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# Non-inferiority of Generic Tenofovir Disoproxil Fumarate/ Emtricitabine, Hivent® to Brand Name, Truvada® in HIV-Infected Patients

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***Abstract***

**Objective:** Antiretroviral agents provided a significant improvement in HIV-related mortality. Generic drugs decrease the cost and provide easier access to treatment. However, there are concerns about efficacy and safety. We assessed non-inferiority of generic tenofovir disoproxil fumarate/ emtricitabine, Hivent® to brand name drug, Truvada® in a retrospective cohort.

**Methods:** Nine centers from Turkey were enrolled and the study included 457 patients followed up between May 2015 and April 2017 with Truvada® (n = 227) and Hivent® (n = 230) in combination with other antiretrovirals. Baseline characteristics were comparable in both groups. Demographic characteristics and laboratory values at baseline and during treatment were recorded. The primary endpoint was virologic response after 12 months of therapy, as determined by Snapshot algorithm from Food and Drug Administration (FDA). The sample size calculation was based on the primary endpoint. Non-inferiority margin was taken as 10%.

**Results:** After 12 months of therapy, both drugs provided a comparable decline in HIV-RNA: The values at baseline, 1st, 3rd, 6th, 9th, and 12th month by Truvada® were 6.32, 3.62, 2.52, 3.53, 3.01, and 1.71 $\log_{10}$ copies/mL, respectively and values by Hivent® were 5.93, 3.89, 2.18, 1.72, 3.63, and 1.54 $\log_{10}$ copies/mL, respectively ($P$ = .33). Both drugs provided a comparable significant increase in CD4+ cell count: values By Truvada® were 338, 412, 472, 497, 511, and 580 cells/mL, respectively and values by Hivent® were 337, 503, 531, 553, 644, and 660 cells/mL ($P$ = .13). The rate and severity of side effects were similar and the changes in biochemical parameters were not different.

**Conclusion:** This retrospective cohort study showed that Hivent® has comparable efficacy and side effect profile and non-inferior to Truvada®.

**Keywords:** Non-Inferiority, Generic TDF/FTC, Hivent®

## Introduction

Human Immundeficiency Virus (HIV) infection is a global health-care problem. Antiretroviral treatment (ART) has provided a significant improvement in disease-related mortality and is an effective way of HIV prevention. Since a combination treatment is needed for long-term use, access to the drug and the cost are main challenges. Most patients with HIV/AIDS live in countries with severe limitations to the treatment.[1] In developing countries, the prices of brand name ARTs are too high. HIV-infected patients on ART continue to increase considering their associated increase

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in life expectancy and addition of newly infected patients. Since a "cure" is not possible yet, HIV-infected patients need to take ARTs lifelong. Antiretroviral treatment accounts for 60% of the projected lifetime medical cost in the United States.[2]

Generic drugs decrease the cost and provide easier access to treatment. The increased use of generic ARTs has provided significant growth in the treatment coverage of HIV-infected patients in the last decade.[3] The antiretroviral marketplace has expanded from 300 000 patients in low- and middle-income countries in 2002 to almost 10 million patients in 2013.[4] A study in the United States in 2013 estimated nearly 1 billion U.S. dollars in the first year if all patients given brand name efavirenz were switched to generic efavirenz.[5]

However, there are concerns about adherence to, efficacy, and safety of generics. Instead of brand name co-formulated one pill, generic multiple pills may adversely affect the adherence and viral suppression. Brand name drugs are developed through in vitro and in vivo studies and receive the regulatory approval. Some generic drugs have bioequivalence studies and are qualified. However because of the need for ART in resource-limited countries, the supply of unqualified ARTs is a common practice and bioequivalence in generics may not be guaranteed.[6]

Although the prevalence of HIV infection is low, it continues to increase in Turkey.[7] Turkish Ministry of Health reported that there were 27 767 cases of HIV infection in 2020.[8] Tenofovir disoproxil fumarate is the backbone of ARTs. Tenofovir disoproxil fumarate/emtricitabine-based regimens are commonly used and brand name and generic drugs are available in the market.

