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ORIGINAL ARTICLE

Toxicity and clinical outcomes in patients with HIV on zidovudine and tenofovir based regimens: a retrospective cohort study

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Background: Adverse drug reactions are a major concern with zidovudine/stavudine treatment regimens. The less toxic tenofovir regimen is an alternative, but is seldom considered due to the higher costs. This study compared adverse drug reactions and other clinical outcomes resulting from the use of these two treatment regimens in India.

Methods: Baseline, clinical characteristics and follow-up outcomes were collected by chart reviews of HIV-positive adults and compared using univariate/multivariate analysis, with and without propensity score adjustments.

Results: Data were collected from 129 and 92 patients on zidovudine (with lamivudine and nevirapine) and tenofovir (with emtricitabine and efavirenz) regimens, respectively. Compared to patients receiving the zidovudine regimen, patients receiving the tenofovir regimen had fewer adverse drug reactions (47%, 61/129 vs 11%, 10/92; $p<0.01$), requiring fewer regimen changes (36%, 47/129 vs 3%, 3/92; p0.01). With the propensity score, the zidovudine regimen had 8 times more adverse drug reactions ($p<0.01$). Opportunistic infections were similar between regimens without propensity score, while the zidovudine regimen had 1.2 times ($p=0.63$) more opportunistic infections with propensity score. Patients on the tenofovir regimen gained more weight. Increase in CD4 levels and treatment adherence (>95%) was similar across regimens.

Conclusions: Patients on a tenofovir regimen have better clinical outcomes and improved general health than patients on the zidovudine regimen.

Keywords: Adverse drug reaction, Clinical outcome, HIV, Propensity score analysis, Tenofovir, Zidovudine

Introduction

In 2012, the adult HIV prevalence in India was 0.27% with approximately 2 million people infected with HIV.[1] Free antiretroviral therapy (ART) has been provided to eligible patients through the government sponsored ART centers since 2005 and by December 2013 approximately one-third of patients living with HIV were covered under the program.[2] The combination ART commonly used to initiate therapy is composed of a non-nucleoside reverse transcriptase inhibitor with a two nucleoside reverse transcriptase inhibitor backbone. At the initiation of combination ART zidovudine or stavudine were the first-line nucleoside reverse transcriptase inhibitor choices for inclusion in the backbone.[3] However, adverse drug reactions (ADRs) are a major concern in patients receiving these drug therapies and approximately one-quarter of patients on treatment containing these regimens experience ADRs.[4–7] These findings led WHO to recommend tenofovir-containing regimens as the preferred first-line treatment of choice.[8] In resource-limited settings, however, stavudine/zidovudine regimens are often still used due to the higher costs of the tenofovir-containing regimens.

Studies in resource-sufficient settings have demonstrated greater efficacy with tenofovir-containing regimens compared to non-tenofovir-containing regimens.[9–12] There are very few

studies from resource-limited settings that have compared tenofovir-containing regimens with other ART treatment modalities. A South African study has demonstrated that tenofovir-containing regimens are associated with fewer toxicity related switches and lower proportions of loss-from-care compared to zidovudine-containing regimens.[13] While a Cochrane review comparing zidovudine- and tenofovir-containing regimens showed that ADR and virologic responses were similar between these regimens, tenofovir-containing regimens were superior to zidovudine-containing regimen in terms of immunological response and adherence.[14] Another study from Lesotho demonstrated that toxicity-related treatment change was two times greater among patients on zidovudine-containing regimen than among patients on tenofovir-containing regimen.[15] A multicenter randomized trial showed that a tenofovir-containing regimen had higher efficacy and better safety outcomes than zidovudine-containing regimen.[16]

In India, efforts are being made to shift to a tenofovir-containing regimen as the preferred first line therapy for patients with HIV, under the free government ART program. To better understand the impact of a tenofovir-containing regimen in India, we examined differences in several clinical outcomes including ADRs, opportunistic infections, CD4 count, BMI, weight and morbidity in patients receiving either the zidovudine- or tenofovir-containing regimens at a single private hospital clinic.

