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**Original Article**

# Assessment of the 24th Week Success of Anti-Retroviral Therapy in the Action against HIV in Istanbul Database: Results from a Region with Increasing Incidence

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**SUMMARY:** We aimed to assess the 24-week virological and immunological success of the treatment of treatment-naive and treatment-experienced patients included in the Action against HIV in Istanbul (ACTHIV-IST) database. The ACTHIV-IST database was screened retrospectively from January 2012 to January 2014. The data for these patients such as age, sex, treatment-naive or treatment-experienced status, date of diagnosis, date of commencing antiretroviral therapy, antiretroviral therapy regimen, CD4+ cell count, and viral load before and after therapy were analyzed. In the 24th week of antiretroviral therapy, there were 40 (17.9%) and 29 (14.1%) virological and immunological failures, respectively. Virological failure (VF) was associated with a baseline viral load > 100,000 copies ($p = 0.004$). A CD4+ cell count lower than 200 cells/μl was not found to be associated with VF ($p = 0.843$). Immunological failure was substantially rare in patients with a baseline CD4+ cell count > 200 cells/μl ($p = 0.005$). Although an HIV-RNA ≤ 100,000 copies/ml was protective against VF in the 24th week, in individuals with an HIV-RNA > 100,000 copies/ml, VF was 3.2 times more likely to occur. Baseline VF was the most predictive parameter to estimate 24th week virological success and VF. VF is an important prognostic parameter resulting in CD4+ cell depletion, AIDS-related events, and increased mortality.

## INTRODUCTION

Potent antiretroviral therapy (ART) for HIV infection has resulted in substantial reductions in mortality, progression to AIDS, opportunistic infections, and hospitalizations, particularly among those who achieve viral suppression (1,2). Viral suppression is also associated with decreased morbidity and mortality related to other comorbidities (e.g., cardiovascular disease, liver disease, and nephropathy) and decreased HIV transmission to un-infected persons. Although the incidence of HIV infection is low in Turkey, new reported cases are increasing. Viral load (VL) is an important and early parameter in the assessment of treatment success. CD4+ cell depletion and subsequent progression to AIDS have been reported to result from a high VL in some studies (3). Causes of virological failure (VF) include high VL or low baseline CD4+ cell count, comorbidities affecting adherence to treatment, drug resistance at baseline or during the treatment, failure of previous treatments, adverse effects of the drugs, suboptimal pharmacokinetic states, and suboptimal virology patency (4). Currently, treatment success may be summarized as the suppression of the VL and achieving of undetectable levels, immunological success, and the prevention of HIV-related events. (3). We aimed to assess the 24-week virological and immunological success of treatment-naive and treatment-experienced patients included in the Action against HIV in Istanbul (ACTHIV-IST) database.

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## MATERIALS AND METHODS

**Data collection:** The ACTHIV-IST database was used in our study. ACTHIV-IST consists of 5 centers following up treatment-naive and treatment-experienced patients in Istanbul, which is the most populated city in Turkey. ACTHIV-IST was established in 2012, and new cases are being enrolled in the database retrospectively.

**Study design and study participants:** The ACTHIV-IST database was screened retrospectively from January 2012 to January 2014. One thousand two hundred eighty-nine patients older than 18-years were included in this study. The ART initiation decision was based on the up-to-date international guidelines at the time of the study. Three hundred thirty-nine treatment-naive and treatment-experienced patients were recorded in the database during the time span of the study. Of those, 256 patients had initiated ART, and 32 were excluded because of the absence of CD4+ cell count and VL follow up results in the 24th week. Two hundred twenty-

four patients were enrolled in the study, and data such as age, sex, treatment-naive or treatment-experienced status, date of diagnosis, date of commencing ART, ART regimen, major ART gene mutations, adherence to treatment, CDC stage, presence of opportunistic and coexisting infections, CD4+ cell count, and VL before and after therapy were analyzed. Adherence to treatment was based on self-reports.

**Definitions:** VF: VF is defined as a VL > 1,000 copies/ml in the WHO guideline updated in 2015 (5–7). Although the Department of Health and Human Services (DHHS) guide updated in April 2015 (4, 8) and the British AIDS Association (BHIVA) guideline updated in January 2016 established a VL > 200 copies/ml as VF, the European AIDS Clinical Society (EACS) 2015 guideline established a VL > 50 copies/ml as VF (9). Taking into consideration laboratory errors, high sensitivity of the novel techniques, and temporary increases (4, 10–12) when VL is 50–200 copies/ml, we used a VL > 200 copies/ml as VF.

