ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4

Journal of Coastal Life Medicine

# Delayed Identification of Treatment Failure causes High Levels of Acquired Drug Resistance and Less Future Drug Options among HIV-1-infected South Indians.

**Received:** 14 February 2023, **Revised:** 16 March 2023, **Accepted:** 18 April 2023

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## Keywords:

ART, HIV drug resistance, Azidothymidine, Tenofovir, Etravirine, Rilpivirine, subtype C resistance.

## Abstract

Objective:
This study aims to investigate the prevalence of HIV-1 drug resistance mutations (DRMs) in individuals experiencing immunological failure (IF) while on first-line regimens based on nucleoside reverse transcriptase inhibitors (NRTIs), namely thymidine analogues (TAs) such as AZT and D4T, as well as non-thymidine analogues (NTAs) like TDF. The objective is to assess the viral drug susceptibility in order to inform the selection of optimal second-line therapeutic alternatives.
Methods
Cross-sectional study comprised 300 people with HIV-1 infection who were on first-line HAART. The HIV-1 pol gene, which spans 20–240 RT codons, was genotyped using IAS-USA 2014 and the Stanford HIV drug resistance database v7.0.
Results:
In total 300 Participant receiving first-line therapy was included. Majority of the TDF failures were on EFV based first-line (89% vs 45%) (p <0.0001), level of resistance for TDF and AZT shows, that resistance to TDF was about one-third (37%) of TDF participants and onefourth (23%) of AZT participants; resistance to AZT was 17% among TDF participants and 47% among AZT participants; resistance to both AZT and TDF was significantly high among AZT participants [21% vs. 8%, OR 3.057 (95% CI 1.4-6.8), p < 0.0001].
Conclusion:
Acquired drug resistance were induced by delayed diagnosis of treatment failure. Therefore, we must take steps to regularize virological monitoring with integrated resistance testing in LMIC (Low and Middle Income Countries), such as India; this will help to preserve the effectiveness of ARV and assure the success of eradicating AIDS as a public health concern by 2030.

## 1. Introduction:

Globally, 38.4 million people were living with HIV (Human Immunodeficiency Virus) at the end of 2021. 6,50,000 people died in 2021 and 1.3 million new infections have been reported during 2021 [1]. A new set of ambitious targets published by UNAIDS (the United Nations Programme on HIV/AIDS) calls for 95% of all HIV-positive people to be aware of their status by 2025, 95% of all HIV-infected people to be receiving sustained antiretroviral therapy, and 95% of all antiretroviral therapy recipients to have viral suppression [2]. It is likely even in the well-managed treatment programs the level of HIV DR (Drug Resistance) may increase with the increase in the people on treatment and their treatment duration. The HIV DR can lead to poor treatment outcomes, increased mortality and durability of regimen and most importantly communities will be at risk due to viremic individuals, who may continue to transmit the

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

infection and limit the usage of ART (Anti-retroviral Therapy) regimen in a given population, which is evidenced by the fact that pre-treatment resistance to EFV (Efavirenz) or NVP (Nevirapine) has reached the threshold of 10% of above in 6 of the 11 countries tested. Since 2013, WHO (World Health Organization) recommended the use of XTC+TDF+EFV as the preferred and XTC+AZT+EFV as the alternative ART option in first-line therapy. However, before 2013, XTC+AZT+EFV was the preferred ART option in first-line therapy [3]. With the revision in guidelines, HIV patients who initiated ART after 2013 started with TDF (Tenofovir) based therapy, however, for patients who initiated ART before 2013, and patients with creatinine clearance <60mL/min and in countries like India, The first-line currently employs AZT. Prior to 2016, when dolutegravir (DTG), a third agent in place of nonnucleoside reverse transcriptase inhibitors (NNRTI), became available as a low-dose efavirenz alternative for adults, the WHO recommended first-line regimen was based on NNRTI [6]. Tenofovir, Lamivudine, and Darunavir, or TLD, was confirmed as the optimal first-line treatment, as of 2019, the WHO's second-line ART recommendations [7,14] As part of a rotation of Nucleos(t)ide Reverse Transcriptase inhibitors (NRTIs), including zidovudine (AZT), recommend transitioning to dolutegravir (for NNRTI-based first-line) and boosting atazanavir, lopinavir, or alternatively darunavir (for TLD) for treatment-resistant HIV-1 infection. Therefore, NRTI and PI (Protease Inhibitor) medications are frequently used together. As a result, this study assesses the mutation pattern of AZT and TDF-based regimens, their potential for resistance, and their influence on the range of ART alternatives.

