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# Brief communication: comparison of changes in metabolic parameters following antiretrovial therapy with treatment regimens containing tenofovir alafenamide and tenofovir disoproxil fumarate

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**Abstract**

Concerns of increased metabolic dysfunction have been heightened for HIV patients on long-term antiretroviral therapy (ART). Among first-line ART agents, Tenofovir alafenamide (TAF) may entail a marked increase in weight compared to Tenofovir disoproxil fumarate (TDF). We retrospectively evaluated changes in weight and glucose regulation among 153 treament-naïve patients. Weight-gain was more pronounced after one year of treatment with TAF versus TDF (3.5 kg versus −1 kg, *P*-value < 0.001). However, weight-gain was attenuated with longer follow-up, and no increase in glucose dysregulation was noted for TAF treatment. Attribution of increased metabolic risk to treatment with TAF remains questionable.

**Keywords** HIV, ART, Tenofovir, Weight, Glucose regulation, Metabolic syndrome

## Background

Increases in weight and body mass index (BMI) after initiation of antiretroviral therapy (ART) have been associated with recovery– an observation categorized as part of a "return to health" phenomenon [1, 2]. However, changes in patient weight are not limited to positive effects of ART on HIV/AIDS and its complications, as a growing rate of obesity has also been reported in people living with HIV [2]. Considering increases in early treatment and the prolonged course of treatment in HIV/AIDS, side effects related to development of metabolic syndrome and subsequent cardiovascular risks are of growing concern [3].

Current recommendations for first-line ART in treatment-naïve patients are the combination of an integrase strand transfer inhibitor (InSTI) with two nucleoside or nucleotide reverse transcriptase inhibitors– Tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) along with emtricitabine or lamivudine [4]. While TAF and TDF have been proposed to be of equal efficacy in HIV RNA suppression [5], TAF has been suggested to

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entail a smaller risk of adverse effects on renal function and bone mineral density [6].

Alternatively, recent studies have suggested treatment with TAF to be associated with accentuated weight-gain compared to TDF [7, 8]. Furthermore, improvements in lipid profile and decrease in weight have been documented following a switch from TAF to TDF [9]. This may be due to an independent favorable effect of TDF on weight loss (as seen in HIV-negative populations) [10]. While, the ultimate effect of these changes on patients' cardiovascular risk remains contentious [11, 12], growing evidence for metabolic side-effects of TAF is complicating the choice of ART regimen in treatment-naïve HIV patients– particularly those at risk for metabolic syndrome.

## Methods

The current is a report from a cross-sectional study of data from outpatient visits to an HIV clinic from Tehran, Iran (March 2019 to March 2023). The study center is a publicly-funded referral center providing both inpatient care to complex cases of HIV/AIDS from across the country. The center also provides outpatient follow-up for these patients and others referred by primary healthcare providers. Patients, although unexamined in this report, are usually of low socioeconomic means.

Patient data was retrieved from the hospital information system. Data from adult (age > 18 years old) treatment-naïve HIV patients initiated on ART regimens including TAF or TDF along with their six-months and one-year follow-ups was included in the report. Glucose dysregulation was defined as a fasting blood glucose > 125 mg/dL or HbA1c > 6.5%. Patients diagnosed with opportunistic infections, malignancy, or a history of corticosteroid use were excluded from this study.

Chi-square and T-tests were used for association between pairs of data. Bivariate analysis was conducted to identify variables likely (*P*-value < 0.1) associated with changes in BMI > 1 kg/m$^2$ in one-year follow-up. Identified variables were included in a multivariate model.

### Findings

153 patients were included in this report: 67 received TAF while 86 had received TDF. Patients were aged 46 ± 13 years old with the TAF group being significantly younger (44 ± 12 years old versus 50 ± 13 years old, *P*-value < 0.001). A quarter of patients were female (*P*-value = 0.17). The most common ART regimens including TAF were in combination with Dolutegravir (78.2%), Lamivudine (55.1%) or Emtricitabine (43.3%), while the most commonly used combinations for TDF included Emtricitabine (70.9%) plus Efavirenz (65.1%) or Dulotegravir (22.1%).

**Table 1** Changes in body mass index and CD4 counts after initiation of antiretroviral therapy

| BMI | TAF group (IQR) | TDF group (IQR) | *P*-value |
|---|---|---|---|
| Baseline | 24.1 (21.7–27.1) | 23.2 (20.3–26.2) | |
| Six-month follow-up | 24.6 (23.1–28.0) | 23.8 (20.7–26.9) | 0.02 |
| One-year follow up | 25.5 (23.6–28.1) | 23.5 (20.7–27.8) | 0.002 |
| **CD4 counts** | | | |
| Baseline | 339 (125–530) | 356 (139–482) | |
| Six-month follow-up | 367 (174–561) | 388 (225–600) | < 0.001 |
| One-year follow up | 368 (225–608) | 416 (234–579) | < 0.001 |

Baseline CD4 cell counts (*P*-value = 0.88) and hemoglobin levels (*P*-value = 0.90) showed no statistical difference between the groups. 19% of patients presented with anemia (*P*-value = 0.27). Baseline metabolic parameters were also similar between groups. The average weight was 68.7 ± 14 kg (TAF: 70.7 ± 13.7 kg versus TDF: 67.1 ± 14.1 kg, *P*-value = 0.20), and eleven patients had a BMI < 18.5 kg/m$^2$ (four treated with TAF and seven with TDF). 19% of patients had glucose dysregulation at baseline (TAF: 25.4% versus TDF: 14.0%, *P*-value = 0.07).

Differences in CD4 cell counts, between TAF and TDF groups, were not found to be significant in six-month (*P*-value = 0.19) and one-year follow-ups (*P*-value = 0.77). Both groups manifested a significant increase in CD4 cell counts at follow-ups (Table 1).

