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Research Article

# The relation between human immunodeficiency virus (HIV)-1 reverse-transcriptase mutations and CD4 T-cell recovery failure in HIV patients in Padang, West Sumatera, Indonesia

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## ABSTRACT

**Introduction:** Highly active antiretroviral (ARV) therapy fails if there are mutations in the human immunodeficiency virus-1 reverse-transcriptase (HIV-1 RT) gene. This study aimed to determine the relationship between HIV-1 RT mutations with the failure of CD4 T-cell recovery in HIV-1 patients receiving ARV therapy for >6 months. **Method:** A total of 105 HIV-1-positive patients who were required to have undergone first-line ARV therapy for 6 months and have their CD4 T=cell number were monitored. Blood samples were stored at 4°C for HIV-1 proviral DNA extraction. HIV-1 proviral DNA was amplified by a nested polymerase chain reaction using 2 RT-specific primers. The relationship between RT sequence mutations and the recovery of >350 CD4T cells/μL was analyzed after patients had ARV therapy for 6 months. **Result:** A total of 17 HIV-1 proviral DNA isolates were sequenced, it only 10 were successfully analyzed. CD4 T-cell recovery occurred in only two of eight samples which aligned and compared with reference sequences. Substitution mutations were found in the eight RT sequences with a frequency of 1.32–5.56%. The mutations at nucleotides 60 and 207, 100%, showed failed CD4 T-cell recovery but not statistically significant. **Conclusion:** There was a trend toward CD4 T-cell failure (>350 cells/μL) in HIV-1 patients treated with first-line ARV drugs for >6 months when a nucleotide mutation was present in position 60 and 207, although this was not statistically significant. Other factors suspected to be associated with CD4 T cell recovery failure need to be investigated in subsequent studies.


**KEY WORDS:** CD4 T-cell recovery, Human immunodeficiency virus, Mutation, Reverse transcriptase

## INTRODUCTION

The failure of CD4 T cell recovery to reach 350 cells/μL after treatment with antiretroviral (ARV) therapy for >6 months is a challenge for patients infected with multidrug-resistant human immunodeficiency virus (HIV) strains. The failure to recover CD4 T-cells leads to disease progression and increased morbidity and mortality of patients infected with HIV.[1-3] Patients who fail to recover CD4 T-cells have higher rates of patient mortality, therapeutic side effects, and progression to acquired immune deficiency syndrome.[4] Various studies have reported a suboptimal immune response ranging from 8 to 42% in patients receiving ARVs.[1]


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Several studies have identified the factors associated with failure of CD4 T-cell recovery in HIV-infected patients treated with ARV drugs. These factors include old age, low baseline level of CD4 T cells, low baseline 7-cell interleukin 7, clinical staging, persistent immune system activation, and host-specific genetic factors. However, the mechanisms underlying the failure of CD4 T cell recovery have only recently been uncovered.[1-3,5-7]

Mutations in targeted therapeutic sequences, especially reverse-transcriptase (RT) mutations, as well as the development of drug-resistance mutations caused by long-term use of ARV drugs, are considered two of the major factors contributing to CD4 T-cell recovery failure.[8] A high mutation rate is one of the characteristics of HIV-1. Mutations may occur naturally or as the result of drug selective

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pressure.[9] This selective pressure favors mutations in viral peptides that allow the virus to avoid the host immune system. This escape mechanism is due to the failure of the mutated peptide to bind to the human leukocyte antigen molecule, which alters its interaction with T-cell receptors. By evading the immune system, the mutant HIV-1 strain can continue replicating within CD4 T-cells. Cytopathic and apoptotic effects on CD4 T-cells have been reported to contribute to the failure of CD4 T-cell recovery.[10,11]

This study aimed to demonstrate the relationship between HIV-1 RT mutation and the failure of CD4 T cell recovery in HIV-1 patients who had been receiving ARV therapy for >6 months at General Hospital of Dr. M. Djamil in Padang, West Sumatera, Indonesia. This study was approved by the Research Ethics Committee of the Faculty of Medicine, Andalas University.

## METHOD

### Design

A total of 105 patients with HIV-1 were included in this study. The patients were required to meet the following inclusion criteria: Aged older than 18 years, treated with first-line ARV therapy for longer than 6 months, and CD4 T-cell counts performed as part of the routine follow-up for ARV use. Blood samples were collected by trained phlebotomists in the Central Laboratory of General Hospital of Dr. M. Djamil Padang. Research subjects were selected by consecutive sampling.