## 2. Methods:

The study was conducted in Chennai, India's YRG Centre for AIDS Research and Education (YRG CARE) and the study was approved by Institutional Review Board of YRG CARE. In total 300 HIV-infected participants visiting YRG CARE, who were failing on NNRTI based were retrospectively enrolled and were subjected to RT sequencing spanning 20-240 codons by validated homebrew method [4]. The bidirectional sequencing of partial reverse transcriptase was performed on ABI 3500 genetic analyzer (Applied Biosystem, Inc., Foster City, CA). Inter-sample contamination was checked by constructing a phylogenetic tree by the neighbor-joining method using MEGA V6.0 [5]. The sequences were aligned using the ClustalX software and compared to a reference sequence of the Indian Subtype C (C.IN.AF067155). The HIV-1 subtype of the sequences was determined using the REGA V3 tool.

## 3. Statistical analysis:

The demographic, and clinical characteristics of the study participants were concise by medians and interquartile range (IQR) for continuous variable and as number and percentage for categorical variable. The statistical significance of mutation difference and level of resistance between two groups were compared using Fisher's exact test. The level of resistance was categorized as susceptible, possible resistance and resistance based on the Stanford HIV DR database output additionally, the risk factor was also studied for variables such as DRMs causing resistance to TDF, AZT - K65R and TAMs and DRMs causing resistance to ETR, RPV - Y181CIV, K101EP, and L100I. Multivariate logistic regression and Fisher's exact test were used for identifying the risk factor.

## 4. Result:

In total 300 Participant receiving first-line therapy were included of which 100 were TDF based first line therapy and 200 were on AZT based first line therapy. Table 1 provides a list of the study participants' demographic details. The participants' average age was 35 years (interquartile range: 29 to 40), and 217 of them (72.3%) were men. CD4 T cell count of TDF failures was low 172 cells/µL (IQR 80-252) compared to AZT failures 216 cells/µL (IQR 111-328) ($p$ 0.029), treatment duration was low among TDF failures (24 months vs. 61 months) ($p$ <0.0001). Majority of the TDF failures were on EFV based first-line (89% vs 45%) ($p$ <0.0001).

### 4.1. Drug Resistance–Associated Mutations

Any class of NRTI resistance was seen in more than 78% of failures (78% for TDF failures and 81% for AZT failures), any NNRTI resistance was seen in more than 90% of failures (92% of TDF failures and 90% of AZT failures), and any dual class (NRTI+NNRTI) resistance was seen in more than 76% of failures (77% of TDF failures and 76% of

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
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AZT failures). Prevalence of individual NRTI resistance between two groups is shown in figure 1. Among discriminatory mutations, M184IV was significantly high among AZT failures (76% vs. 62%) (*p* 0.0146); whereas K65R (25% vs. 2%, *p* <0.0001), K70EG (21% vs. 2%, p<0.0001), L74IV (10% vs. 2%, *p*0.0012) and Y115F (13% vs. 1%, *p*<0.0001) were significantly high among TDF failures. In total TAMs was seen in 144 (48%) participants, overall TAMs (54% vs. 36%, *p* 0.0047) and TAM 1 & 2 (20% vs. 9%, *p* 0.03) was significantly high among AZT failures. Among individual TAMs, M41L (30% vs. 15%, *p* 0.02), L210W (8% vs. 1%, *p* 0.014), T215Y (27% vs. 8%, *p* 0.0001), K70R (24% vs. 9%, *p* 0.0026), and K219QE (19% vs. 8%, *p* 0.0168) were significantly high among AZT participants. Among all study participants, most frequent NNRTI mutations observed was K103NS 132 (44%), Y181CIV 78 (26%) and Y188LCH 75 (25%); mutations such as L100I (9% vs. 0%, *p* <0.0001) and V106AM (37% vs. 17%, *p* 0.0001) was high among TDF based failures and K101EP (14% vs. 5%) was significantly high among AZT based failures (Figure 2). The prevalence of NNRTI mutation among both groups has been shown in figure2. On further studying based on their NNRTI regimen [EFV (n=180) and NVP (n=120)], mutations such as L100I (5% vs. 0%, *p* 0.0126), K103NS (49% vs. 36%, *p* 0.0241), and V106AM (30% vs. 13%, *p* 0.0008) were significantly high among EFV based failures and K101EP (7% vs. 16%, *p* 0.022), E138AGKQ (14% vs. 6%, *p* 0.025), Y181CIV (42% vs. 15%, *p* <0.0001), and Y188LCH (32% vs. 21%, *p* 0.043) were significantly high among NVP based failures (Figure 3&4).

