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Authors

Modongo, Chawangwa
Wang, Qiao
Dima, Mbatshi
et al.

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Clinical and virological outcomes of TB/HIV co-infected patients treated with dolutegravir-based HIV antiretroviral regimens: Programmatic experience from Botswana

Chawangwa Modongo[1], **Qiao Wang**[2], **Mbatshi Dima**[1], **Ogopotse Matsiri**[1], **Botshelo Kgwaadira**[3], **Goabaone Rankgoane-Pono**[3], **Sanghyuk S Shin**[2], **Nicola M Zetola**[4]

[1]Botswana-UPenn Partnership

[2]Sue & Bill Gross School of Nursing University of California Irvine

[3]Botswana National Tuberculosis Program

[4]Department of Radiation Oncology, University of Pennsylvania

Abstract

Background: Dolutegravir (DTG) has recently been recommended as a preferred first-line regimen for the treatment of new and treatment experienced HIV infected patients. However, potential drug interactions between DTG and rifampicin remain a clinical and public health concern.

Methods: We analyzed HIV and TB treatment outcomes of HIV-infected patients concomitantly receiving rifampicin- and DTG-based regimens under programmatic conditions in Botswana. The outcomes of interest were successful TB treatment and viral load suppression. We used multivariable logistic models to determine predictors for each outcome of interest.

Results: A total of 1,225 patients were included in the analysis to evaluate predictors of successful TB outcome. Among patients on DTG and non-DTG regimens, 90.9% and 88.3% achieved favorable TB treatment outcomes, respectively. Of those who received DTG-based regimen; 44% received once-daily dosing and 53% twice-daily dosing. We found that DTG was associated with favorable TB treatment outcome (adjusted odds ratio [aOR] = 1.56; 95% confidence interval [CI] = 1.06, 2.31), after adjusting for age, gender, and CD4 cell counts. High rates of viral load suppression were found across all ART regimen categories (>92% for all). We did not find an independent association between DTG and viral suppression after adjustment of other covariates

Conclusions: The use of DTG-based ART regimens in patients coinfected with TB and HIV lead to favorable TB and HIV treatment outcomes, comparable to those achieved with alternative ART regimens. Our results provide reassurance to TB and HIV programs about the overall

Correspondence: Chawangwa Modongo, Botswana-UPenn Partnership, cmodongo@gmail.com.

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programmatic concomitant use of these first-line treatment regimens for the management of HIV and TB coinfected patients.

Keywords

Tuberculosis; HIV; anti-tuberculosis treatment; dolutegravir; outcomes

BACKGROUND

Tuberculosis (TB) remains the number one killer of HIV-infected people worldwide. HIV infection increases the risk for progression to active TB disease even among those well-controlled on HIV antiretroviral therapy (ART). Nevertheless, ART reduces TB-related morbidity and mortality and it is indicated for all TB/HIV coinfected patients.

Dolutegravir (DTG) is a second-generation integrase strand transfer inhibitor recently recommended by the World Health Organization (WHO) as a preferred first-line regimen for the treatment of new and ART-experienced HIV infected patients[1]. However, early studies indicate that drug-drug interactions between DTG and Rifampicin may result in decreased concentrations of DTG, raising concerns about safety and potential development of HIV resistance in the context of sub-therapeutic DTG levels [2-4].

In the sub-Saharan region, where HIV and TB remain endemic, TB/HIV coinfection rates are high. In Botswana the TB/HIV coinfection rate is approximately 60%, leading to a large number of patients requiring concomitant treatment for both diseases. In 2016 Botswana adopted “Test and Start” strategy and switched to a DTG-based regimen as first-line treatment for ART naïve patients, as well as for those who are already on ART requiring regimen change due to adverse effect or treatment failure. These recommendations also included HIV-infected patients coinfected with TB[5]. Here, we report the virological and TB treatment outcomes of TB/HIV coinfected patients concomitantly receiving Rifampicin based TB regimen and a DTG-based ART regimen under programmatic conditions in Botswana.

METHODS

Study Design:

We conducted a retrospective cohort study that included individuals coinfected with HIV and TB from July 01, 2016 through April 30, 2018.