We assessed non-inferiority of generic tenofovir disoproxil fumarate/emtricitabine, Hivent® to brand name Truvada® in HIV-infected patients in a retrospective cohort setting.

## Patients and Methods

Nine centers from Turkey were included in the study. The patients with HIV infection older than 18 years who were treated with a regimen including Truvada® or Hivent® in combination with other ARTs (all brand names) between May 2015 and April 2017 were enrolled. Study centers included every patient given at least one dose of Truvada® or Hivent® in combination with other ARTs sequentially. The study included 457 patients given Truvada® (n = 227) or Hivent® (n = 230) and in combination with other ARTs. The characteristics of age, gender, CD4+ cell count, HIV-RNA level, and the levels of total cholesterol, Low density lipoprotein (LDL) cholesterol, High density lipoprotein (HDL) cholesterol, triglycerides, Alanine aminotransferase (ALT), and creatinine at baseline and during treatment were recorded.

The study was approved by Ethics Committee of İstanbul University-Cerrahpaşa (Date: November 28, 2017, Number: 83045809-604.01.02). Due to the retrospective design of the study, informed consent was not taken.

Patients were followed up monthly after treatment initiation. At each follow-up visit, patients were assessed for adherence, complications, and acute toxicity. Adherence was determined by self-report.

CD4 counts and HIV-RNA studies were determined at baseline and months 1, 3, 6, 9, and 12. Urinalysis and measurement of serum creatinine levels were done at baseline and months 3, 6, and 12 and additional studies were done as clinically indicated. Creatinine clearance was calculated using the Cockroft–Gault formula. Virologic failure was defined as inability to achieve or maintain an undetectable HIV-RNA (<200 copies/mL) at or after 6 months of initiation of ART or rebound of viral loads to above detectable limits (excluding blips) after suppression.[9] Immunologic failure was defined as a decline >50% from on-treatment peak CD4 values or a return to, or a fall below, baseline levels after 6 months of treatment and persistent CD4 cells below 100/mm$^3$ after 6 months of treatment.[10] Clinical failure was defined as new or recurrent World Health Organization (WHO) stage 4 HIV/AIDS 6 months after initiation of the regimen. Virologic and immunologic failures were reconfirmed 2 to 4 weeks later by repeated determinations of viral load and CD4 counts, respectively.

Toxicity was graded according to the system described in the WHO ART scale-up guidelines (modified from the grading system of Division of AIDS, National Institute of Allergic and Infectious diseases, USA).[11]

### Primary Endpoint

The primary endpoint was proportion of patients with viral load lower than 50 copies/ mL at month 12 among those individuals who received any dose of brand name or generic medications. Subjects' responses (<50 copies/mL) were calculated according to the U.S. Food and Drug Administration's Snapshot algorithm.[12]

Virologic success (<50 copies/mL) or virologic failure is typically determined by the last available HIV-RNA measurement within the visit window of interest (12 months ± 2 months) while the subject is on treatment.

When no HIV-1 RNA data are available within window of interest, the subject is considered a nonresponder. Depending on the reason for the lack of data, the subject will be classified as a virologic failure or reported as "no virologic data at week 48," in the latter case, the algorithm further classifies the nature of the missing data. Subjects withdrawn due to adverse event or for another reason yet were suppressed at the time, will be counted as "no virologic data at week 48." If subjects withdraw for reasons other than adverse events and were not suppressed at the time, they would be classified a virologic failure. Since changes in antiretroviral therapy are not permitted in the protocol, all such subjects who change antiretroviral therapy are considered virologic failure.

### Secondary Endpoints

Drop in viral load compared to that in baseline, CD4 count in every visit, AIDS-defining disease or death, and duration to AIDS-defining disease or death were the secondary endpoints.