### 4.2. Future ART Options:

Based on the NRTI DRM pattern, the level of resistance for TDF and AZT was studied between two groups, and the result shows, that resistance to TDF was about one-third (37%) of TDF participants and one-fourth (23%) of AZT participants; resistance to AZT was 17% among TDF participants and 47% among AZT participants; resistance to both AZT and TDF was significantly high among AZT participants [21% vs. 8%, OR 3.057 (95% CI 1.4-6.8), *p* < 0.0001]. Based on the NNRTI DRM pattern, the level of resistance for third-generation NNRTI, RPV, and ETR was studied between NVP and EFV-based failures. The result has shown, NVP has selected more cross-resistance DRM compared to EFV, resulting in significantly high RPV resistance [67% vs. 39%, OR 3.14 (CI 1.9 – 5.1), *p* < 0.0001], ETR resistance and ETR RPV resistance [53% vs. 25%, OR 3.43 (CI 2.1 – 5.6), *p* < 0.0001] among NVP participants (Figure 3&4).

### 4.3. Risk Factors for RT Drug Resistance Mutations

Table 2 summarizes the risk factors for developing NRTI and NNRTI resistance. Age was found to be the risk factor for TDF resistance (OR 1.03, *p* <0.05), and treatment duration (OR 1.01 *p* 0.001) and age (OR 1.04, *p* 0.02) was the risk factor for AZT resistance. For TDF and AZT resistance, AZT therapy was found to be the risk factor (OR 3.06, *p* 0.005). For ETR resistance (OR 3.34, *p* <0.0001), RPV resistance (OR 3.04, *p* <0.0001) and combined ETR and RPV resistance (OR 3.04, *p* <0.0001), NVP preferred with low confounding factors. Similarly, for NNRTI mutations, Y181CIV (OR 4.1, *p* <0.0001) and K101EP (OR 2.4, *p* <0.0001), NVP therapy was found to be the risk factor and for L100I mutation, EFV therapy (OR 13.5, *p* 0.012) was found to be the risk factor.

## 5. Discussion

To our knowledge, this is the first significant study to compare HIV medication resistance and its consequences among patients who are failing first-line AZT and TDF-based HAART in India. AZT has remained the part of the preferred alternative regimen in first-line therapy and second-line therapy. TDF was approved by FDA in the year 2001, and WHO recommended its use in first-line and second-line therapy in 2013. In recent revisions of HIV treatment guidelines, WHO has recommended the fixed use of XTC in first and second-line and has recommended the use of AZT and TDF interchangeably in first and second-line therapy. This fact has been the motivation of this study in investigating the DRM pattern in AZT failures and TDF failures and how these mutations may jeopardize their counterpart. The overall prevalence of NRTI mutations was similar among the two groups; however, there are few discriminatory mutations that were significantly high among a particular group. M184IV was significantly high among AZT failures, which is similar to the findings from a meta-analysis conducted to study AZT and TDF failures [6]. The individual or combination `of