### CD4 T-Cell Count

The CD4 T-cell count was performed in whole blood EDTA samples using a Pima CD4 test consisting of a disposable Pima CD4 test cartridge, which is analyzed using a Pima analyzer. This tool can determine the absolute number of CD4 T-cells in the blood. The disposable Pima CD4 test cARTridge required a sample of 25 µL, which was added to a dry reagent. The Pima CD4 test cARTridge was inserted into the analyzer. The sample was moved into the incubation chamber where it was reacted with specific antibodies, a monoclonal anti-human complement-dependent lysis antibody, and a monoclonal anti-human CD4 antibody, which was conjugated to two different fluorescent dyes that emitted light at two different wavelengths (dye 1 and dye 2, respectively).

After incubation, the samples were transferred into the cARTridge detection channel. The Pima Analyzer is a multicolor fluorescence imaging device, which detects fluorescent signals using the in-tool camera and analyzes them using specific software. T-helper cells express CD3 and CD4 surface antigens, enabling their detection from the emission of light at specific wavelengths for both conjugated antibody dyes. This allows the T-helper cells to be differentiated from other cells. The results are presented as the number of cells per microliter.

### Isolation of HIV-1 Proviral DNA

HIV-1 proviral DNA was extracted from 2 mL of the whole blood EDTA samples. The extraction was performed using the PureLink Genomic DNA kit (Invitrogen). The procedure was followed according to the manufacturer's recommendations, consisting of the following steps: (1) Blood thinning, (2) DNA binding, (3) DNA leaching, and (4) DNA elution. The extract was electrophoresed to ensure the success of the isolation procedure.

### Amplification by Nested Polymerase Chain Reaction (PCR)

Amplification of the RT gene was performed over two stages. Phase I required aDNA template of HIV-1 proviral DNA. The specific primers (HIV-RT1-R, 5'-GGA CTA CAG TCY ACT TGT CCA TG-3'; and HIV-RT1-F, 5'-ATG ATA GGG ATG GGA ATG GGT TT-3') were added to the PCR master mix (Invitrogen). Amplification was performed over 30 cycles with the following settings: Initial denaturation 92°C 10', denaturation 92°C 30", annealing 55°C 30", extension 72°C 45", and extension72°C 5'. Phase II used the PCR product from Phase I as the DNA template, which was added to DNA primers (HIV-RT2-R, 5'-TTA AAA TCA CTA RCC ATT GYT CTC C-3'; and HIV-RT2-F, 5'-GAC CTA CAC CTG TCA ACA TAA TTG G-3') and the PCR master mix (Invitrogen). Amplification was conducted for 30 cycles with the same conditions as that used in Phase I.

### Electrophoresis of PCR Products

The nested PCR products were electrophoresed on a 0.8% agarose gel with SYBR green colorants at 100 V for 40 min. The results were viewed using UV light.

### Sequencing and Analysis of RT Sequence Mutations

Sequencing of the nested PCR products was performed by 1st BASE, Singapore. The sequencing results were analyzed with specific software which identified mutations by nucleotide changes in the RT gene. The sequence was aligned with CLUSTAL-W software version 1.81 and edited using BioEdit sequence editor version 7.0.4. The type and position of mutations and amino acid changes were determined by comparing a reference sequence.

## RESULTS

### The Mutation Distribution of RT

The PCR results were positive in 17/105 samples, but only 10 sequences could be analyzed (eight RT

sequences and two protease sequences). From the eight RT isolates, only two patients reached CD4 T-cell recovery of 350 cells/μL. The eight RT sequences contained between 16 and 56 substitution mutations (range 1.32–5.56% and mean 2.63 ± 1.02%). Insertion/deletion mutations were found in five RT sequences, ranging from 0.08% to 0.59%. The distribution of RT mutations is presented in Table 1.

In this study, six of eight research subjects (75%) did not experience CD4 T-cell recovery. The relationship of HIV-1 RT mutations with the recovery of CD4 T-cells was analyzed using the Chi-square test for the eight RT sequences. The relationship between the RT mutations and CD4 T-cell recovery is shown in Table 2.