Materials and methods

Study population

The study population consisted of all adult ART naïve patients with a confirmed diagnosis of HIV infection, with a CD4 value <200 cells/μl, who attended and initiated treatment at the Infectious Disease clinic at the Christian Medical College, Vellore, India, between January 2001 and June 2008. The free roll-out of government sponsored ART was initiated at this center in August 2008. Until that time, patients were required to buy their antiretroviral regimens; treatment was dependent on their ability to afford therapy. Approval for this study was obtained from the institutional review board at the Christian Medical College. As this study is a retrospective data analysis of data collected from medical records, patient consent was not required.

ART regimens

The zidovudine-containing regimen was a single combination pill including 150 mg zidovudine, 200 mg lamivudine and 300 mg nevirapine given as two daily doses. The tenofovir-containing regimen was a single combination pill including 300 mg tenofovir, 200 mg emtricitabine and 600 mg efavirenz given as a single daily dose.

Data collection

Data were extracted from electronic- and paper-based clinical records by a trained physician for a period of three years from the time of initiation of treatment (baseline). A second reviewer independently extracted data from a random 10% (20/221) sample of these records for quality assurance. Discrepancies were rectified by mutual consensus. Baseline demographic characteristics included patient's age at the time of clinic enrollment, gender, religion and occupation. Baseline clinical details including baseline health conditions, weight, BMI, CD4 count, clinical stage, time to treatment from the date of diagnosis of HIV, chronic health conditions, as well as comorbidities and opportunistic infections were documented.

Outcome measures included drug specific ADRs, treatment change due to ADRs, opportunistic infections, treatment failure and requirement for inpatient admissions, change in CD4 counts, change in weight and change in BMI. All the outcomes were documented based on the written record of the treating physician. Since the toxicity with each of the ART regimens being compared was specific to the drugs in the regimens, we included all ADRs, even if they occurred immediately after starting the treatment. Opportunistic infections that occurred immediately after the initiation of treatment may have been present sub-clinically before ART was begun, therefore, we only included in the analysis those opportunistic infections that developed more than three months after the initiation of ART. Treatment failure was diagnosed based on the immunologic parameters (steady decline in CD4: reduction in CD4 values compared to previous measurements, CD4 below the pretreatment value, CD4 less than 50% of the maximum documented value). Adherence was measured using pill counts and patient interviews. Other clinical conditions diagnosed during the follow-up period were also documented.

Statistical analysis

Bivariate comparisons between zidovudine and tenofovir regimens were performed for all baseline characteristics. Two sample t tests were used for continuous variables with normal distributions, non-parametric tests for continuous variables with non-normal distributions, and the χ^2 test for categorical variables. The proportion of patients with treatment-related ADRs, opportunistic infections and treatment failure in the zidovudine- and tenofovir-containing regimens were compared. Change in CD4 count and BMI from treatment initiation to the end of follow-up were compared between the two regimens.

Since our study was observational and ability to pay may have been associated with both selection of treatment regimen and other characteristics potentially influencing health, we used propensity score (PS) analysis to mitigate the potential confounding. The initial PS model included all covariates measured before treatment and related to treatment and outcomes. A logistic regression model was used to estimate the PS.

To estimate the average treatment effect in the population we used the Inverse Probability of Treatment Weights conditioning method. This approach weights individuals by the inverse of their probability of receiving the treatment that the patient may have actually received. Individuals in one regimen receive an Inverse Probability of Treatment Weights equal to $1/p_i$ and in other regimen receive a weight equal to $1/(1-p_i)$. The weights are then used in the weighted least squares regression model along with other predictor covariates.[17,18] Univariate and multivariate comparison of the two regimens were performed using general linear model and logistic regression procedures for continuous and categorical variables respectively. The treatment effect was estimated as adjusted differences in the mean for continuous variables and as adjusted odds ratios for categorical variables. Type III sum-of-squares analysis was performed to ensure

that outcome differences are tested after adjusting for PS. We performed a multivariate analysis for important outcomes including ADR, opportunistic infections, patient weight and CD4 count at end of follow-up. The purpose of the analysis was to assess the influence of various factors on the outcomes. All covariates, including baseline patient weight and CD4 count, age, occupation, gender, clinical stage at baseline and time to treatment were considered clinically significant and were included in the regression analysis. Since we hypothesized that patients with a higher level of employment will tend to buy more expensive drugs, we also included an interaction term between treatment group and patient occupation. Since less than 10% (24/221) of the data were missing, we did not use multiple imputation techniques in our analysis. All the analysis was done in SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Study population characteristics