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

all DRMs such as K65R, K70E, L74IV, and Y115F were significantly high among TDF failures. These mutations were TDF-associated mutations and the former two mutations confer high-level resistance to TDF. Though the latter mutation does not confer high-level resistance to TDF, it often coexists with K65R, and favourably, L74IV hyper-sensitizes AZT and TDF susceptibility [7, 8]. Our study reported K65R prevalence of 25% and K70E prevalence of 21% among TDF failures. Previous studies from India have shown the range of K65R prevalence from 22% to 28% and K70E in 19%. Studies from the South African Subtype C virus have shown a prevalence of 25% - 70% [9,10,11]. TenoRes study conducted from data collected from 36 countries has shown, that TDF resistance is 36% in total, of which a high proportion are from LMIC [12]. The high prevalence of K65R among LMICs is due to the non-programmatic substitution of TDF from AZT/D4T after guideline revision or sustained virologic suppression may not be confirmed before substitution, due to the less access to viral load testing. Settings due the absence of regular virologic surveillance demonstrated by signs of advanced disease, such as low CD4, more RT mutations, and potentially longer-lasting therapeutic failure [13, 14]. Lower K65R rates have been reported from reports from resource-limited settings (RLS) where virologic monitoring is common, including South Africa [15]. Our findings thus suggest the use of routine VL monitoring for earlier detection of treatment failure and the consideration of individual resistance testing to maximize the efficacy of the treatment program in LMIC, in accordance with the findings of other research as expected, the accumulation of TAMs was significantly high among AZT based failures, though TDF failing participants have not been previously exposed to thymidine analogue drugs, the prevalence of TAMs among them was 36%. This is similar to the prevalence observed in subtype C infected TDF failing participants from India [16, 17] and South Africa [18, 19]. The high prevalence of TAMs among TDF failing participants is worrying, as the presence of 3 or more TAMs can confer resistance to TDF, even in the absence of K65R [20]. NNRTI mutations are widely known to be selected by both NVP and EFV, in line with our results, a study conducted in South African sequences has also made similar observations [21]. NRTI DRMs, L100I and V106AM were significantly high among TDF based failures and K101EP was significantly high among AZT-based failures. Though there is no direct evidence of association of these NNRTI DRMs with NRTI therapy, these differences observed could be due to the differences in NRTI+NNRTI combination, as most participants (90%) on TDF therapy have received EFV as NNRTI combination and 55% of AZT failures have received NVP as NNRTI combination, On the basis of the DRM pattern, future therapeutic options were assessed. The assessment was carried out for TDF or AZT for NRTI therapy and not for XTC, as this drug will be recycled irrespective of their resistance. Similarly, for NNRTI therapy, ETR and RPV resistance was assessed as EFV and NVP will no longer be recycled after first line failure [28,29,30]. Interestingly, for NRTI therapy, the number of participants who can be recycled for the same drug and the number of participants who can be switched for alternate NRTI therapy was higher among TDF-based failures. Similar to our observation results from Tenores study showed, that among the Asian population 61% of TDF failures can opt same for second-line therapy. Similarly, the number of participants who cannot be recycled to either TDF or AZT was high among AZT-based failures. This indicates that TDF therapy is better than AZT in terms of resistance profile. However, the fewer future treatment options among AZT failures could be due to the long ART exposure compared to TDF failures. The result also indicates that AZT confers more cross-resistance to TDF, whereas TDF counter selects AZT resistance (Phenotypic antagonism), this emphasizes that TDF therapy be strategically used before AZT therapy, as proposed before [11]. For NNRTI therapy, more participants can opt for ETR or RPV among EFV-based failures. This shows that from a resistance perspective, EFV is better than NVP, this observation is in line with the previous findings [22]. Risk factors associated with various characteristics such as TDF, AZT, TDF+AZT, ETR, RPV, ETR+RPV resistance, and key mutations conferring resistance to it were studied among the study participants. Most of the risk factors which was found to be significantly associated had almost neutral association. The clinically relevant risk factors were AZT therapy which was significantly associated with AZT+TDF resistance. As already discussed, this could be due to cross-resistance caused by AZT-selected multiple TAMs. Similarly, NVP therapy was found to be the risk factor for ETR, RPV, and ETR+RPV resistance, this could be due to the

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

high proportion of ETR and RPV-associated mutations such as Y181C and G190A seen in NVP failures [26, 27], similar observation has also been seen in other settings [23]. our study also accepts that delayed identification of failure has likely contributed to the increased resistance [24, 25].

## 6. Conclusion:

Despite the considerable prevalence of acquired drug resistance that our investigation discovered, which was caused by the treatment failures delayed discovery. The present difficulty in LMICs is to find effective means to measure HIV viral load and, in the long run, to acquire access to genotyping. Other current challenges include identifying effective techniques to track HIV viral load. Gaps and discrepancies in testing and treatment coverage between nations, subnational regions, and population categories must be removed if AIDS is to be eradicated by 2030 and the global AIDS response is to be equitable.

**Acknowledgments:**

We are most grateful to the clinical and laboratory staff at YRG CARE (Chennai, India) for their facilitation of the study.

