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Maintenance of non-HIV cardiometabolic comorbidity control among HIV-infected veterans' affairs patients: a comparison between single tablet and multiple tablet antiretroviral regimens

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ABSTRACT

Background: Cardiometabolic comorbidity control (CMCC) is an important non-HIV outcome for patients with HIV-infection as this is one of the leading non-HIV causes of death. The advent of single-tablet antiretroviral (ART) regimens (STR) have decreased medication regimen complexity compared to multiple-tablet regimens (MTR) among HIV-infected patients. It is unclear if the use of STR versus MTR results in improved maintenance of CMCC. The study objective was to determine if CMCC was predicted by use STR or MTR.

Material/methods: A retrospective cohort study, employing repeated subject sampling, was performed among adult HIV-infected patients receiving care in the Upstate New York Veterans' Healthcare Administration from 2000-2013. Inclusion criteria were: 1) receipt of ≥ 3 ART medications for ≥ 3 months, 2) normal/controlled baseline blood pressure (BP), glucose, or lipid values and 3) availability of on-treatment BP/glucose/lipids. Patients on fixed-dose monotherapy with AZT/ABC/3TC were excluded. Data elements collected from medical records included demographics, comorbidities, concomitant medications, and BP/glucose/lipid values. The outcomes of interest was maintenance of BP/glucose/lipid control, as defined by current treatment guidelines (JNC-8/ADA/ATPIII guidelines). For each outcome under study (BP, glucose and lipid maintenance), bivariate and multivariate (MV) analyses were performed to assess the relationship between STR/MTR and maintenance of BP/glucose/lipid control. Variables associated (p<0.2) with outcome in bivariate analyses were eligible for entry into MV models.

Results: The proportion of individuals on STR was 16.1%. Among the 757 patients with normal BP at baseline, maintenance of BP control significantly differed between STR/MTR recipients (60.7% versus 69.9%, p=0.04). In MV analyses STR use was not significantly associated with maintenance of BP control (odds ratio, OR: 1.52, 95% CI: 0.98-2.33, p=0.06), after adjustment of prior diagnosis of hypertension (OR: 3.64, 95% CI: 2.61-5.08, p<0.001), use of ≥ 9 non-ART drugs (OR: 2.80, 95% CI: 1.37–5.70, p=0.005) and IV heroin (OR: 1.64, 95% CI: 1.09-2.48, p=0.02). For 784 subjects with normal baseline glucose values, maintenance of glucose control did not significantly differ between STR/MTR recipients (68.5% versus 68.3%, p=0.96). In MV analyses, STR use was not independently associated with maintenance of glucose control (OR: 1.02, 95% CI: 0.66–1.55, p=0.95) after adjusting for baseline glucose values (OR: 1.03, 95% CI: 1.01-1.04, p<0.001) and prior diagnosis of diabetes (OR: 2.77, 95% CI: 1.83–4.19, p<0.001). Among the 388 subjects with normal baseline lipids, maintenance of lipid control did not statistically differ between STR and MTR recipients (81.2% vs 79.9%, p=0.82). This persisted in the MV analyses (OR: 0.97, 95%: 0.50-1.88, p=0.92) after adjusting for number of concomitant comorbidities (OR: 1.03, 95% CI: 1.00–1.05, p=0.03).

Conclusions: Among HIV-infected patients with CMCC, use of STR/MTR was not independently associated with improved maintenance of BP/glucose/lipid control. Future studies should elucidate if this relationship is modified by type of ART regimen.

BACKGROUND

- Several ART regimens are now coformulated into single tablet regimens (STR).
- STR are perceived to be more convenient than multiple tablet regimens (MTR) and may impact the ability to control non-HIV comorbidities.
- Cardiovascular disease is a leading cause of death among HIV-infected patients.
- The relationship between use of STR and cardiometabolic comorbidity control (CMCC) has not been evaluated.

OBJECTIVE

- Compare the frequency of CMCC between STR and MTR recipients
- Determine if STR is a predictor of CMCC

METHODS

Setting and Study Population

- This study was performed among patients receiving care at one of the 5 sites in the Upstate New York Veterans' Healthcare Administration (VISN2)
- Study Design:
  - Retrospective cohort study utilizing repeated subject sampling among HIV-infected subjects receiving care between 2000 – 2013.
- Inclusion criteria:
  - Age ≥ 18
  - Documented HIV infection (ICD-9: 042 series)
  - Receipt of ≥ 3 ART medications for ≥ 3 months
  - Normal/controlled baseline blood pressure (BP), blood glucose and lipids
  - Availability of on-treatment BP/glucose/lipids
- Exclusion criteria:
  - Patients on incomplete ART regimens (monotherapy with fixed dose zidovudine/lamivudine/abacavir, etc.) were not included in these analyses.

Data Collection

Trained reviewers collected the following information from the patients' medical records:

- Demographics and comorbidities
- Year of HIV infection
- Medication history
  - Drug name, dose, and frequency
  - Number of drugs
  - Refill history
- Laboratory and vital data
  - Blood glucose, hemoglobin A1C, lipid panel and blood pressure

Exposure Variable

- The exposure of interest in this study was the use of single tablet ART medication regimens (STR).
  - STR was defined as all components of the HIV treatment regimen coformulated into a single product (eg. fixed dose efavirenz/emtricitabine/tenofovir disoproxil fumarate)
  - All others were considered multiple tablet ART medication regimens (MTR).