### RT Mutation Relation with CD4 T Cell Recovery Failure

Analysis of the relation between RT mutations and CD4 T-cell recovery showed that no RT mutation positions were associated with CD4 T-cell recovery in patients after treatment with ARV. Analysis of several mutation positions showed that mutations at amino acid positions 60 (S60I) and 207 (Q207A) were most closely associated with CD4 T-cell recovery. At codon 60, 100% of the mutant samples exhibited failure of CD4 T-cell recovery, while 40% of the samples without mutations showed immune system improvement, but this difference was not statistically significant ($P > 0.05$). At codon 207, 100% of the mutant samples showed CD4 T-cell recovery failure, while 66.7%

**Table 1: The mutation distribution of reverse transcriptase**

| Analyzed nucleotide numbers | Mutation substitution numbers (%) | Insersion/deletion numbers (%) |
|---|---|---|
| 1240 | 26 (2.09) | - |
| 1006 | 56 (5.56) | 3 (0.29) |
| 1015 | 19 (1.87) | - |
| 1240 | 26 (2.09) | - |
| 1240 | 26 (2.09) | 1 (0.08) |
| 1210 | 16 (1.32) | 1 (0.08) |
| 895 | 29 (3.24) | 3 (0.34) |
| 1019 | 28 (2.74) | 6 (0.59) |

**Table 2: Reverse transcriptase mutation relation with immunologic reconstitution**

| Mutation position | Mutation group | With recovery CD4 T-cell (f,%) | Without recovery CD 4 T-cell (f,%) | *P* |
|---|---|---|---|---|
| 6 | Mutated | 1 (33.3) | 2 (66.7) | 1.000 |
| | Not mutated | 1 (20.0) | 4 (80.0) | |
| 35 | Mutated | 1 (20.0) | 4 (80.0) | 1.000 |
| | Not mutated | 1 (33.3) | 2 (66.7) | |
| 39 | Mutated | 1 (33.3) | 2 (66.7) | 1.000 |
| | Not mutated | 1 (20.0) | 4 (80.0) | |
| 43 | Mutated | 1 (33.3) | 2 (66.7) | 1.000 |
| | Not mutated | 1 (20.0) | 4 (80.0) | |
| 60 | Mutated | 0 (0.0) | 3 (100.0) | 0.464 |
| | Not mutated | 2 (40.0) | 3 (60.0) | |
| 122 | Mutated | 2 (33.3) | 4 (66.7) | 1.000 |
| | Not mutated | 0 (0.0) | 2 (100.0) | |
| 123 | Mutated | 2 (40.0) | 3 (60.0) | 0.464 |
| | Not mutated | 0 (0.0) | 3 (100.0) | |
| 173 | Mutated | 1 (25.0) | 3 (75.0) | 1.000 |
| | Not mutated | 1 (25.0) | 3 (75.0) | |
| 174 | Mutated | 1 (20.0) | 4 (80.0) | 1.000 |
| | Not mutated | 1 (33.3) | 2 (66.7) | |
| 177 | Mutated | 2 (40.0) | 3 (60.0) | 0.464 |
| | Not mutated | 0 (0.0) | 3 (100.0) | |
| 200 | Mutated | 1 (33.3) | 2 (66.7) | 1.000 |
| | Not mutated | 1 (20.0) | 4 (80.0) | |
| 207 | Mutated | 0 (0.0) | 5 (100.0) | 0.107 |
| | Not mutated | 2 (66.7) | 1 (33.3) | |
| 211 | Mutated | 2 (28.6) | 5 (71.4) | 1.000 |
| | Not mutated | 0 (0.0) | 1 (100.0) | |
| 245 | Mutated | 1 (20.0) | 4 (80.0) | 1.000 |
| | Not mutated | 1 (33.3) | 2 (66.7) | |
| 272 | Mutated | 1 (16.7) | 5 (83.3) | 0.464 |
| | Not mutated | 1 (50.0) | 1 (50.0) | |
| 291 | Mutated | 2 (33.3) | 4 (66.7) | 1.000 |
| | Not mutated | 0 (0.0) | 2 (100.0) | |
| 293 | Mutated | 2 (33.3) | 4 (66.7) | 1.000 |
| | Not mutated | 0 (0.0) | 2 (100.0) | |

of the samples without mutations showed immune system improvement. However, this difference also did not reach statistical significance ($P > 0.05$).