### Safety Endpoints

Any adverse event, any severe adverse event, and abnormalities in hematological and biochemical laboratory studies were considered as safety endpoints.

### Subgroup Analyses

All subgroup analyses were prespecified and unadjusted for multiplicity. For the statistical analysis of the primary endpoint, 4 subgroups were formed: baseline plasma HIV RNA (≤ vs. >100 000 copies/mL) and baseline CD4 cell count (≤ vs. >200 cells/mm$^3$). The Cochran Mantel Haenszel stratified analysis procedure was used to assess the assumption of a common difference in unadjusted proportions across strata.

### Statistical Analysis

*Sample Size Calculation*

The sample size calculation was based on the primary outcome (virologic response at treatment week 48). Significance (α value) was taken as 5% and the power of the study was taken as 90%. The success rate of tenofovir disoproxil fumarate/emtricitabine was taken as 85%.[13-16] Non-inferiority margin was taken as 10%.[17]

The calculation was based on the formula:

$$n = f(\alpha, \beta) \times [\pi_s \times (100 - \pi_s) + \pi_e \times (100 - \pi_e)]/(\pi_s - \pi_e - d)^2$$

**Table 1.** Baseline Characteristics of the Patients

| | Truvada® (n = 227) | Hivent® (n = 231) | *P** |
|---|---|---|---|
| Age (years) | 38.1 ± 11.7 | 38.0 ± 12.3 | >.05 |
| Gender (male) | 212 | 213 | >.05 |
| CD4 count (/mm$^3$) | 339 ± 230 | 338 ± 219 | >.05 |
| HIV-RNA (copies/mL) | 1 657 730 ± 14 400 549 | 853 869 ± 2 872 719 | >.05 |
| Creatinine (mg/dL) | 0.85 ± 0.15 | 0.86 ± 0.17 | >.05 |
| eGFR | 112.6 ± 25.5 | 109.9 ± 27.6 | >.05 |
| HBV-seropositive | 18/220 | 9/222 | >.05 (.07) |
| HCV-seropositive | 1/218 | 1/219 | >.05 |
| MSM | 81/178 | 63/180 | .04 |
| Dolutegravir | 110 | 143 | <.00001 |
| Raltegravir | 28 | 52 | |
| Lopinavir/Ritonavir | 46 | 28 | |
| Efavirenz | 28 | 5 | |
| Darunavir, Ritonavir | 15 | 3 | |
| ART(s) | | | |

eGFR, estimated glomerular filtration rate; MSM, men who have sex with men; ART, antiretroviral treatment.
*Student's *t*-test and chi-squared tests.

**Table 2.** Side Effects Reported by the Patients During the Treatment

| | Truvada® (n = 227) | Hivent® (n = 231) | *P** |
|---|---|---|---|
| Asthenia | 21 | 22 | >.05 |
| Pruritus | 14 | 15 | >.05 |
| Insomnia | 10 | 9 | >.05 |
| Headache | 9 | 8 | >.05 |
| Dizziness | 12 | 5 | >.05** |
| Nausea | 8 | 5 | >.05 |
| Nightmares | 9 | 3 | >.05*** |
| Depression | 2 | 2 | >.05 |
| Rash | 1 | 2 | >.05 |
| Diarrhea | 2 | 1 | >.05 |
| Memory problem | 1 | 0 | >.05 |

*Chi-squared or Fisher's exact test.
**$P$ = .077.
***$P$ = .074.

where $\pi_s$ and $\pi_e$ are the true percent "success" in the standard and experimental treatment group respectively, and $f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$, $\Phi^{-1}$ is the cumulative distribution function of a standardized normal deviate.[18,19] The patients required in each arm were calculated as 219 (a total of 438).