During the study period, 129 patients were started on the zidovudine-containing regimen and 92 patients on the tenofovir-containing regimen. The mean age was 40 (SD-8.7) years and 71% (157/221) of the subjects were male. The median (interquartile range) patient weight and CD4 count at the start of treatment were 60 kg (50–68) and 159 cells/μl (63–228), respectively, and the values were comparable between regimens (Table 1). Patients on the tenofovir-containing regimen had more professional or semi-professional jobs, were older, had more severe infections and there was less time between diagnosis and initiation of treatment than patients on the zidovudine-containing regimen (Table 1).

Outcome measures

There was a significant difference between the zidovudine- (47%; 61/129) and tenofovir- (11%; 10/92) containing regimens in terms of the proportion of patients who experienced ADRs ($p<0.01$) (Table 2). After adjusting for PS, patients on the zidovudine-containing regimens were 8.7 times (95% CI 4.03–18.88) more likely to experience an ADR compared to patients on the tenofovir-containing regimen (Table 2). When adjusting for the PS and other baseline variables, the likelihood of the patients receiving the zidovudine-containing regimen developing an ADR increased to 12.6 times (95% CI 5.2–30.7) that of the patients receiving the tenofovir-containing regimen. In the multivariate regression model, none of the other variables had significant influence on ADR (Supplementary Table 1).

Zidovudine was associated with anaemia (47%; 37/78), which was the most frequently diagnosed ADR, followed by the

Table 1. Baseline characteristics of the study population

Variable	Zidovudine-containing regimen	Tenofovir-containing regimen	p-value[c]
Gender: male[a] n (%)	92/129 (71.3)	65/92 (70.6)	NS
Median age in years[b] (IQR)	37 (33–41)	40 (34–46)	<0.001
Occupation[a] n (%)			<0.001[d]
Professional	6/129 (4.7)	11/92 (12)	
Semi-professional	12/129 (9.3)	15/92 (16.5)	
Clerical, shop-owner, Farmer	36/129 (28.1)	25/92 (27.5)	
Skilled worker	15/129 (11.7)	7/92 (7.7)	
Unskilled worker	32/129 (25)	5/92 (5.5)	
Unemployed	27/129 (21.1)	28/92 (30.8)	
WHO clinical stage before treatment[a] n (%)			0.03[e]
Stage 1	42/129 (32.5)	22/92 (23.9)	
Stage 2	21/129 (16.3)	6/92 (6.5)	
Stage 3	19/129 (14.7)	16/92 (17.4)	
Stage 4	47/129 (36.4)	48/92 (52.1)	
Co-opportunistic infection[a] n (%)	43/129 (33.3)	39/92 (42.4)	NS
Median delay in treatment from the time of diagnosis in days[b] (IQR)	118 (29–779)	36 (11–49)	<0.01
Median BMI at the start of treatment in kg/m^2 [b] (IQR)	22.3 (19.3–24.6)	21.1 (19–24.7)	NS
Median CD4 at the start of treatment in cells/μl[b] (IQR)	168 (72–228)	134 (54–227)	NS

IQR: inter quartile range; NS: not significant.
Co-opportunistic infection: patients who had opportunistic infections at the time of initiation of therapy.
[a] χ^2 test performed for comparing categorical variables.
[b] Non-parametric test (Kruskal-Wallis test) performed for comparing difference in median.
[c] p-value significance <0.05.
[d] p-value common for all categories of occupation.
[e] p-value common for all categories of WHO clinical stage.