## DISCUSSION

The results of this study showed that the eight RT sequences contained between 16 and 56 substitution mutations per sequence or a rate of 1.32–5.56% compared with the number of nucleotides analyzed in each sequence (between 895 and 1240 nucleotides per sequence). Insertion/deletion mutations were found in five RT sequences, with 1–6 mutations per sequence (0.08–0.59%). All mutations found in the eighth RT sequence caused amino acid changes (missense mutations) in the sequence. Most mutations were found at five nucleotide positions, namely K122E, R211S/E, A272P, E291D, and I293V.

Previous studies that identified the molecular diversity of HIV-1 RNA isolated from local populations (referral sequence K03455.1) revealed that substitution mutations were the most common type, followed by deletion and insertion mutations.[12] The HIVRT enzyme shows very high molecular variation. Amino acid changes can be found in the same positions in different individuals. These variations can be caused by natural mutations, host cell mechanisms, and selective pressure from ARV treatment. The variation in each nucleotide/amino acid position against RT sequences for >100.000 individuals.[9] This study found amino acid variation ≥1% in 37% of RT nucleotide positions. This high level of molecular variation poses a challenge for the development of diagnostic methods, genotypic resistance testing, and treatment strategies.[9]

### Relation of HIV-1 RT Mutations with CD4 T Cell Recovery Failure

The relationship between RT mutations with CD4 T cell recovery failure was analyzed in eight samples. This analysis was only performed for substitution mutations and missense mutations found in more than two samples. We analyzed a total of 17 mutation positions in this study, but no statistically significant relations were found. Two mutation positions were more closely associated with CD4 T-cell recovery failure, namely mutations in amino acid positions 60 (S60I) and 207 (Q207A). In both of these positions, 100% of the mutant samples exhibited immunologic reconstitution failure ($P > 0.05$).

No previous studies have evaluated the association between molecular variation in RT sequences and the failure of CD4 T-cell recovery in an Indonesian HIV-positive population. The variations in molecular RT in a Ugandan population and then obtained the association between a mutation in position 184 (M184V) and thymidine analog mutations (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) with failure to achieve immunological recovery.[8] The relation between specific RT mutations and CD4 T-cell recovery failure in 102 HIV-positive individuals who had been treated with ARVs for >6 months.[11] These researchers identified similar mutation types and positions to those reported by Reynolds, namely acquisition of the M184V mutation, thymidine analog mutations, Y181C mutation, and K103N mutation.

Some articles in the literature have reported that mutations that occur over HIV replication cycles may either be beneficial or harmful for the virus. Mutations harm the virus if they cause the cessation of protein synthesis necessary for viral replication. However, mutations are advantageous if they lead to antigenic variation, allowing the virus to evade the host immune response due to a change in the epitopes previously recognized by cells of the cellular and humoral immune systems. Changes that cause variations in antigenic epitopes block the interaction/binding of the virus to T-cell and B-cell receptors.[10-11,14,15] These mutant strains have a higher viral fitness and replication capacity.[14] Infection and CD4 T-cell apoptosis occur progressively through the increased expression of tumor necrosis factor-associated apoptosis-inducing ligands (TRAIL) expressed on CD4 T cells. TRAIL expression induces the activation of TRAIL death receptor 5, leading to CD4 T-cell apoptosis.[16]

## CONCLUSION

This study reports a trend toward an association between CD4 T cell failure (>350 cells/μL) in HIV patients treated with first-line ARV drugs for >6 months with a nucleotide mutation at position 60 and 207, although this did not reach statistical significance. Other factors suspected to be associated with failure of CD4 T-cell recovery need to be investigated in further studies.

### What is Known about this Topic

- RT sequences contained between 16 and 56 substitution mutations per sequence.
- The mutations in RT sequence caused amino acid changes (missense mutations) in the sequence.
- CD4 T-cell failure in HIV-1 patients treated with first-line ARV drugs for >6 months when a nucleotide mutation was present in position 60 and 207.

### What this Study Adds

There is an association between CD4 T cell failure in HIV patients treated with first-line ARV drugs for >6 months with a nucleotide mutation at position 60 and 207.

## COMPETING INTEREST

The authors declare no competing interest.

## AUTHORS' CONTRIBUTIONS

Efrida E. designed this study and Andani E.P participated in the data collection. Efrida E. and Andani E.P analyzed and interpreted the data. All authors have read and agreed the final version of this manuscript.

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