Collected data were analyzed by the Statistical Package for the Social Sciences software version 17.0. Categorical and continuous variables were compared by chi-square and Student's *t*-test respectively. CD4 count, HIV-RNA level, creatinine level, and estimated glomerular filtration rate (eGFR) changes on treatment were compared by analysis of variance by repeated measures. $P < .05$ was accepted as significant.

## Results

### Patients and Follow-Up

Five hundred patients were assessed for eligibility and 461 underwent randomization to either drug; 230 and 231 patients were assigned to Truvada® and Hivent® in combination with other ARTs, respectively. In Truvada® group, 227 patients received the assigned drug while 230 were in Hivent® group. Baseline characteristics of the patients were given in Table 1.

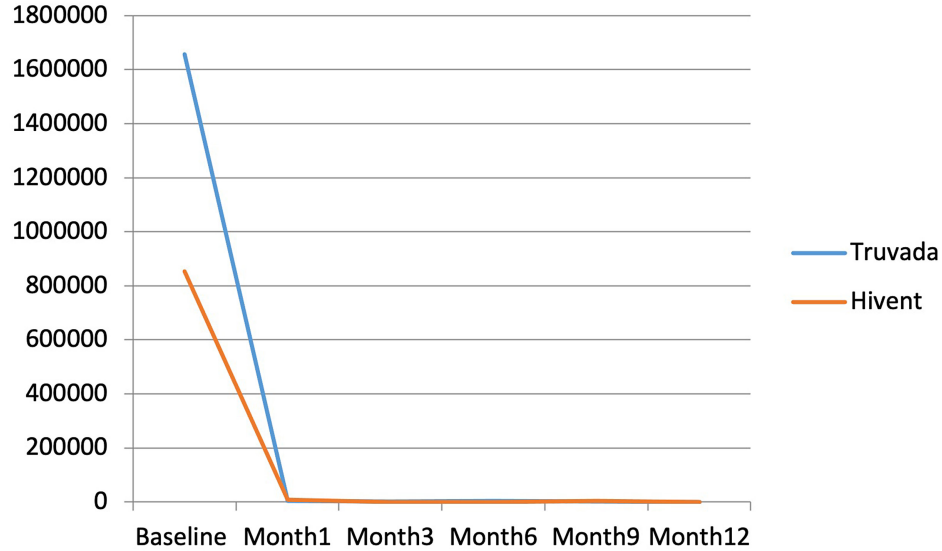


**Figure 1.** HIV-RNA level (copies/mL) decline in the treatment groups.

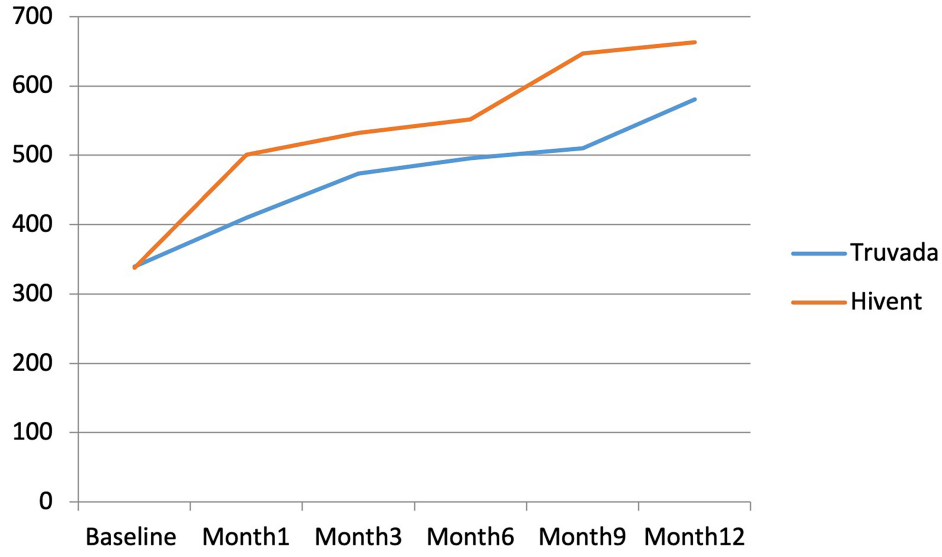


**Figure 2.** CD4 cell (per $mm^3$) count increase in the treatment groups.

Among patients receiving Truvada®, 15 patients were withdrawn from the study (adverse events, n = 9; lack of efficacy, n = 3; lost to follow-up, n = 3), there were no virologic data for 22 patients, and 18 patients had viral failure. Virologic success was determined as 165/227, 72.7%. Among patients receiving Hivent®, 6 patients were withdrawn from the study (adverse events, n = 1; lack of efficacy, n = 1; lost to follow-up, n = 4), there were no virologic data for 51 patients, and 14 patients had viral failure. Virologic success was determined as 164/230, 71.3% ($P > .05$). The virological success was comparable when tested according to the strata of CD4 (>200/$mm^3$ vs. ≤200/$mm^3$) and HIV RNA (>5 $\log_{10}$ copies/mL vs. HIV-RNA ≤ 5 $\log_{10}$ copies/mL). Viral failure rates in the groups were comparable when tested for the combination drugs (integrase inhibitors, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors, $P > .05$).

### Treatment Effectiveness

After 12 months of therapy, both drugs provided a significant but comparable decline in HIV-RNA: The values at baseline, 1st, 3rd, 6th, 9th and 12th months by Truvada® were 6.32, 3.62, 2.52, 3.53, 3.01, and 1.71 $\log_{10}$ copies/mL, respectively and values by Hivent® were 5.93, 3.89, 2.18, 1.72, 3.63, and 1.54 $\log_{10}$ copies/mL, respectively ($P = .33$) (Table 2 and Figure 1).

