PATTERNS OF ADHERENCE IN BICTEGRAVIR AND DOLUTEGRAVIR-BASED REGIMENS

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1. BACKGROUND

Regimen complexity can adversely affect adherence, leading to virologic failure. It is unknown whether this occurs with regimens that contain the second-generation integrase inhibitors (INSTIs), bictegravir (BIC), and dolutegravir (DTG), both of which are recommended in the current U.S. Department of Health and Human Services (DHHS) Guidelines for initial therapy. This study evaluated adherence and rates of viral suppression in patients receiving single-tablet BIC and DTG-containing regimens as well as multi-tablet DTG-containing regimens.

2. METHODS

Electronic medical records, prescription and dispensing data for 2,217 patients initiating or switching to BIC/FTC/TAF, DTG/ABC/3TC, DTG+TDF/FTC or DTG+TAF/FTC between August 2013 - August 2019 were collected from 5 practices with patients residing in 17 US states. Patients on prior DTG or BIC regimens were excluded from DTG or BIC groups, respectively.

Adherence was defined as proportion of days covered (PDC) through the first 6 months of regimen treatment. Two thresholds of adherence were considered: ≥95% and ≥80%.

To determine association of regimen with adherence, we (1) used multiple imputation with predictive posterior matching for baseline labs, (2) employed propensity score matching (PSM) using baseline labs and demographics, (3) used mixed effects logistic regression, using BIC/FTC/TAF vs DTG-regimens with random intercept for practice, (4) and adjusted models using demographics and relevant baseline clinical data.

Additionally, we assessed viral suppression (<200 copies/mL) in a subset of 655 patients at 6 months (-1 week/+2 months) after starting BIC or DTG with Fisher exact test.

3. RESULTS

Of 2,217 patients who qualified for the study, 1060 (48%) were dispensed BIC/FTC/TAF. Compared to DTG-treated patients, BIC/FTC/TAF treated patients were more likely to be male, white, older, with higher proportion of virally suppressed, higher baseline CD4 count, BMI, LDL cholesterol, total cholesterol, triglycerides, and lower baseline AST [Table 1].

In observed (unadjusted) data, adherence through 6 months was significantly higher for BIC/FTC/TAF compared to both DTG/ABC/3TC [p<0.01] or DTG+TDF/FTC and DTG+TAF/FTC regimens [p<0.01] at 80% and 95% adherence thresholds and for DTG/ABC/3TC in comparison to DTG+TDF/FTC or DTG+TAF/FTC at the 80% adherence level [p=0.02] [Figure 1].

After matching and adjusting for age, race, gender, CD4 count, HIV viral load, baseline AST, ALT, lipids, eGFR, hemoglobin A1C, and year of regimen initiation, 95% and 80% adherence was significantly different for BIC/FTC/TAF vs all DTG regimens. However, this difference was primarily due to increased adherence in BIC/FTC/TAF vs MTR DTG [Figure 2].

Unadjusted assessment of viral suppression at 6 months for patients with measures (n=655) was favorably impacted by adherence ≥80% and ≥95% [Figure 3]. Small sample of non-adherent patients for 80% threshold in BIC and MTR DTG subgroups likely caused insignificant result for difference in suppression. P-values were computed by Fisher's Exact Test.