Study population and setting:

We included all TB/HIV coinfected patients treated in 97 facilities considered to have high TB/HIV burden in Botswana. Management of TB and HIV are fully integrated into the primary health care system and are provided by nurse practitioners and medical doctors in each of these 97 facilities. A dedicated medical officer or nurse practitioner at the HIV clinic determines the ART regimen for each TB/HIV coinfected patient in full coordination with TB clinicians and according to national guidelines. The TB clinicians (also a medical officer or nurse practitioner) prescribe the TB treatment for a duration of 6 months. The first two

months of TB treatment is a fixed dose combination (FDC) of rifampicin, isoniazid, ethambutol and pyrazinamide followed by four months of continuation phase with ethambutol, rifampicin and isoniazid. Since the beginning of 2016, the Botswana National ART guidelines were updated to recommend all new HIV patients to be started on DTG, together with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), as preferred regimen (DTG/TDF/FTC)[1]. According to national guidelines, DTG dosing was recommended to be administered either once daily for patients not receiving rifampicin or twice daily for those on rifampicin-based TB regimen. The DTG night dose was made available to those receiving the twice a day regimen. Prior to the DTG-based regimen Efavirenz or Lopinavir together with FTC and TDF was the preferred regimen. Patients on this ART regimen were to be switched to DTG-containing regimens, whenever possible[5].

For follow up, TB/HIV coinfected patients are reviewed monthly during TB treatment and every 3 to 6 months thereafter for HIV care. A follow-up sputum smear for microscopy is obtained at two months before change of treatment from intensive to continuation phase. A sputum is also collected at 6 months to determine TB treatment outcome. Follow up chest X-rays are not routinely required. Baseline labs, CD4 cell count and HIV viral loads are measured at 3 months and repeated at 6 months and then repeated every 6 months thereafter

Data collection:

Data for this study were obtained directly from the combined national registry for TB and HIV. TB cases were identified through TB case registers at the 97 healthcare facilities. Age, sex, date of TB diagnosis and anti-tuberculosis treatment (ATT) initiation, and TB treatment outcomes were abstracted from medical records at the facilities. Date of HIV diagnosis and ART initiation, ART regimen, DTG dosing schedule, CD4 cell count, and viral load were obtained from the patients' electronic medical records. Only HIV viral loads collected during TB treatment were included in the study.

Definitions:

The main objective of this study is to describe the virological and TB treatment outcome response of patients concomitantly receiving Rifampicin-based TB regimen and DTG-based ART. Successful TB treatment outcome was defined as a patient documented as cured or completed TB treatment[6]. Unfavorable TB treatment outcome was defined as a TB patient having one of the following: 1) treatment failure, defined as sputum smear or culture is positive at month 5 or later during treatment; 2) lost to follow up (defaulted from treatment or transferred out of the clinic); or 3) died whilst on TB treatment. Among newly diagnosed HIV patients and those recently started on ART, successful HIV viral suppression was defined by a suppressed HIV viral load (<400 copies/ml) at any point during follow up while on TB treatment. For HIV-infected patients already receiving ART, viral suppression was defined by a suppressed HIV viral load at any point during the duration of TB treatment.

Data analysis:

The outcomes of interest were successful TB treatment and viral load suppression. The risk of each outcome was calculated as the observed number of each outcome divided by the total number of patients included in the respective analysis. Independent covariates selected

for analyses include age, gender, DTG (yes or no), and CD4 cell counts. Among patients who received DTG regimen, we further categorized the variable by daily dosage (once daily, twice daily, or missing dosage). Logistic regression modeling was applied to evaluate the bivariate association between each covariate and the outcomes of interest. Finally, multivariable logistic models were constructed to include all available independent covariates as predictors for each outcome of interest (age, gender, CD4 cell count, DTG, DTG dose frequency). Odds ratios were estimated for all independent variables adjusted for all other variables in the model. We presented separate analyses for DTG (yes or no) and DTG categorized by daily dosage.

Data cleaning and statistical analysis were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, U.S.). No alpha cutoff was specified for statistical significance as recommended by the American Statistical Association[7].