Immunological failure (IF): According to the 2010 WHO criteria, definitions of IF (13) include (i) a CD4 cell count of < 100 cells/μl after 24 weeks of therapy, (ii) a return to, or a decrease below, the baseline CD4 cell count after the 24th week of therapy, or (iii) a > 50% decrease from the on-treatment peak CD4 cell count (5).

Complete responder patients: Both virological and immunological responders in the 24th week of ART.

Non-responder patients: Both virological and immunological non-responders in the 24th week of ART.

Immunological-only responders: Patients in whom viral replication persists despite an immunological response.

Virological-only responders: Patients who exhibit a virological response in the absence of an immunological response.

**Microbiological analyses:** Plasma HIV-1 RNA was measured using quantitative real-time reverse transcriptase polymerase chain reaction (RT-PCR; COBAS Taq-Man HIV-1 test Roche Molecular Systems, Pleasanton, CA, USA) with a lower limit of detection of 47 HIV-1 RNA copies/ml. For CD4 cell count, the samples were prepared and run on a flow cytometer (FACS Calibur, Beckton Dickinson Biosciences, Franklin Lakes, NJ, USA) according to the manufacturer's instructions.

**Statistical analyses:** Descriptive statistics for the continuous quantitative data (age, CD4+ cell count before the treatment and in the 24th week, HIV-RNA VL) are expressed as ratios and intervals, whereas counts and percentages are used to express the frequency distribution of categorical data (sex, treatment-naive or treatment-experienced status, ART regimen, treatment success). The normal distribution of continuous quantitative data was checked with the one-sample Kolmogorov-Smirnov test. Normally distributed data are expressed as the mean ± standard deviation, and non-normally distributed data are expressed as the median (interquartile range [IQR]). The independent-samples Mann-Whitney U test and independent samples t-test were used to compare the means of continuous variables. The relationship between categorical variables was tested with the Pearson Chi-Square test (or Fisher's exact test when applicable). Comparisons of median baseline CD4+ cell count and 24th week median CD4+ count of treatment-naive and treatment-experienced patients were performed using the Friedman test. The association of an increase in the 24th week median CD4+ cell count with ART regimen was assessed with the independent-samples Kruskal-Wallis test. Correlations of VL before ART with CD4+ cell count in the 24th week and correlations of viral failure with variables were investigated using Pearson and Spearman's correlation test. A binary logistic regression ("backwards: LR" method) model was developed to predict the 24th week viral failure of treatment-naive and treatment-experienced patients. Data were analyzed using Statistical Package for Social Sciences version 17 (SPSS Inc., Chicago, IL, USA). A statistical test was considered significant at $p \leq 0.05$ and a 95% confidence interval.

## RESULTS

Two hundred twenty-four patients were enrolled in the study. The mean age was 39.08 ± 11.51 years. Of the total, 184 (82.1%) were male, and 209 (93.3%) were treatment naive. The median baseline CD4+ cell was 241 cells/mm$^3$ (IQR, 93.75–324), and the median baseline HIV-RNA VL was 177.05 copies/ml (IQR, 55.35–680.150) (Table 1). The ART dose skipping ratio was 4.5% ($n$ = 10). Of the total, 9 (4%) had HIV-related malignancies, 40 (17.9%) had concurrent opportunistic infections, and 19 (8.5%) had co-infections. In the treatment-naive patient group, a major ART gene mutation was detected in 12 (5.7%) individuals. In a treatment-experienced patient who had both VF and IF, an M184V nucleoside reverse transcriptase inhibitor (NRTI) gene mutation was detected as well as a V90I major ART gene mutation for NNRTI. Four patients died during follow up.