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Journal of Coastal Life Medicine

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ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

susceptibility in HIV patients with prior failure to nonnucleoside analogues. Aids. 2008; 22: 2395-8.

**Table 1:** Demographic characteristics of the study participants

| Characteristics | All participants (n=300) | TDF (n=100) | AZT (n=200) | P value |
|---|---|---|---|---|
| **Age (Years)** * | 35 (29-40) | 35 (30-39) | 35 (29-40) | 0.9482 |
| **Sex**# | | | | |
| **Male** | 217 (72.3%) | 65 (65%) | 152 (76%) | 0.0551 |
| **Female** | 83 (27.7%) | 35 (35%) | 48 (24%) | |
| **Mode of transmission**# | | | | |
| **Heterosexual** | 281 (93.7%) | 94 (94%) | 187 (93.5%) | 0.108 |
| **Blood** | 9 (3%) | 5 (5%) | 4 (2%) | |
| **Vertical** | 10 (3.3%) | 1 (1%) | 9 (4.5%) | |
| **Baseline CD4 T cell count (cells/µL)** * | 207 (102-329) | 187 (74-308) | 212 (124-343) | 0.1416 |
| **CD4 T cell count at failure (cells/µL)** * | 206 (97-310) | 172 (80-252) | 216 (111-328) | 0.0291 |
| **Treatment duration (months)** * | 52 (19-87) | 24 (13-57) | 61 (39-91) | <0.0001 |
| **Regimen**#& | | | | |
| **XTC+TDF+EFV** | 90 (30%) | 90 (90%) | - | <0.0001 |
| **XTC+TDF+NVP** | 10 (3.3%) | 10 (10%) | - | |
| **XTC+AZT+EFV** | 90 (30%) | - | 90 (45%) | |
| **XTC+AZT+NVP** | 110 (36.7%) | - | 110 (55%) | |

* median (IQR), # number (%), & comparison between TDF and AZT

**Table 2:** Multivariate analysis of the risk factors associated with genotypic drug resistance

| Variables | Risk factor | Positive association | Negative | P value |
|---|---|---|---|---|

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

| | | (Odds Ratio) | association (Odds Ratio) | |
|---|---|---|---|---|
| TDF Resistance | CD4 T cell count at failure | | 0.998 | 0.045 |
| | Baseline CD4 T cell count | | 0.998 | 0.056 |
| | Age | 1.03 | | 0.046 |
| | TDF therapy | 1.96 | | 0.014 |
| | AZT therapy | | 0.51 | 0.014 |
| AZT Resistance | Treatment duration | 1.01 | | 0.001 |
| | CD4 T cell count at failure | | 0.996 | 0.001 |
| | Age | 1.04 | | 0.021 |
| | TDF therapy | | 0.23 | 0.0001 |
| | AZT therapy | 4.33 | | 0.0001 |
| TDF and AZT Resistance | CD4 T cell count at failure | | 0.996 | 0.007 |
| | TDF therapy | | 0.33 | 0.0048 |
| | AZT therapy | 3.06 | | 0.0048 |
| K65R | TDF therapy | 16.3 | | <0.0001 |
| | AZT therapy | | 0.06 | <0.0001 |
| TAMs | Treatment duration | 1.01 | | 0.019 |
| | CD4 T cell count at failure | | 0.998 | 0.009 |
| | TDF therapy | | 0.5 | 0.007 |
| | AZT therapy | 2.0 | | 0.007 |
| ETR resistance | Baseline CD4 T cell count | | 0.998 | 0.038 |
| | NVP therapy | 3.34 | | <0.0001 |
| | EFV therapy | | 0.3 | <0.0001 |
| RPV resistance | NVP therapy | 3.04 | | <0.0001 |
| | EFV therapy | | 0.33 | <0.0001 |
| ETR and RPV resistance | Baseline CD4 T cell count | | 0.998 | 0.038 |
| | NVP therapy | 3.04 | | <0.0001 |
| | EFV therapy | | 0.33 | <0.0001 |

ISSN: 2309-5288 (Print)
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Journal of Coastal Life Medicine