Ethics Statement:

This study was approved by the ethics committee and institutional review board at Botswana Ministry of Health and Wellness. As this study involved analysis of programmatic data, no informed consent was required.

RESULTS

During the study period, 1,770 TB/HIV patients were on concomitant TB treatment and ART. We excluded patients with missing information on gender (n=7), age (n=3), those who were not on ART (n=16), and those who were still on TB treatment at the time of data extraction (n=519). Overall, 739 TB/HIV coinfected patients received Rifampicin- and -DTG-based regimens. Amongst those who received DTG, 322 (43.6 %) received single dose and 390 (52.8%) received the recommended double dose DTG (Table 1). Patients with missing DTG information (n=27), gender (n=7), and age (n=3) and another 16 not on ART were excluded from the study. The group of patients with DTG-based regimens were comparable to those receiving other ART regimens for age and gender (Table 1). Amongst patients with CD4 cell counts hundred or less, 94 (12.7%) were on DTG based regimen. Notably, a higher proportion of patients on DTG had CD4 cell counts ≤ 200 (28.1%; vs. 18.5% for patients not on DTG).

A total of 1,225 patients were included in the analysis to evaluate predictors of successful TB outcome (Table 3). Among patients on DTG and non-DTG regimens, 90.9% and 88.3% achieved favorable TB treatment outcomes, respectively. We found that DTG was associated with favorable TB treatment outcome (adjusted odds ratio [aOR] = 1.56; 95% confidence interval [CI] = 1.06, 2.31), after adjusting for age, gender, and CD4 cell counts. Furthermore, once daily DTG was also associated with successful TB outcome (aOR = 1.93; 95% CI = 1.16, 3.23). A slightly lower association was observed between twice daily DTG and favorable TB outcome (aOR = 1.42; 95% CI = 0.91, 2.23), but the difference between the two dosages was minimal (adjusted p-value=0.270). Among those who had unfavorable TB treatment outcome in the DTG group, there were 6 (9.0%), 48 (71.6%), 13 (19.4%) patients who had treatment failure, died, and lost to follow-up, respectively (Table 1). In the non-DTG group, there were 5 (8.8%), 35 (61.4%), 15 (26.3%) patients who had treatment

failure, died, and lost to follow-up, respectively (Table 1). The breakdown numbers are comparable between the two groups.

High rates of viral load suppression were found across all ART regimen categories (>92% for all). As expected, patients receiving DTG were on ART for significantly shorter periods of time prior to this study (Table 1). We did not find an independent association between DTG and viral suppression after adjustment of other covariates (Table 3). Moreover, similar rates of viral suppression were found between those who were on once daily vs. twice daily DTG regimen while on Rifampicin-based TB treatment (adjusted p-value=0.309).

DISCUSSION

Given its efficacy, high threshold for development of resistance, safety profile and the possibility for a once-a-day dosing, DTG-based regimens are now recommended as the preferred first-line ART in developed countries, largely replacing prior recommendations for efavirenz (EFV)- or protease inhibitor-based ones. Updated WHO guidelines recommending DTG-based regimens as one of the preferred first-line ART, together with increasing availability of low-cost generics and single-pill fixed combined formulations with TDF and FTC have rapidly increased the adoption of these regimens in developing countries [18]. In this context, great concern exists among TB and HIV programs worldwide about the efficacy and safety of DTG-based regimens for patients being treated for active TB using Rifampicin based TB regimen. Our initial programmatic experience indicates that concomitant administration of DTG-based ART and Rifampicin based TB regimen is associated with viral suppression and successful TB treatment outcomes.

DTG is metabolized by glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) 1A1, and by the cytochrome CYP3A isoenzyme. Rifampicin is a strong inducer of both, UGT1A1 and CYP3A and it has shown to decrease DTG serum levels[9]. Current recommendations require dosage adjustment of DTG when administered with Rifampicin [9-12]. According to those recommendations, doubling the DTG dose from 50mg per day to 50mg twice a day is indicated when Rifampicin is being co-administered.