Both drugs provided a significant increase in CD4+ cell count in a comparable trend: Values by Truvada® were 338, 412, 472, 497, 511, and 580 cells/mL, respectively and values by Hivent® were 337, 503, 531, 553, 644, and 660 cells/mL ($P = .13$) (Figure 2).

### Safety

Drugs were generally well tolerated in both treatment groups. Asthenia, pruritus, insomnia, headache, dizziness, and nausea were the most frequent side effects (Table 3). Nightmares were more frequent and dizziness tended to be more frequent in Truvada® group (11/227 vs. 3/230, $P = .03$ and 13/227 vs. 5/230, .057, respectively).

The rate and severity of side effects were similar in both arms and the changes in biochemical parameters were not different.

Withdrawal from the study due to side effects was higher in Truvada® group than Hivent® (9 vs. 1, $P < .01$). These adverse events in Truvada® group were asthenia and dizziness (2), nightmares and dizziness (2), nightmares (1), dizziness and insomnia (1), dizziness (1), memory problems (1), and headache and diarrhea (1). A patient given Hivent® and raltegravir observed a creatinine level increase (1.46 mg/dL), proteinuria, and the therapy was discontinued.

**Table 3.** CD4, HIV-RNA, Creatinine Levels, and eGFR in Treatment Groups

| | | Truvada® | Hivent® | *P** |
|---|---|---|---|---|
| CD4 count (cells/$mm^3$) | Baseline | 339 | 338 | >.05 |
| | Month 1 | 410 | 501 | |
| | Month 3 | 474 | 532 | |
| | Month 6 | 496 | 552 | |
| | Month 9 | 510 | 647 | |
| | Month 12 | 581 | 663 | |
| HIV-RNA (copies/mL) | Baseline | 1 657 730 | 853 869 | >.05 |
| | Month 1 | 4436 | 7729 | |
| | Month 3 | 334 | 152 | |
| | Month 6 | 3384 | 52 | |
| | Month 9 | 1033 | 4300 | |
| | Month 12 | 50 | 35 | |
| Creatinine (mg/dL) | Baseline | 0.85 | 0.86 | >.05 |
| | Month 3 | 0.95 | 0.97 | |
| | Month 6 | 0.96 | 0.96 | |
| | Month 12 | 0.93 | 0.97 | |
| eGFR (mL/min) | Baseline | 112.6 | 109.9 | >.05 |
| | Month 3 | 99.7 | 97 | |
| | Month 6 | 99.0 | 97.4 | |
| | Month 12 | 102.2 | 98.6 | |

* Analysis of variance by repeated measures.