Significant weight gain was observed in patients treated with TAF, as opposed to those treated with TDF in one-year follow-up (P-value < 0.001). The TAF group showed significant weight gain at both six-month (2.5 kg, *P*-value = 0.001) and one-year (3.5 kg, *P*-value < 0.001) follow-up. Patients in the TDF manifested weight-gain after six months (1.3 kg, *P*-value = 0.03), followed by a return to their initial weight in one year (-1 kg, P-value = 0.30). Table 1 shows changes in patients' BMI in follow-up. Prevalence of glucose dysregulation showed no significant difference between groups in six-month (*P*-value = 0.16) and one-year (*P*-value = 0.60) follow-ups.

Bivariate analysis found CD4 counts < 200 (*P*-value = 0.002), anemia (P-value = 0.004), treatment group (*P*-value < 0.001), and treatment with Dolutegravir (*P*-value < 0.001) and Efavirenz (*P*-value < 0.001) to be likely predictors of increased BMI in one-year follow-up. Table 2 presents results from a multivariate

**Table 2** Multivariate analysis of factors likely associated with increased BMI after initiation of antiretroviral therapy

| Factor | Adjusted Odds Ratio | CI 95% for OR | *P*-value |
|---|---|---|---|
| TAF or TDF | 1.55 | 0.58–4.19 | 0.39 |
| Dolutegravir | 4.12 | 0.70-24.67 | 0.12 |
| Efavirenz | 1.22 | 0.22–6.88 | 0.82 |
| CD4 < 200 | 3.17 | 1.37–7.34 | 0.007 |
| Anemia | 3.19 | 1.45–7.02 | 0.01 |

analysis including factors found likely to be associated with increased BMI.

## Discussion

Consistent with previous studies we found the use of InSTIs, Dulotegravir in particulars (OR = 5.13, CI 95% 2.47–10.62, *P*-value < 0.001), as opposed to those Efavirenz (OR = 0.27, CI 95% 0.13–0.55, *P*-value < 0.001) to be associated with weight gain [13]. This is proposed to follow increased adipogenesis and lipid accumulation in adipocytes caused by InSTIs [14]. We also found the use of TAF to be associated with significant increases in weight (*P*-value < 0.001) and BMI (*P*-value = 0.002) compared to TDF in one-year follow-up. Weight gain, as expected, was associated with baseline severity of disease (CD4 counts < 200 and anemia) [15]. These findings suggest a "return to health" phenomenon, attenuated by TDF effects favoring weight loss [10].

Supporting TAF's possible role in weight-gain, increases in weight gain have been observed comparing TAF with non-Tenofovir regimens [1, 8]. Increases in weight following a switch from TDF to TAF have also been documented [7, 16]. However, the peak in weight gain was found not to be sustained beyond 9–12 months [16, 17]. Our findings show a concordant slowing of weight gain on TAF: 2.5 kg versus 1.0 kg in the first and second six months. Furthermore, a study from a population on long-term ART found no significant changes in patients' weight after switch from TDF to TAF [18]. In other studies, discontinuation of TAF in favor of non-Tenofovir regimens has showed no reduction in patients' weight [9]. These findings suggest TAF's long-term weight-neutrality [19, 20].

The current report found no significant difference between TAF and TDF groups regarding the prevalence of glucose dysregulation (*P*-value = 0.60). Several studies have also found no negative effect on glucose regulation and cardiovascular risk when comparing TAF to TDF [21, 18]. This is despite consistent findings of TAF's negative impact on patients' lipid profiles [7, 18]. Furthermore, both treatment groups showed a steady increase in CD4 cell counts (*P*-value < 0.001), with no significant difference in CD4 counts between TAF and TDF groups in the first year of treatment (*P*-value = 0.77)– adding to previous literature suggesting similar antiretroviral efficacy for TAF and TDF [14]. With this and considering previous evidence of TDF's negative long-term impact on renal function and bone mineral density [6], the choice of Tenofovir prodrug in ART regimens remains dependent on further long-term evaluations of metabolic effects associated with the use TAF.

## Limitations

The foremost limitation of the current report is a small sample size and subsequent lack of power for analysis. The retrospective observational design further precludes us from minimizing the possible effects of heterogeneity in ART regimens used. There was also a lack of data on several relevant factors in analyzing the full metabolic effects of drugs examined, mainly, patient lipid profiles and cardiovascular risk. Furthermore, the short follow-up period prevents complete visualization of trends in patients' weight following initiation of ART.

### Abbreviations

| | |
|---|---|
| ART | antiretrovial therapy |
| InSTI | Integrase strand transfer inhibitor |
| TAF | Tenofovir Alafenamide |
| TDF | Tenofovir Disoproxil Fumarate |

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### Author contributions

LA and SG conceptualized and supervised the study. SS devised the study methodology. HM collected the relevant data. HM and KS carried out the formal analyses, and drafted the final manuscript. HE, SD, and MH provided the resources for the study. SG edited the final manuscript. All authors read and approved the final manuscript.

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No funding was received for the current study.

### Data availability

Dataset(s) supporting the conclusions of this article are available upon reasonable request from the corresponding author (subject to institutional approval by the Research Ethics Committee of Tehran University of Medical Sciences).

## Declarations

### Ethics approval and consent to participate

The current study was conducted in accordance with the Declaration of Helsinki. The Research Ethics Committee of Tehran University of Medical Sciences has approved the following study as part of a thesis (approval ID: IR.TUMS.IKHC.REC.1402.270). Informed consent for possible future use of deidentified information in research had been obtained from all patients upon presentation– per institutional protocols. All patient data was anonymized and no identifying data were collected. The retrospective nature of the study eliminated any possible impact on patient care.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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