Our data show that once daily dosing of DTG is adequate in patients on Rifampicin based TB regimen. There was no statistical significance amongst patients who received DTG twice daily and once daily dosing whilst on TB Rifampicin regimen. Patients concomitantly receiving single dose DTG-based ART and ATT who failed to achieve full viral suppression were 10 of 214 (4.7%) compared to 13 of 254 (5.1%) patients who were on twice daily dose DTG based regimen under programmatic conditions. The potential for development of resistance is therefore a concern. However, to our knowledge, the risk for development of resistance has not been evaluated using empiric clinical data for any of the dosing regimens. We believe the lack of virologic suppression indicates lack of medical compliance as the most likely explanation.

According to national guidelines, twice a day DTG dosing was recommended for patients receiving rifampicin-based TB regimen. However, many patients received the once a day dosing recommended for HIV patients not on rifampicin. While this deviation from national

recommendations allowed us to study its safety and association with clinical outcomes, it highlights the potential for bias and deviation from protocols intrinsic to observational pragmatic studies. While there were no significant differences among patients receiving each of those dosing regimens, it is impossible to determine if the lack of randomization at the time of dose assignment led to unmeasured bias. While our results provide a significant degree of confidence to clinicians and public health officials worldwide over the safety of once a day DTG regimens, our results are not yet conclusive due to the intrinsic limitations of an observational study. Future PK/PD studies and controlled trials are required to confirm our results. Our results should be interpreted with caution given the observational nature of our study design and confounders intrinsic to the analyses of programmatic data. Most notably, we were unable to carefully assess for adherence and primary resistance among our failing patients. Similarly, lack of longer-term virologic data prevents us from drawing stronger conclusions regarding the mid- and long-term virological outcomes. Nevertheless, while preliminary in nature, our results provide reassurance to TB and HIV programs about the overall programmatic positive outcomes associated with the concomitant use of these first-line treatment regimens for the management of HIV and TB[9-13].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of the study population by HIV antiretroviral regimen (Dolutegravir-based vs no Dolutegravir-based regimen)

Characteristic		Dolutegravir n (%) or mean (SD) N=739	No Dolutegravir n (%) or mean (SD) N=486
Age, median (IQR)		39.8 (11.0)	40.1 (13.4)
TB outcome	Success	672 (90.9)	429 (88.3)
	Unfavorable	67 (9.1)	57 (11.7)
Viral load	Undetectable	541 (73.2)	396 (81.5)
	> 400 copies	40 (5.4)	26 (5.3)
	Missing	158 (21.4)	64 (13.2)
Gender	Female	332 (44.9)	223 (45.9)
	Male	407 (55.1)	263 (54.1)
DTG dose	50 mg OD	322 (43.6)	N/A
	50 mg BD	390 (52.8)	N/A
	Missing dosage	27 (3.6)	N/A
CD4	≤ 100	94 (12.7)	35 (7.2)
	101-200	114 (15.4)	55 (11.3)
	201-350	172 (23.3)	107 (22.0)
	> 350	198 (26.8)	212 (43.6)
	Missing	161 (21.8)	77 (15.8)
Time on ART (in months)		10.8 (31.1)	41.2 (51.0)
Detailed Unfavorable TB outcome	Treatment failure	6 (9.0)	5 (8.8)
	Died	48 (71.6)	35 (61.4)
	Lost to follow-up	13 (19.4)	15 (26.3)
	Other	0	2 (3.5)
TB site	Pulmonary	556 (75.2)	243 (50.0)
	Extrapulmonary	134 (18.1)	69 (14.2)
	Both	5 (0.7)	3 (0.6)
	Missing	44 (6.0)	171 (35.2)

IQR=Interquartile range; SD=standard deviation.

Table 2.