TABLE 1: PATIENT CHARACTERISTICS

Variables with statistically significant differences (p<0.05) are shown in bold font	BIC N=1060 (STR=1060)	DTG N=1157 (STR=542, MTR=615)
Age; median (IQR)	**48 (37,56)**	**47 (36,54)**
Male; n/N (%)	**755/895 (84.4)**	**829/1063 (78.0)**
White race; n/N (%)	**537/892 (60.2)**	**496/1039 (47.7)**
Black; n/N (%)	**264/892 (29.6)**	**456/1039 (43.9)**
Hispanic; n/N (%)	**57/892 (6.4)**	**41/1039 (3.9)**
Other race; n/N (%)	**34/892 (3.8)**	**46/1039 (4.4)**
Naive; n/N (%)	**61/1060 (5.8)**	**105/1157 (9.1)**
Prior Treatment Known; n/N (%)	**607/1060 (57.3)**	**402/1157 (34.7)**
Prior Treatment Unknown; n/N (%)	**392/1060 (37.0)**	**650/1157 (56.2)**
Suppressed at baseline (<200 copies/ml or undetectable); n/N (%)	**799/1004 (79.6)**	**767/1085 (70.7)**
CD4 <200 cells/ml; n/N (%)	**77/1054 (7.3)**	**112/1073 (10.4)**
AST ≥30; n/N (%)	**216/1060 (20.4)**	**339/1157 (29.3)**
ALT ≥30; n/N (%)	347/1060 (32.7)	390/1157 (33.7)
Low HDL cholesterol (<50 mg/dL for females or <40 mg/dL for males); n/N (%)	**274/840 (32.6)**	**369/968 (38.1)**
LDL Cholesterol ≥100; n/N (%)	**541/995 (54.4)**	**421/1058 (39.8)**
Total Cholesterol ≥200; n/N (%)	**297/1003 (29.6)**	**214/1062 (20.2)**
Triglycerides ≥150; n/N (%)	**385/999 (38.5)**	**353/1061 (33.3)**
eGFR <60 mL/min/1.73m^2; n/N (%)	72/1060 (6.8)	100/1157 (8.6)
eGFR 60<90 mL/min/1.73m^2	421/1060 (39.7)	429/1157 (37.1)
eGFR ≥90 mL/min/1.73m^2	567/1060 (53.5)	628/1157 (54.3)
Body Mass Index (BMI) Underweight; n/N (%)	**7/637 (1.1)**	**21/633 (3.3)**
BMI Normal	**205/637 (32.2)**	**235/633 (37.1)**
BMI Overweight	**250/637 (39.2)**	**206/633 (32.5)**
BMI Obese	**175/637 (27.5)**	**171/633 (27.0)**

4. LIMITATIONS

With the retrospective nature of the study and lack of randomization to studied treatments, we may not have been able to adjust for all baseline variables influencing outcome, though propensity score matching decreased differences between cohorts (not shown).

There was a lack of complete data on prior treatments, and naïve status could not be included in adjustments.

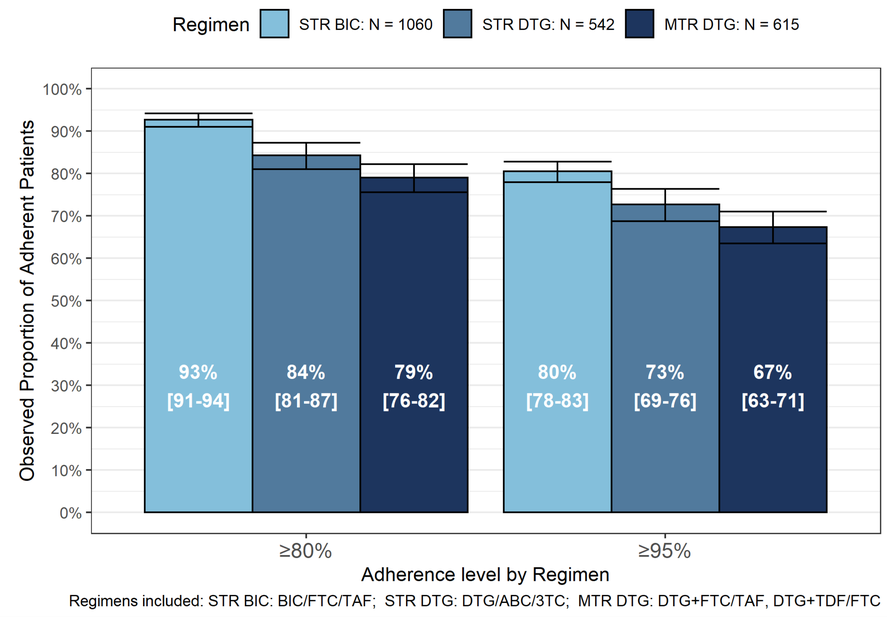
Caution should be used when evaluating rates of viral suppression by adherence level due to small sample of patients with viral load results 6 months after starting BIC or DTG (30% of the cohort).