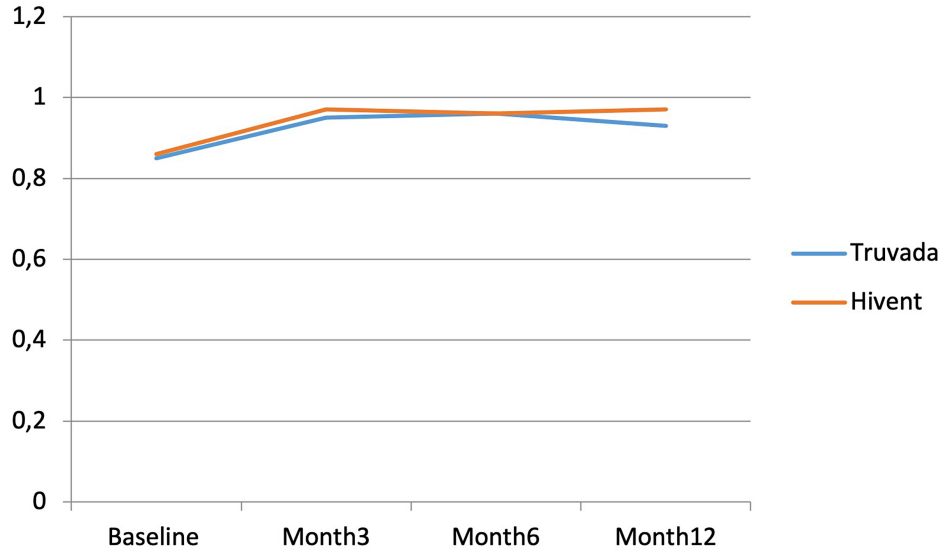


**Figure 3.** Creatinine levels (mg/dL) in the treatment groups.

Virologic failure was observed in 3 patients under Truvada® combined with lopinavir/ritonavir.

Creatinine levels tended to increase and eGFR decreased at month 3, but then remained stable in other visits (Table 2 and Figures 3 and 4). No side effects about bone were reported in the groups.

## Discussion

This retrospective cohort study showed that a generic tenofovir disoproxil fumarate/emtricitabine drug, Hivent® has comparable efficacy and side effect profile with brand name, Truvada® and non-inferior to it in HIV-infected patients. The findings of this study can assist clinicians in HIV infection management in resource-limited settings. HIV treatment is indicated for every HIV-infected patient and ART is given lifelong. It requires a combination treatment and the cost of drugs makes up the majority of HIV management budgets. In settings of limited resources, this represents a big challenge for the treatment of infected patients. Generic drugs, in many therapeutic areas, provide relief of budgetary limitations. Generic antiretroviral drugs are presented to the market at a cost as low as 97% less than the brand name.[20]

Savings from generic ARV drugs can be related to high rate of low-price generic utilization and also to brand price reduction. In a recent study, it has been shown that between 2006 and 2015, median ARV drug utilization increased from 234 defined daily doses per 1000 inhabitants per year to 385 in 14 European countries.[21] The median cost increased from ğ3751/1000 inhabitants/year to ğ9158. Between 2013 and 2015, savings of ğ0.9, ğ1.6, and ğ33.7 million were respectively observed in Denmark, Czech Republic, and France by the use of generics. In Turkey, generic drugs are available in almost every therapeutic area. The social security system reimburses the drugs either the cheapest one or up to 10% more expensive than the cheapest one. For the more expensive ones, the patient should pay the difference enforcing practicing physicians to prescribe the cheapest drug, generally the generic one. For that reason, in the country, the entrance of generic drugs to the market led to a significant decline in the price of brand name drugs. The generic tenofovir disoproxil fumarate/