Patients were grouped according to their response to treatment as complete responders, virologic-only responders, immunological-only responders, and non-responders. Considering the virological and immunological responses in all patients, 148 (66.1%) were complete responders, 12 (5.4%) were non-responders, 36 (16.1%) were virological-only

Table 1. Demographical data, HIV RNA level and CD4 cell count before initiation of ART

| Variable | |
|---|---|
| Sex *n* (%) | |
| Female | 40 (17.9) |
| Male | 184 (82.1) |
| Age (mean ± SD)<br>Female<br>Male | 39.08 ± 11.51<br>38.35 ± 11.85<br>39.23 ± 11.46 |
| Treatment Status (*n*,%) | |
| Naive | 209 (93.3) |
| Experienced | 15, 6.7% |
| HIV RNA copies/ml | 177,05 (IQR, 55,35-680,150) |
| CD4 cells/μl | 241.5 (IQR, 93.75-324) |

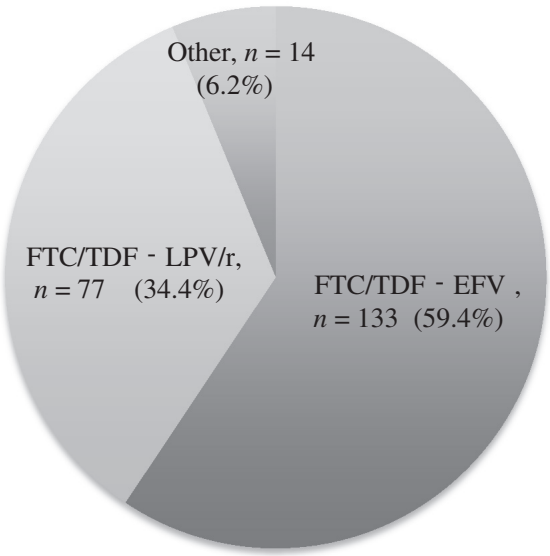
SD, standard deviation; IQR, interquartile range.

responders, and 28 (12.5%) were immunological-only responders in our patient group. Being treatment naive was found to be a significant factor affecting the complete response ($p$ = 0.0001). Taking into account only the 15 treatment-experienced patients, 9 (60%) exhibited a discordant response ($n$ = 8 virological-only responders, $n$ = 1 immunological-only responder). Baseline CD4+ cell count was not different among the groups ($p$ = 0.154) except that a baseline VL ≤ 100,000 copies/ml was significantly associated with a complete response ($p$ = 0.05).

In the 24th week of ART, VF and IF were detected in 40 (17.9%) and 29 (14.1%) treatment-naive and treatments-experienced patients, respectively. Sex, adherence to treatment, and existence of major ART gene mutations were not associated with VF ($p$ = 0.398, $p$ = 0.29, $p$ = 0.39, respectively) and IF ($p$ = 0,119, $p$ = 1, $p$ = 1, respectively). The VF ratio was not associated with HIV stage at admission ($p$ = 0.7), whereas the immunological success ratio was significantly higher in patients in whom HIV stage at admission was 1–2 ($p$ = 0.008). Initial and 24th week levels of CD4+ cell were not different among age groups ($p$ = 0.284). VF was associated with IF (OR, 2.4; 95% CI, 0.98–5.7; $p$ = 0.05). A baseline VL ≤ 100,000 copies/ml was protective against VF (OR, 0.3; 95% CI, 0.13–0.7; $p$ = 0.004). However, a baseline CD4+ cell count of 200 cells/μl or less was not found to be associated with VF (OR, 1.07; 95% CI 0.51–2.2; $p$ = 0.843). On the other hand, a baseline CD4+ cell count > 200 cells/μl was protective against IF (OR, 0.22; 95% CI, 0.07–0.66; $p$ = 0.004) (Table 2). The median time spans between diagnosis and initiation of treatment in the VF and IF groups were 2.13 (IQR, 1.24–8.44) and 2.33 (IQR, 1.1–23.9) months, respectively. The difference was not statistically significant ($p$ = 0.96). This time span also did not differ between the virological and immunological success groups ($p$ = 0.57).

The 24th week VL in ART naive and experienced patients was < 50 copies/ml in 142 (63.4%), 50–200 copies/ml in 42 (18.8%), and > 200 copies/ml in 40 (17.8%) patients. One hundred thirty-two (58.9%) treatment-naive patients had a VL < 50 copies/ml. An HIV-RNA ≤ 100,000 copies/ml was associated with a VL < 50 copies/ml in the 24th week ($p$ = 0.001).

The most common ART regimen was tenofovir disoproxil fumarate/emtricitabine-efavirenz (TDF/FTC+EFV) ($n$ = 133, 59.4%), followed by tenofovir disoproxil fumarate/emtricitabine-lopinavir/ritonavir (TDF/FTC+LPV/r) ($n$ = 77, 34.4%) (Fig. 1). The TDF/




FTC/TDF-LPV/r: tenofovir disoproxil fumarate/emtricitabine-lopinavir/ritonavir; and FTC/TDF-EFV: tenofovir disoproxil fumarate/emtricitabine-efavirenz.