Patients in database may not be representative of the US HIV populations as a whole.

TABLE 2: OBSERVED VIRAL SUPPRESSION BY ADHERENCE AND TREATMENT FOR A SUBSET WITH 6 MONTH VIRAL LOAD DATA

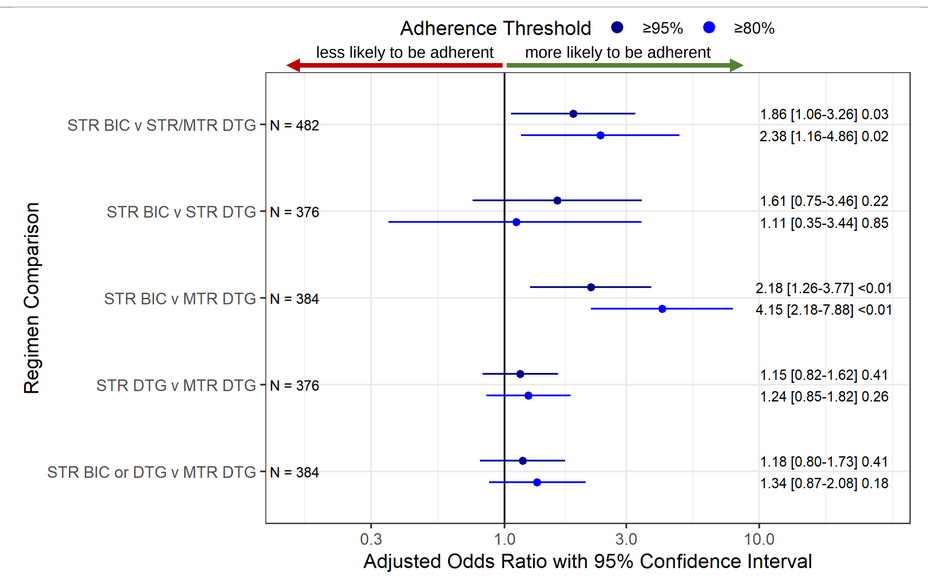
	Observed Adherence; n/N (%)	Virally Suppressed; n/N (%)		p-value
Regimen	**≥80% Adherent**	**<80% Adherent**	**≥80% Adherent**	
STR/MTR DTG	325/406 (80)	64/81 (79.0)	295/325 (90.8)	**0.006**
STR DTG	171/213 (80)	33/42 (78.6)	156/171 (91.2)	**0.029**
MTR DTG	154/193 (80)	31/39 (79.5)	139/154 (90.3)	0.093
STR BIC	225/249 (90)	19/24 (79.2)	201/225 (89.3)	0.173
All Patients	550/655 (84)	83/105 (79.0)	496/550 (90.2)	**0.002**
Regimen	**≥95% Adherent**	**<95% Adherent**	**≥95% Adherent**	
STR/MTR DTG	289/406 (71)	91/117 (77.8)	268/289 (92.7)	**<0.001**
STR DTG	152/213 (71)	48/61 (78.7)	141/152 (92.8)	**0.007**
MTR DTG	137/193 (71)	43/56 (76.8)	127/137 (92.7)	**0.006**
STR BIC	205/249 (82)	37/44 (84.1)	183/205 (89.3)	0.311
All Patients	494/655 (75)	128/161 (79.5)	451/494 (91.3)	**<0.001**

FIGURE 1: ADHERENCE THROUGH 6 MONTHS VIA DISPENSING DATA: OBSERVED FREQUENCIES BY REGIMEN & ADHERENCE LEVEL WITH 95% CONFIDENCE INTERVAL



Regimens included: STR BIC: BIC/FTC/TAF; STR DTG: DTG/ABC/3TC; MTR DTG: DTG+FTC/TAF, DTG+TDF/FTC