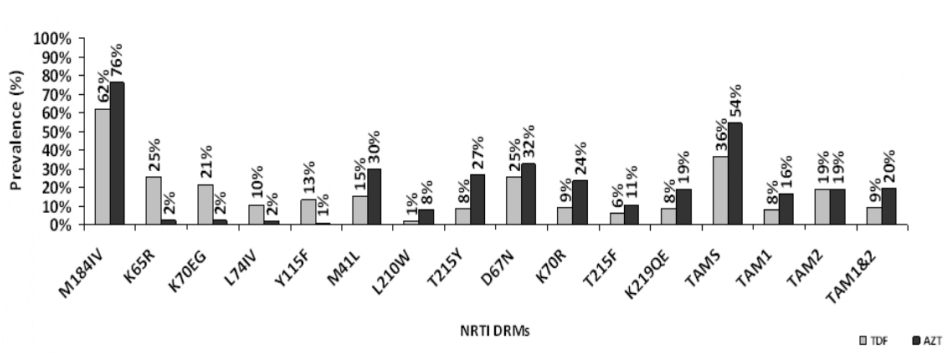



**Figure1: Prevalence of NRTI DRMs among patients failing AZT and TDF based first line HAART**

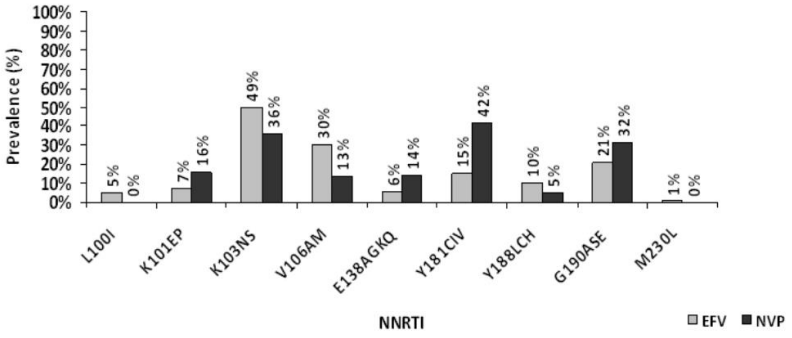
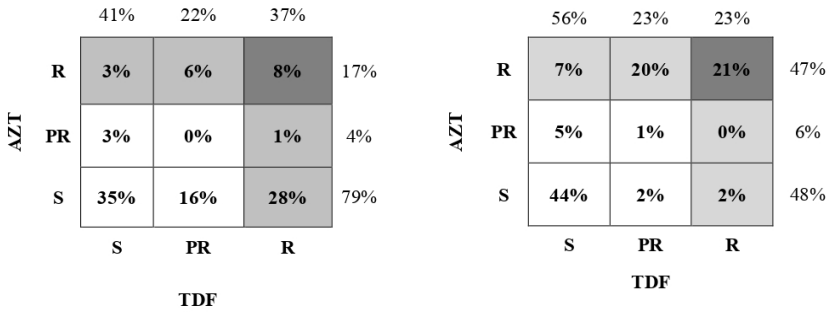



**Figure2: Prevalence of NNRTI DRMs among patients failing EFV and NVP based first line HAART.**




**(a) TDF Failures** **(b) AZT Failures**

**Figure 3: Level of resistance to AZT and TDF among a) TDF failures and b) AZT failure**

**S: Susceptible; PR: Possible resistance; R: Resistance**

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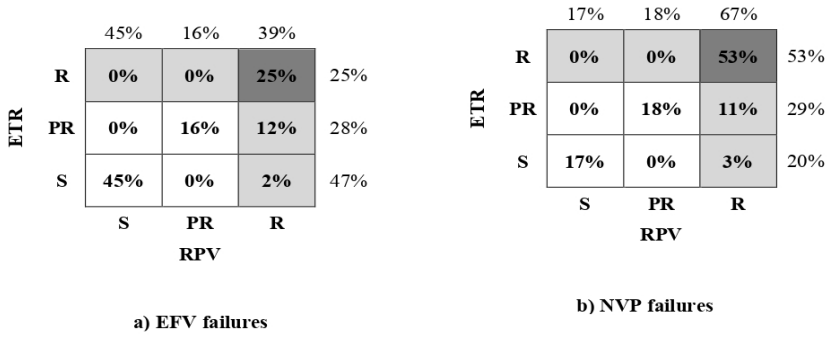


**Figure 4: Level of resistance to ETR and RPV among a) EFV failures and b) NVP failure**
**S: Susceptible; PR: Possible resistance; R: Resistance**