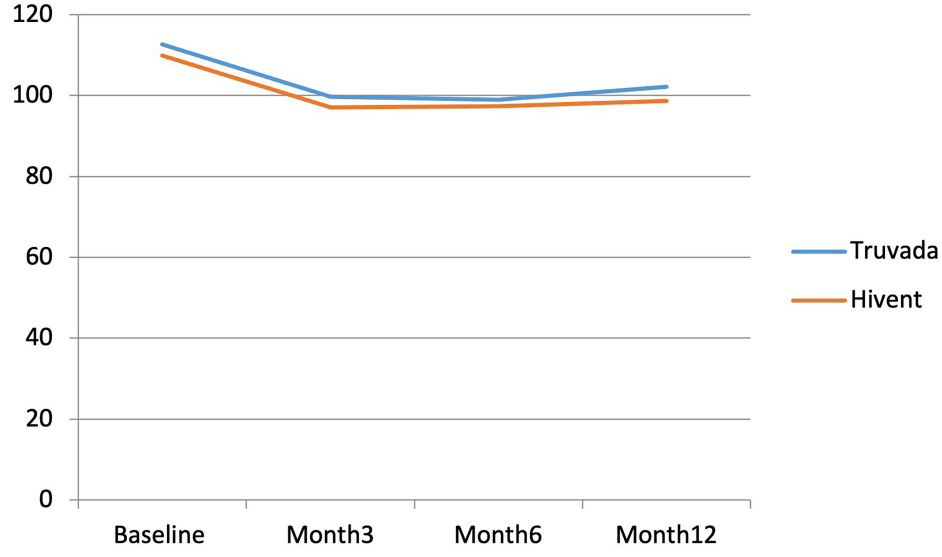


**Figure 4.** Erythrocyte glomerular filtration rate (mL/min) in the treatment groups.

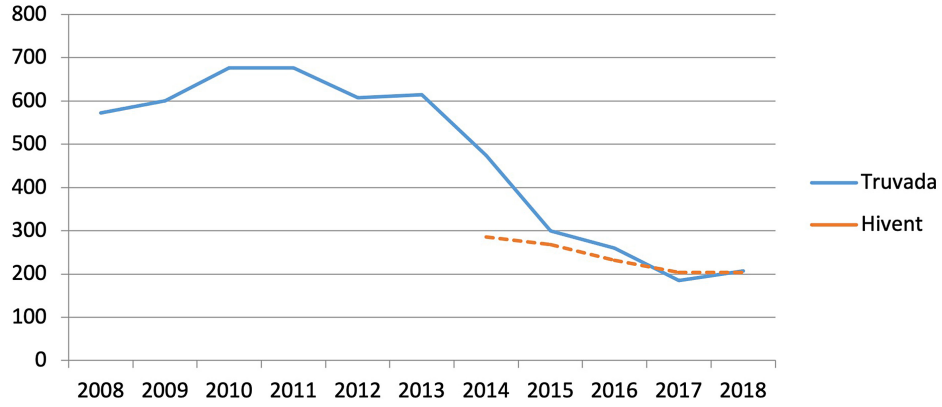


**Figure 5.** Costs of 1-month treatment by brand name (Truvada®) and generic (Hivent®) over the years (in US dollars) (22).

emtricitabine, Hivent® was eligible since 2014 in Turkey with a cost of nearly 200 US$, causing a drop of the cost of brand name tenofovir disoproxil fumarate /emtricitabine, Truvada® from 600 US$ to 200 US$ (Figure 5).[22]