Fig.1. Distribution of ART regimens.

Table 2. Univariate analysis of virological failure and immunological failure groups

| Characteristic | VF | VS | $p$ -Value | OR | 95% CI | IF | IS | $p$ -Value | OR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| Sex: Male ($n$, %) | 31, 16.8 | 153, 83.2 | 0.398 | 1.43 | 0.62-3.3 | 22, 75.9 | 148, 84.1 | 0.29 | 1.68 | 0.65-4.31 |
| Age (median, IQR) | 35, 28-47.5 | 39.5, 30.2-48 | 0.17 | | | 39, 30.5-50.5 | 38, 30-47 | 0.49 | | |
| Age < 50 years ($n$, %) | 35, 18.7 | 152, 81.3 | 0.45 | 1.47 | 0.53-4.05 | 22, 75.9 | 151, 85.8 | 0.17 | 0.52 | 0.2-1.34 |
| HIV related malignencies:($n$, %) | No data | 9, 4.9 | 0.36 | | | 2, 6.9 | 4, 2.3 | 0.2 | 0.31 | 0.05-1.79 |
| Coinfection:($n$, %) | 1, 2.5 | 18, 9.8 | 0.2 | 4.2 | 0.54-32.6 | No data | 19, 10.8 | 0.08 | | |
| Opportunistic infection:($n$, %) | 7, 17.5 | 33, 17.9 | 0.94 | 1.03 | 0.42-2.53 | 4, 13.8 | 34, 19.3 | 0.47 | 1.49 | 0.48-4.58 |
| CDC stage:1 and 2 ($n$, %) | 25, 62.5 | 109, 59.2 | 0.7 | 1.1 | 0.56-2.32 | 24, 82.8 | 100, 56.8 | 0.008 | 3.64 | 1.33-10 |
| Time on ART (months) (median, IQR) | 2.13, 1.24-8.44 | 2.23, 1.1-9.26 | 0.96 | | | 2.33, 1.1-23.96 | 2.23, 1.2-9.1 | 0.57 | | |
| Treatment:Naive ($n$, %) | 37, 17.7 | 172, 82.3 | 0.735 | 0.86 | 0.23-3.2 | 19, 65.5 | 171, 97.2 | 0.0001 | 0.05 | 0.01-0.18 |
| Major ART mutation gene: (treatment naive and experienced)($n$, %) | 2, 5 | 11, 6 | 1 | 1.2 | 0.25-5.67 | 1, 3.4 | 9, 5.1 | 1 | 1.5 | 0.18-12.3 |
| ARTnonadherence: ($n$, %) | 3, 7.5 | 7, 3.8 | 0.39 | 2.05 | 0.5-8.2 | 3, 10.3 | 6, 3.4 | 0.11 | 3.2 | 0.7-13.8 |
| InitialVL ≤ 100,000 copy/ml ($n$, %) | 29, 14.9 | 165, 85.1 | 0.004 | 0.3 | 0.13-0.7 | 26, 89.7 | 154, 87.5 | 1 | 1.23 | 0.34-4.43 |
| InitialCD4+> 200 cell/μl ($n$, %) | 21, 17.2 | 101, 82.8 | 0.843 | 1.07 | 0.51-2.2 | 23, 85.2 | 90, 55.9 | 0.004 | 0.22 | 0.07-0.6 |

VL, viral load; IQR, interquartile range; VF, Virological Failure; VS, Virological Succeeding; IF, Immunological Failure; IS, Immunological Succeeding.