Table 2. Study outcomes with and without propensity score (PS) adjustment

Variables	Without PS adjustment			With PS adjustment		
	Zidovudine-containing regimen n (%)	Tenofovir-containing regimen n (%)	p-value	OR[a,b]	95% CI	p-value[c]
Adverse drug reaction	61/129 (47.3)	10/92 (10.9)	<0.001	8.725	4.032–18.883	<0.001
OI after 3 months	26/129 (20.1)	17/92 (18.5)	NS	1.182	0.591–2.364	NS
In-patient admissions	30/129 (23.3)	18/92 (20)	NS	1.006	0.52–1.947	NS
	Zidovudine-containing regimen	Tenofovir-containing regimen	p-value	Zidovudine-containing regimen	Tenofovir-containing regimen	p-value[d]
Mean change in BMI[e] (SD)	1.8 (2.5)	3.6 (3)	<0.01	1.9 (2.3)	3.7 (3.1)	<0.01
Mean change in CD4[e] count (SD)	359 (220)	388 (198)	NS	358 (212)	358 (208)	NS

NS: not significant; OI: opportunistic infections.
[a] Reference category: tenofovir-containing regimen.
[b] PS adjusted odds ratio.
[c] p-value significance <0.05.
[d] PS adjusted comparison of means.
[e] Change in BMI in kg/m^2 and CD4 cells/μl between treatment initiation and end of follow-up.

Table 3. Adverse drug reactions diagnosed and treatment change

Adverse drug reaction	Drug	Number of cases (%)[a] n=78	Required change of regimen (%)[b] n=49
Anemia	Zidovudine	37 (47)	26 (53)
Pancytopenia	Zidovudine	3 (4)	3 (6)
Skin rash	Nevirapine	9 (12)	8 (16)
Hepatitis	Nevirapine	4 (4)	4 (8)
GI disturbances	All drugs[c]	7 (9)	0
Lipodystrophy	Stavudine	5 (6)	2 (4)
Peripheral neuropathy	Stavudine	3 (4)	0
Lactic acidosis	Stavudine	3 (4)	3 (6)
Renal tubular acidosis	Tenofovir	2 (3)	2 (4)
Hypophosphatemia	Tenofovir	3 (4)	1 (2)
CNS disturbances	Efavirenz	2 (3)	0

GI: gastro-intestinal.
[a] Percentage out of total number of cases with adverse drug reaction.
[b] Percentage out of total number of cases requiring change of regimen.
[c] GI disturbances common to any of the drugs listed.

nevirapine associated skin reactions (12%; 9/78). Approximately 60% of the patients with ADRs required a drug change; approximately half of these were due to zidovudine-associated anemia (Table 3). The proportion of patients requiring regimen change due to ADRs with the zidovudine-containing regimen was 36% (47/129) as compared to 3% (3/92) with the tenofovir-containing regimen. Stavudine was used in place of zidovudine in 36% (26/72) of patients with zidovudine-associated anemia; of these, 42% (11/26) had an additional ADR due to stavudine, requiring a drug change back to zidovudine. Of the 13 patients with nevirapine-associated ADRs, 12 (92%; 12/13) patients switched back to taking efavirenz, while of the 5 patients with tenofovir-associated ADRs, 3 (60%; 3/5) were switched to taking abacavir (Table 3).

The proportion of patients experiencing opportunistic infections more than 3 months after initiation of ART was the same in the zidovudine-containing (20%; 26/129) and tenofovir-containing (19%; 17/92) regimens (Table 2). However, after adjusting for PS, patients receiving the zidovudine-containing regimen developed opportunistic infections 1.2 times (95% CI 0.591–2.364; p=0.63) more often than patients on the tenofovir containing regimen. After adjusting for PS and other baseline variables, this increased further to 1.5 times (95% CI 0.67–3.2; p=0.34) more than seen in the tenofovir group. None of the other baseline variables had a significant influence on opportunistic infections (Supplementary Table 1). Bacterial skin infections (31%; 14/45) were the most common opportunistic infection followed by candidal infections (13%; 6/45) (Table 4).

The comparison of both regimens to determine the proportion of patients who had opportunistic infections at the time of initiation of therapy found no difference between the two (Table 1). However, after adjustment for PS, the patients in the

Table 4. Opportunistic infections diagnosed during the study period

Opportunistic infections	Zidovudine-containing regimen (n=28)	Tenofovir-containing regimen (n=17)	Total (%)[a] (n=45)
Pneumocystis pneumonia	2	0	2 (4)
Candidal infection	6	0	6 (13)
Chronic diarrhea	3	3	6 (13)
Herpes zoster	3	3	6 (13)
Herpes simplex	3	0	3 (7)
Bacterial skin infections	6	8	14 (31)
Non-alcoholic chronic liver disease	1	0	1 (2)
Pulpitis	1	0	1 (2)
CMV retinitis	1	0	1 (2)
Tuberculosis	3	2	5 (11)

CMV: cytomegalovirus.
[a] Percentage of patients out of total number of cases of opportunistic infections.

zidovudine-containing regimen were 40% less likely to have had an opportunistic infection at the time of initiation of therapy than the patients in the tenofovir containing group (OR0.61; 95% CI 0.35–1.06; p=0.08). Similar results were seen while comparing opportunistic infections during the first 3 months of treatment (OR 0.6, 95% CI 0.3–1.23) and all opportunistic infections together (OR 0.5, 95% CI 0.28–0.88).