Characteristics of the study population by tuberculosis treatment success and HIV viral load suppression

Characteristic		TB treatment success n/N (%)	Viral load suppressed n/N (%)
Age	≤ 30	199/228 (87.3)	129/143 (90.2)
	31-40	430/469 (91.7)	307/317 (96.8)
	41-50	289/319 (90.6)	187/200 (93.5)
	> 50	183/209 (87.6)	131/137 (95.6)
Gender	Female	502/555 (90.5)	339/360 (94.2)
	Male	599/670 (89.4)	415/437 (95.0)
Dolutegravir	No DTG	429/486 (88.3)	288/307 (93.8)
	50 mg OD	298/322 (92.6)	204/214 (95.3)
	50 mg BD	352/390 (90.3)	241/254 (94.9)
	Missing dosage	22/27 (81.5)	21/22 (95.4)
CD4 (cells/ml^3)	≤ 100	100/129 (77.5)	64/77 (83.1)
	101-200	157/169 (92.9)	116/124 (93.5)
	201-350	261/279 (93.6)	207/217 (95.4)
	> 350	378/410 (92.2)	302/309 (97.7)
	Missing	205/238 (86.1)	65/70 (92.9)
TB site	Pulmonary	739/799 (92.5)	466/497 (93.8)
	Extrapulmonary	171/203 (84.2)	118/122 (96.7)
	Both	7/8 (87.5)	3/4 (75.0)
	Missing	183/215 (85.1)	161/174 (92.5)

IQR=Interquartile range

Table 3.

Correlates of successful TB treatment outcome and viral load suppression of patients concomitantly receiving Rifampicin based anti-tuberculosis and DTG based ART regimen from June 2016 to April 2018

Characteristic		Correlates of successful TB treatment outcome (n=1,225)			Correlates of successful viral load suppression (n=797)		
		Crude *OR (95% CI)	Adjusted OR (95% §CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age		0.996 (0.98-1.01)	0.99 (0.98-1.01)	0.99 (0.98-1.01)	1.02 (0.99-1.05)	1.02 (0.99-1.05)	**1.02 (0.99-1.05)**
Gender	Female	1.00	1.00	1.00	1.00	1.00	**1.00**
	Male	0.89 (0.61-1.30)	0.94 (0.64-1.39)	0.94 (0.64-1.39)	1.17 (0.63-2.16)	1.19 (0.63-2.25)	**1.18 (0.62-2.24)**
DTG	No	1.00	1.00	N/A	1.00	1.00	**N/A**
	Yes	1.33 (0.92-1.94)	**1.56 (1.06-2.31)**	N/A	1.28 (0.69-2.38)	1.64 (0.86-3.12)	**N/A**
DTG	No DTG	1.00	N/A	1.00	1.00	N/A	**1.00**
	50 mg ¶OD	1.65 (1.00-2.72)	N/A	**1.93 (1.16-3.23)**	1.35 (0.61-2.96)	N/A	**1.76 (0.78-3.95)**
	50 mg #BD	1.23 (0.80-1.90)	N/A	1.42 (0.91-2.23)	1.22 (0.59-2.53)	N/A	**1.51 (0.71-3.20)**
	Missing dosage	0.59 (0.21-1.60)	N/A	0.83 (0.29-2.34)	1.39 (0.18-10.86)	N/A	**2.15 (0.26-17.81)**
CD4	≤ 100	1.00	1.00	1.00	1.00	1.00	**1.00**
	101-200	**3.80 (1.85-7.78)**	**3.93 (1.91-8.09)**	**3.88 (1.88-7.99)**	**2.95 (1.16-7.48)**	**3.09 (1.21-7.91)**	**3.12 (1.21-7.99)**
	201-350	**4.21 (2.24-7.91)**	**4.53 (2.39-8.57)**	**4.46 (2.35-8.47)**	**4.21 (1.76-10.04)**	**4.38 (1.82-10.56)**	**4.43 (1.83-10.70)**
	> 350	**3.43 (1.98-5.93)**	**3.88 (2.20-6.82)**	**3.83 (2.18-6.75)**	**8.76 (3.36-22.83)**	**10.07 (3.79-26.80)**	**10.15 (3.81-27.03)**
	Missing	**1.80 (1.04-3.13)**	**1.84 (1.06-3.22)**	**1.83 (1.05-3.20)**	2.64 (0.89-7.84)	**3.03 (1.01-9.15)**	**2.99 (0.99-9.05)**

*OR=Odds ratio;

§CI=Confidence interval.

¶OD=once daily,

#BD twice daily dosing, HIV viral load <400 copies/mm^3 was considered undetectable/suppressed and HIV viral load >400 copies/mm^3 was detectable