Table 3. Univariate analyses of FTC/TDF-EFV and FTC/TDF-LPV/r regimens

| | FTC/TDF-EFV *n* (%) | FTC/TDF-LPV/r *n* (%) | *p*-value | OR | CI %95 |
|---|---|---|---|---|---|
| CDC: stage 1-2 (n, %) | 88, 66.2 | 36, 46.8 | 0.006 | 2.2 | 1.25-3.95 |
| Initial CD4+>200 cell/µl (*n*, %) | 82, 66.7 | 32, 46.4 | 0.006 | 0.4 | 0.23-0.79 |
| Initial VL>100,000 copy/ml(*n*,%) | 18, 13.5 | 10, (14.3) | 0.87 | 1 | 0.47-2.39 |
| VF | 19, 14.3 | 17, 22.1 | 0.14 | 0.5 | 0.28-1.21 |
| IF | 11, 9.1 | 12, 17.1 | 0.09 | 0.4 | 0.2-1.16 |
| ART nonadherence:(*n*, %) | 128, 96.2 | 72, 93.5 | 0.5 | 0.5 | 0.47-2.39 |

FTC/TDF-LPV/r, tenofovir disoproxil fumarate/emtricitabine-lopinavir/ritonavir; FTC/TDF-EFV, tenofovir disoproxil fumarate/emtricitabine-efavirenz.

FTC+LPV/r regimen was preferred over the TDF/FTC+EFV regimen for individuals who were CDC stage 1–2 on admission ($p = 0.006$) and had a baseline CD4+ cell count > 200 cells/µl ($p = 0.006$). On the other hand, the use of these regimens was similar in terms of VF, IF, adherence to treatment, and a baseline VL > 100,000 copies/ml ($p = 0.14$, $p = 0.09$, $p = 0.5$, $p = 0.87$, respectively) (Table 3).

Logistic regression analysis revealed that baseline HIV-RNA > 100,000 copies/ml was an independent risk factor for 24th week VF in treatment-naive and treatment-experienced patients (OR, 3.2; 95% CI, 1.33–7,71; $p = 0.009$).

## DISCUSSION

In HIV-infected individuals on ART, the decision on when to switch from first-line to 2nd-line therapy is dictated by treatment failure, and this can be measured in 3 ways: clinically, immunologically, and virologically (14). Biologically, VF occurs earlier, followed by IF and clinical failure. Although immunological monitoring may result in a premature switch, it is a more accurate parameter than clinical monitoring for assessing treatment success.

We assessed the treatment success using both immunological and virological parameters in our study. VF was 17.9%, and IF was 14.1%. VF was independent of age, sex, ART regimen, time elapsed from diagnosis to treatment, baseline CD4+ cell count, baseline VL, adherence to treatment, major ART gene mutations, and CDC stage in univariate and multivariate analyses (4, 15–17). However, baseline VL was also an important determining factor of treatment success in the complete responders group. A baseline CD4+ cell count < 200 cells/µl was associated with IF. A literature search using both English and Turkish keywords for studies from Turkey revealed a conference paper from the Glasgow Congress 2014. This study included 693 patients infected with HIV diagnosed in 2011–2012 in 24 centers (HIV-TR cohort) in Turkey. In this cohort, 24th week HIV-RNA was found to be below 50 copies/ml in 385 patients (63.4%) (18). The authors did not discuss risk factors in patients with an HIV-RNA > 50 copies/ml.

In another study that compared treatment regimens using VF and IF, in which TDF/FTC was the backbone and LPV/r or EFV was the 3rd agent, the authors concluded that the regimen that included LPV/r was more successful immunologically. In this study, the success of certain treatment regimens, adherence to treatment, and adverse effects were assessed rather than factors influencing treatment success (19). Therefore, to the best of our knowledge, our study is the first in Turkey to assess treatment success with regard to probable risk factors.

Non-adherence to treatment, drug resistance, and subtherapeutic drug level have been shown to be causes of VF in previous studies. However, VL monitoring was shown to be one of the best predictors of clinical progression and a major parameter affecting response to treatment in a study of 3,675 patients from Johannesburg (20). Ingole et al. demonstrated that baseline VL was an important risk factor for 24th week VF, and IF criteria had very low sensitivity and positive predictive value for predicting VF (14). Baseline VL was found to be the most important factor associated with the treatment success in our study. The rate of IF was lower than that of VF, which is consistent with the literature, suggesting that virological criteria are more predictive for assessment of treatment success and that treatment may be switched in the early period based on virological monitoring. Thus, treatment switching may be delayed if treatment success is assessed according to only immunological criteria. In a study by Rawizza et al. that advocated this point, median VF and median IF were 10.4 and 15.6 months, respectively, and VL monitoring was found to be the gold standard for assessing the treatment success in high-income countries (21). However, Phillips et al. reported that a high baseline VL was not associated with VF but that viral suppression was slower in patients with a baseline VL > 100,000 copies/ml (22). In our study, a baseline VL > 100,000 copies/ml was associated with VF in univariate and multivariate analyses. We think that VL monitoring and immunological criteria may be beneficial for determining the treatment switch at the appropriate time and assessing treatment success in high-income countries.