BMI increased in patients on both the regimens. In patients on the tenofovir-containing regimen, the change in BMI from treatment initiation to the end of follow-up was twice that seen in the patients on the zidovudine-containing regimen. This was true whether or not PS adjustment was done (Table 2). The change in CD4 count from treatment initiation to the end of follow-up did not differ between those on either regimen. Again, this was true whether or not PS adjustment was done (Table 2). When adjusted for other covariates, it was patients with severe disease (WHO clinical stages 3 and 4[19]) and young patients who gained more weight and had increased BMI. Compared to male patients, female patients had a significant increase in CD4 counts (Supplementary Table 2). Four patients taking the zidovudine-containing regimen had treatment failure, compared to none who were taking the tenofovir-containing regimen. The adherence to treatment was more than 95% in both the regimens and did not differ with and without PS adjustment. The number of inpatient admissions was similar between the treatment regimens and did not differ with or without PS adjustment (Table 2). No patients died or were lost to follow-up over the course of the study.

Discussion

Tenofovir is a nucleotide reverse transcriptase inhibitor that has been approved by the Food and Drug Administration for the treatment of HIV infection since 2001. It has become widely used as it is perceived to be a well-tolerated and effective antiviral. It is considered by WHO to be on the list of Essential Medicines, which are the most important medications needed in a basic health system[20]. The major toxicity of concern is the association of tenofovir with renal disease.[21,22] Tenofovir can cause acute renal failure, Fanconi's syndrome, proteinuria or tubular necrosis.[23]

Our study compared the long-term clinical outcomes in patients with HIV receiving zidovudine- or tenofovir-containing ART. Patients on the zidovudine-containing regimen had significantly more ADRs compared to patients on the tenofovir-containing regimen. More patients required a regimen change because of ADRs in the zidovudine-containing regimen than in the tenofovir-containing regimen. At the time of initiation of ART, patients on the tenofovir-containing regimen had more opportunistic infections, but once on ART this changed and patients on the tenofovir-containing regimen had fewer opportunistic infections compared to patients on the zidovudine-containing regimen. ART patients on the tenofovir-containing regimen gained more weight and had a greater increase in BMI than patients on the zidovudine-containing regimen. Increase in CD4 count was similar between both the regimens.

ADRs are one of the major complications of ART. The results of our study agree with the studies that have shown that patients on a zidovudine-containing regimen tend to experience more ADRs and require treatment change more frequently than patients on a tenofovir-containing regimen.[24,25] Two additional studies from our study center in South India showed that 25–30% of patients on the zidovudine containing regimen have ADRs during the first six months of treatment.[6,7] In this study approximately 50% of the patients on the zidovudine-containing regimen experienced an ADR compared to 11% in the tenofovir-containing regimen. Sixty percent of the patients on the zidovudine-containing regimen with an ADR required a change in ART regimen. Anemia is the most common ADR in patients receiving a zidovudine-containing regimen.[4,6,25] Our study documented anemia in 47% of patients who developed an ADR on the zidovudine-containing regimen. Renal toxicity is a major concern in patients receiving a tenofovir-containing regimen[16,22,24] with 1–8% of patients on

tenofovir experiencing renal toxicity.[21,24] In our study 5/92 (5%) patients receiving tenofovir experienced renal toxicity at some point in the 3 year follow-up period.

We believe that the ADRs associated with individual agents in the combination pills are well enough described that toxicity can be ascribed to an individual agent in a combination pill. The ADRs associated with zidovudine are clear enough and the similarity between lamivudine and emtricitabine[26] is strong enough to allow us to consider this study a comparison of the impact of the zidovudine or tenofovir in these regimens. Since the ADRs are specific to the agents, we compared only toxicity incidence rates and not the severity or types of toxicity.