Compared to the use of branded once-daily pill efavirenz-emtri citabine-tenofovir disoproxil fumarate, a once-daily, 3-pill generic alternative decreases cost but there are concerns about adherence and virologic suppression. Walensky et al., in their study assesed the clinical effect, costs, and cost-effectiveness of a 3-pill, generic-based regimen compared with a branded, co-formulated regimen and projected the potential national savings in the first year of a switch to generic-based ART. Compared to no ART, generic-based ART increased the quality of life. Compared with generic-based ART, branded ART increases lifetime costs and quality of life. The study showed that generic-based ART in the United States could yield substantial budgetary savings to HIV programs.[5]

Brand-name drugs are developed in a well-defined process. However for generic drugs, bioequivalence studies are not provided in many resource-limited countries and even counterfeit drugs are available in the market. The concerns about the efficacy and safety of generics can be cleared by antiretroviral drug concentrations and comparative studies. For a brand-name drug, there may be several generics and bioequivalence studies or comparative clinical studies with or without drug concentrations are not available in the majority.

In 2011, 2 batches of a combination drug of zidovudine, lamivudine, and nevirapine found to be molding, friable, and discolored in a Médecins Sans Frontiéres supported-HIV/AIDS treatment program in Nairobi, Kenya.[23] This has been a key event to defend against the entry of falsified medicines into the supply chain of Kenya. However, independent studies (not conducted or sponsored by the producer) show that the generics have no big problems. The majority of antiretroviral and opportunistic medications obtained from various sources, including South Africa, the United States, China, Ethiopia, Thailand, Laos, Mexico, Nigeria, and 5 Internet pharmacies were found to meet the predefined criteria.[24] Another study tested the antiretroviral drugs freely accessible in Cameroon and showed that they are of good quality.[25]

In Turkey, the drug companies supplying a generic provide a bioequivalence study. A clinical study was not performed and the current study represents the first clinical, non-inferiority of an anti-infective drug. Although HIV infection is not prevalent, it is gradually increasing in the country: the first case was described in 1985. In 2018, 2019, and 2020, 3953, 4037, and 1492 new cases were added and reached a cumulative number of 27 767 in 2020.[8] Antiretroviral treatments are reimbursed by the social security system. After the generic tenofovir disoproxil fumarate, Hivent® was presented to the market, the price of brand name tenofovir disoproxil fumarate decreased significantly.

The main limitation of the study is that it has a retrospective design. Since the patients were not randomized to brand name or generic blindly, the clinician may have been biased in choosing brand name or generic tenofovir disoproxil fumarate and also other ARTs used in combination. The ARTs used in combination are not used in similar rate. Truvada® was combined with integrase inhibitors less frequently and with protease inhibitors more frequently. This makes a challenge in analyzing and comparing the efficacy and safety of the brand name and generic tenofovir disoproxil fumarate. Dizziness and insomnia in our cohort, for example, tended to be more frequent in Truvada® group which may be attributed to more frequent use of efavirenz in this group. Another limitation is the lack of blood drug concentrations, which may potentially clear the debate whether generic drugs provide therapeutic concentrations.

In conclusion, the current study demonstrated that Hivent®, the generic of tenofovir disoproxil fumarate, is an affordable, safe, and effective alternative to the brand name drug, Truvada®. Considering that ART is recommended for life, the use of safe generic backbone drugs with similar efficacy provides a more cost-effective treatment option.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee of İstanbul University-Cerrahpaşa (Date: November 28, 2017, Number: 83045809-604.01.02).

**Informed Consent:** Due to the retrospective design of the study, informed consent was not taken.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – O.K., F.T.; Design – Ş.K., D.İ.; Supervision – B.K., Ö.A.A.; Material – B.B., F.G.; Data Collection and/or Processing – B.B., M.M.K.; Analysis and Interpretation – B.M., P.Ö.; Literature Review – S.G., N.Ö.; Writing – B.M., A.G.; Critical Review – O.K., F.T.

**Declaration of Interests:** The authors declare that they have no competing interest.

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