Several studies have demonstrated that the immune reconstitution of individuals diagnosed and treated at older ages was poor compared with that of those diagnosed and treated at younger ages despite successful ART and viral suppression (15). However, Patterson et al. advocated that immune reconstitution and viral suppression did not differ among treatment regimens classified according to age (23). We grouped patients

according to whether they were < 50 and found no difference between VF and IF. In addition, the CD4+ cell count in the 24th week and mean change in CD4+ cell count from baseline were similar in the 2 groups contrary to most studies. Likewise, virological success did not differ between the 2 groups studied by Althoff et al. (16). The better virological success reported in other studies is attributed to better adherence to treatment by older patients in those studies. Furthermore, they showed that virological success was higher in NNRTI-based regimens compared with that in protease inhibitor (PI)-based regimens in all groups (16). This trend might be explained by the reduction in pill count with NNRTI-based regimens and higher adherence to the treatment. In a study from Turkey, the authors reported good adherence to PI-based regimens with advanced stage of the disease and fewer adverse effects of PI-based regimens compared with NRTI-based regimens even with lower pill counts (19). In the subgroup analyses of the NRTI-based regimen group in our study, it is notable that patients were not in advanced CDC stages of the disease and had a higher baseline CD4+ cell count. However, treatment regimens were not associated with adherence to treatment. Prospective studies are needed to assess the association of adherence to different treatment regimens with the stage of the disease, age, educational status, and marital status in Turkey.

The presence of major ART gene mutations was not associated with VF or IF in our study. The incidence of gene mutations was lower than that in other studies from our country (24). We think VF and IF should be assessed in cohorts with a high incidence of ART gene mutations.

A decrease in the VL and an increase in the CD4+ count are often anticipated with the commencing of ART, but this may not happen in every case. Of all the patients in our study, 66.1% were complete responders, 5.4% were non-responders, 16.1% were virological-only responders, and 12.5% were immunological-only responders. The ratio of complete responders was significantly higher in the treatment-naive group, consistent with the literature (14, 25). In industrialized countries, discordant responses have been reported to occur in 20–30% of patients 6 months to 2 years after starting therapy (26). There are limited data on discordant responses in patients who are treated in developing countries. Risk factors for an immunological-only response include younger age, a lower baseline CD4 count, higher baseline VL, poor adherence to therapy, and antiretroviral drug resistance. A virological-only response is associated with increased age, low baseline CD4 count, and low VL (26–28). Nicastri et al. reported that the median baseline CD4+ cell count was higher and VL was lower in virological-only responders, whereas the median baseline CD4+ cell count was lower and VL was higher in immunological-only responders in their multicenter study (29). The VL of virological-only responders was lower in our study. Contrary to expectations, the probability of detectable viremia has been found to be higher with PI/r-based ART regimens than with NNRTI-based regimens in cohort studies and clinical trials (30, 31). There have been studies with conflicting results. Treatment success with PI-based regimens was reported to be higher than that with NNRT-based regimens because the HIV replicative capacity is higher in patients on NNRTI-based regimens than in patients receiving PI-based regimens, perhaps reflecting different barriers to the selection of resistant virus (14). In our study, the ART regimen was not found to be associated with the 24th week virological success in treatment-naive and treatment-experienced patients, but immunological success was higher with NNRTI-based regimens. There are some limitations of this study. The small size of the patient group, especially the small proportion of treatment-experienced patients, was the major limitation. We did not assess the factors involved in non-adherence to treatment. Adherence to treatment was based on self-reports rather than objective criteria. Furthermore, other factors that might influence VF and IF could not be investigated because of the lack of short-term follow up data.

Baseline VL was found to be the most predictive parameter to estimate the 24th week virological success, and 24th week VF was 3.2 times more likely to occur in individuals with a VL > 100,000 copies/ml. VF is an important prognostic parameter that can be used to predict CD4+ cell depletion, AIDS-related events, and increased mortality. In conclusion, our study is a valuable addition to the literature because it is the first study to assess treatment success using virological and immunological criteria in treatment-naive and treatment-experienced patients in Turkey.

**Conflict of interest** None to declare.

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