Our study suggests that under ART, patients on the tenofovir-containing regimen developed fewer opportunistic infections than patients on the zidovudine-containing regimen compared to baseline. This may suggest that the tenofovir-containing regimen is more potent than the zidovudine-containing regimen or that the regimen is more tolerable and that adherence is better. In our study, more patients with severe illness were started on the tenofovir-containing regimen than on the zidovudine-containing regimen. This may reflect a bias in the provider's belief that the tenofovir-based regimen is more potent than the zidovudine-based regimen.

Viral load monitoring has been the standard procedure for monitoring treatment failure in resource sufficient settings.[19] But in resource-limited settings CD4 counts are used for monitoring the effects of ART, since viral load monitoring is expensive and often not available. In our study viral load was done in only 9% of the patients and could not be used as a marker for treatment failure. A systematic review demonstrated a reduction in treatment failure with tenofovir-containing regimens,[27] while a multicenter randomized trial showed that patients receiving both tenofovir- and zidovudine-containing regimens have similar treatment failure outcomes.[16] In our study, four patients on the zidovudine-containing regimen had treatment failure as defined by CD4 counts in the methods section. There were no treatment failures in the tenofovir-containing regimen. The CD4 count did not differ between patients in both the regimens at initiation of therapy and at end of follow-up and there was a significant increase in CD4 count from baseline in both regimens. This could be attributed to the high percentage of adherence to the treatment in both the regimens.[28,29] Both the treatment regimens used in this study are single combination pills that are easy to take and patients on single combination regimens tend to be more adherent to treatment.[30,31] Patients on the tenofovir-containing regimen gained more weight and BMI, suggesting improvement in general health condition compared to those on the zidovudine-containing regimen.

We used occupation as a marker for socio-economic status in this study. Patients with higher levels of occupation were likely to be well educated and belong to a higher income category. In this study patients on the tenofovir-containing regimen were more likely to have professional or semi-professional jobs, suggesting that they were of high socio-economic status and were able to afford the more expensive regimen. However, more patients in the tenofovir group were unemployed, when compared to patients on the zidovudine-containing regimen. This could be because patients on the tenofovir-containing regimen had more severe disease at the time of initiation of treatment and could not work.

Strengths and limitations

One of the strengths of this study is the use of PS adjustment to account for the differences in the baseline characteristics between the drug regimens. To our knowledge this is the first study to compare these two drug regimens in India. As with any other observational study, our study also has certain limitations and bias. Though PS adjustment accounts for measured confounders, it does not account for unmeasured confounders such as substance abuse (alcohol) and sexual behavior. Outcomes were ascertained based on the written record of the treating physician. As a non-randomized, retrospective study we cannot eliminate the bias of providers in prescribing the tenofovir- or zidovudine-based regimen for a particular patient; nor could we control for the ability of a particular patient to be able to afford the tenofovir-containing regimen rather than the zidovudine-containing regimen.

Conclusions

Patients on a tenofovir-containing regimen have better clinical outcomes including fewer ADRs and opportunistic infections with improved general health than patients on a zidovudine-containing regimen. Hence in resource limited settings steps should be taken to implement tenofovir-containing regimen as the first-line treatment for HIV. Future prospective studies comparing clinical outcomes, quality of life and treatment costs in India will further help understand the treatment effects of both of these regimens and help make policy decisions to implement a tenofovir-containing regimen as the first-line treatment of choice through the government sponsored free ART programs.

Supplementary data

Supplementary data are available at Transactions Online (http://trstmh.oxfordjournals.org).

Authors' contributions: SVT, GK, JM and CAW conceived the study; SVT, CAW, FN, MM, GK and JTC designed the study protocol; ACO, GMV, PR, RK, SAP, DP, LG carried out clinical assessment and patient management; SVT and RS carried out the data collection; RS and PC were responsible for patient counselling and follow-up; SVT, CAW, FN, MM and JTC carried out data analysis and interpretation of results; SVT drafted the manuscript; CAW, FN, MM, JTC, JM and GK critically revised the manuscript for intellectual content. All the authors have read and approved the final manuscript. SVT is the guarantor of the manuscript.

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