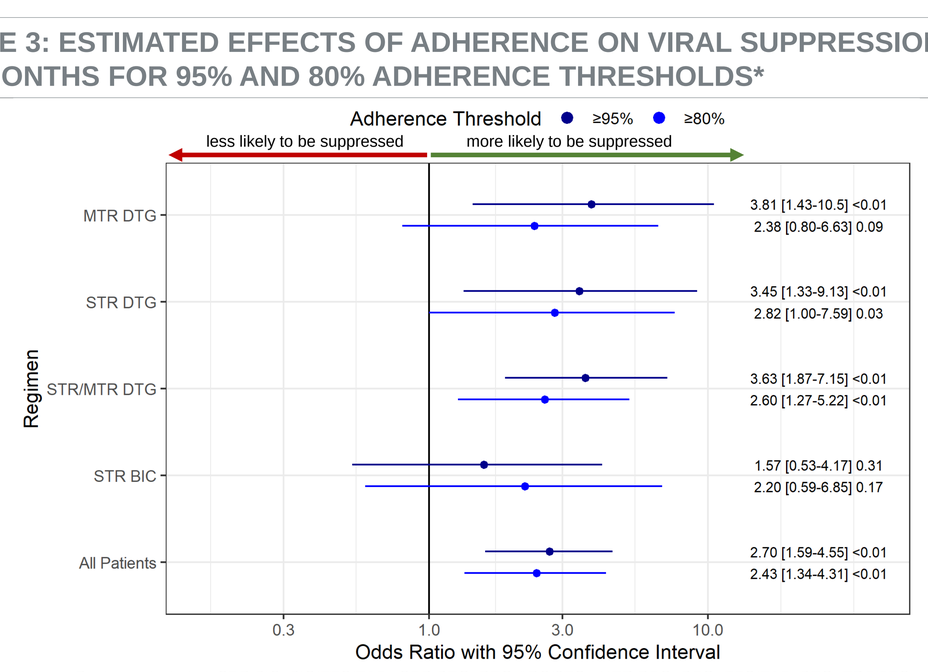
FIGURE 2: ASSOCIATION OF ADHERENCE AND REGIMEN AT 6 MONTHS FOR 95% AND 80% THRESHOLDS*



Regimens included: STR BIC: BIC/FTC/TAF; STR DTG: DTG/ABC/3TC; MTR DTG: DTG+FTC/TAF, DTG+TDF/FTC

*Accounting for differences in baseline characteristics, adjusted odds ratios describe likelihood of being adherent at 80% and 95% level on the regimen: <1 less likely to be adherent, >1 more likely to be adherent. Reference category for regimen comparison is the latter within each label. Matched sample size for each group listed on left side of the figure.

FIGURE 3: ESTIMATED EFFECTS OF ADHERENCE ON VIRAL SUPPRESSION AT 6 MONTHS FOR 95% AND 80% ADHERENCE THRESHOLDS*



Regimens included: STR BIC: BIC/FTC/TAF; STR DTG: DTG/ABC/3TC; MTR DTG: DTG+FTC/TAF, DTG+TDF/FTC

*Odds ratios describe likelihood of being suppressed if adherent on the regimen: <1 less likely to be suppressed when adherent, >1 more likely to be suppressed when adherent. DTG group includes STR and MTR, while BIC group includes only STR.

5. CONCLUSION

In a real-word database that included data on medication dispensing, we found that starting or switching to regimens consisting of a single-tablet was associated with higher rates of ≥80% and ≥95% adherence compared to two-pill regimens. BIC/FTC/TAF-treated patients had higher adherence than those treated with DTG plus either TDF/FTC or TAF/FTC. Adherence influenced subsequent rates of viral suppression at 6 months in a subset of patients with viral load, but this was not observed within the BIC/TAF/FTC arm potentially due to inadequate sample size of suboptimal adherence. These differences suggest advantages of single pill treatments even in regimens that include the second-generation integrase inhibitors, bictegravir and dolutegravir.

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