CD4 T cell restoration is sustainable problem and the mechanism of is not known. Some study proposed hypothesis about immunologic and virologic discordance. Continuous damages to the immune system of patients in an advanced stage may lead to dysfunction of cells and defects of CD4 cell restoration [26]. The impaired immunological restoration following HAART may be related to a reduced thymic function such as the thymic involution observed with age [27]. A low level of viral replication under treatment would be responsible for a prolonged damage on the immune system, thereby preventing a reconstitution of the CD4 lymphocyte pool [28]. It remains unclear whether patients with an undetectable pVL under the lowest level of detection still have an ongoing viral replication, either in the blood or in the immune organs, able to overcome the turnover of new CD4 lymphocytes.

We tried to including a relatively large sample of Korean HAART naïve HIV infected patients (n= 610) with various factors as much as possible. We represent a sample that differs significantly in age, nadir CD4 cell count, Tbc co-infection, initial HAART regimen from most US and European cohorts used in previously published analysis on CD4 cell recovery [8, 17, 22, 29-34].

It has been known of high incidence of tuberculosis in Korean general population, this study presented more higher prevalence of TB co-infection at diagnosis of HIV infection.

We included relatively large sample of HIV patients with Tbc co-infection, it may possible to overestimate of discordant response with association of active tuberculosis. The majority of our patients were young males (>90%), there was a higher probability of incorrect statistical results between gender and discordant response. At the time of the study, we enrolled a largest cohort in Korea. But during the course of the study, missing values were increased due to poor compliance, side effect of HAART and death. Various ART initiation regimen and times were another limitation in our study.

In summary, we demonstrate that a significant proportion of participants initiating HAART in Korea fail to restoration immune system despite adequate virologic suppression. Significant risk factors are low nadir CD4 cell count, Tbc co-infection, low pre BMI and initial HAART regimen containing NNRTI. These data suggest that greater efforts are needed to identify and treat HAART eligible patients prior to significant CD4 cell decline, Tbc co-infection and poor nutrient condition. Poor immune restoration related with initial HAART regimen containing NNRTI is not consistent with previously published data from industrialized countries, therefore, more comparative study are needed.

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- 국문요약 -

Characteristics and Determinants of Discordant Virological and Immunological Responses to Antiretroviral Therapy in ART naïve patients in Korean HIV infected patients

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배경: 고강도 항레트로바이러스 요법의 궁극적인 목표는 바이러스의 억제와 면역계의 회복이다. 효과적인 바이러스 반응애도 불구하고, 몇몇 경우 면역계의 회복의 실패를 보인다. 그리고 이러한 면역 회복에 실패한 경우 질환의 이환율과 사망률과 관련이 있다.

목적: 이 연구의 목적은 한국의 HIV 감염자 중 (1) 고강도 항레트로바이러스를 시작한 환자군에서 12 개월, 36 개월, 60 개월 시점에서 바이러스 억제 정도와 면역학적인 회복 정도를 비교하여 보고, (2) 바이러스 반응과 면역계의 회복 반응 정도의 부조화에 미치는 영향 인자를 알아보고자 하였다. 또한 추후의 이런 부조화 반응과 연관한 이환율과 사망률에 관한 연구에 도움이 되고자 한다.

방법: 우리는 1997 년 8 월부터 2011 년 8 월까지 처음 고강도 항레트로 바이러스 요법을 받기 시작한 환자 610 명의 자료를 수집하였다. 바이러스 반응은 치료 시작 후 검사 시점에서 HIV viral load <75copies/ml 가 된 경우로 정의하였고

면역학적인 반응은 12 개월과 36 개월 시점에서는 CD4 T 세포의 수가 최소 연간 100cells/μl 이상 증가하거나 60 개월 시점에서는 500cells/μl 인 경우로 정의하였다.

결과: 12 개월, 36 개월 그리고 60 개월 시점에서 부조화 반응은 각각 17.3%, 18.1% 그리고 13.6% 였다. 12 개월과 36 개월 시점에서는 낮은 기저 CD4 T 세포의 수가 부조화반응과 연관이 있었으며, 36 개월 시점에는 활동성 결핵에 감염되었거나, B 형 간염바이러스 동시 감염이 연관이 있었다. 60 개월 시점에서는 고강도 항레트로바이러스요법에 NNRTI 가 병합된 경우와 낮은 체질량지수가 관련이 있었다. 이전의 연구 결과와는 다르게 고령, 기저 빈혈이 있는 경우, C 형 간염 바이러스 동시감염은 부조화 반응과 관련이 없었다.

결론: 바이러스 수의 억제와 면역학적인 회복의 부조화 반응은 독립적으로 낮은 기저 CD4 T 세포의 수, 활동성 결핵의 동시감염, B 형 간염바이러스 동시 감염, 초기 고강도 항레트로바이러스 용법에 NNRTI 가 병합된 경우와 낮은 체질량지수가 관련이 있다.

핵심어: 바이러스 감소, 면역학적인 회복, 부조화반응, 낮은 기저 CD4 T 세포의 수, 활동성 결핵의 동시감염, B 형 간염바이러스 동시 감염, NNRTI 병합요법, 체질량지수