Outcome Measures

- The primary outcome of this study was maintenance of cardiometabolic comorbidity control (CMCC)
- The specific CMCC outcomes evaluated were blood pressure control, blood glucose control and lipid control
  - Blood pressure control was defined using Joint National Commission (JNC)-8 and was:
    - Age ≥ 60 years: < 150/<90 mmHg
    - Age < 60 years: < 140/<90 mmHg
  - Blood glucose control was defined using American Diabetes Association 2015 Standards of Medical Care in Diabetes and was considered controlled if:
    - Blood glucose was between 80 - ≤ 130 mg/dL (4.4 - ≤ 7.2 mmol/L)
  - Lipid control was defined using the National Heart, Lung and Blood Institute Framingham 10-year cardiovascular mortality risk and patient's personal LDL goal.
    - LDL goals were:
      - Coronary heart disease (CHD) or CHD risk equivalents: LDL goal was < 100 mg/dL (2.6 mmol/l)
      - 2+ risk factors: LDL goal was < 130 mg/dL (3.4 mmol/l)
      - 0-1 risk factors: LDL goal was < 160 mg/dL (4.1 mmol/l)

Statistical Analysis

- Categorical variables were compared using the Chi-square or Fisher's Exact test.
- Continuous variables were compared using the Student's t test or Mann Whitney U test.
- Multivariate logistic regression was used to determine if STR was independently associated with the outcomes of interest.
  - Three sets of regression models were performed for the following outcomes:
    - Blood pressure control
    - Blood glucose control
    - Lipid control
- A p-value ≥ 0.25 in the bivariate analyses were included at the model entry into the multivariate model and a backwards stepwise approach was used to identify the most parsimonious model that adjusted for confounding variables

RESULTS

Table 1: Bivariate Relationship between Clinical/Demographic Characteristics and Single/Multiple Tablet Regimen

Covariate	Multiple tablet regimen recipients (n = 1037)	Single tablet regimen recipients (n = 165)	P-value
Age, mean (standard deviation, SD)	**50.3 ± 8.8**	**53.0 ± 9.0**	**<0.001**
Race			**0.95**
• **Caucasian**	**473 (45.6)**	**77 (46.7)**	
• **Black**	**519 (50.0)**	**80 (48.5)**	
• **Hispanic**	**33 (3.2)**	**6 (3.6)**	
• **Asian/Pacific Islander**	**3 (0.3)**	**1 (0.6)**	
• **Other**	**9 (0.9)**	**1 (0.6)**	
Sex, male (%)	**1010 (97.4)**	**158 (95.8)**	**0.24**
Risk behavior			**0.02**
• **MSM**	**252 (24.3)**	**37 (22.4)**	
• **MSM/IVDU**	**57 (5.5)**	**8 (4.8)**	
• **IVDU**	**299 (28.8)**	**31 (18.8)**	
• **Heterosexual sex**	**328 (21.6)**	**74 (44.8)**	
• **Female-female**	**2 (0.2)**	**0 (0)**	
• **Unknown**	**99 (9.5)**	**15 (9.1)**	
Number of comorbidities, median (IQR)	**14 (8 – 21)**	**15 (9 – 21)**	**0.42**
ART regimen type			**<0.001**
• **NNRTI**	**287 (27.7)**	**162 (98.2)**	
• **PI**	**437 (42.1)**	**0 (0)**	
• **INSTI**	**35 (3.4)**	**3 (1.8)**	
• **Non-traditional/mixed class**	**278 (36.8)**	**0 (0)**	
Baseline blood pressure control (n = 757)			
• **Systolic BP, mean ± SD**	**121 ± 12**	**122 ± 10**	**0.30**
• **Diastolic BP, mean ± SD**	**75 ± 8**	**77 ± 9**	**0.08**
Blood pressure medications	**283 (44.6)**	**55 (45.1)**	**0.92**
Baseline blood glucose control (n = 784)			
• **Blood glucose, mean ± SD**	**97 ± 12**	**98 ± 11**	**0.26**
Oral anti-diabetic medications	**39 (5.9)**	**7 (5.6)**	**0.91**
Insulins	**15 (2.3)**	**4 (3.2)**	**0.53**
Baseline lipid control (n = 388)			
• **Total cholesterol, mean ± SD**	**171 ± 41**	**165 ± 30**	**0.28**
• **LDL, mean ± SD**	**92 ± 27**	**90 ± 24**	**0.63**
• **HDL, mean ± SD**	**41 ± 16**	**43 ± 17**	**0.54**
HMG CoA Reductase inhibitors (statins)	**75 (23.5)**	**19 (27.5)**	**0.54**

All data presented as n (%) or mean (standard deviation), or median (inter-quartile range), unless otherwise noted.
*a classification and regression tree (CART)-derived breakpoint; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; INSTI = integrase strand transfer inhibitor.

Figure 1: Maintenance of Comorbidity Control between STR and MTR recipients

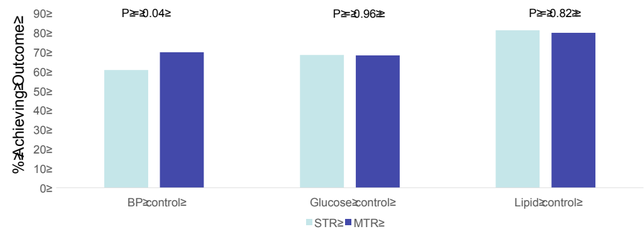

Table 2: Multivariate Analyses of Relationship between STR use and Blood Pressure Control (n = 757)

Covariate	Adjusted odds ratio	95% confidence interval	P-value
Use of single tablet regimen	1.52	0.98 - 2.33	0.06
Prior diagnosis of hypertension	3.64	2.61 - 5.08	<0.001
> 9 non-HIV medications	2.80	1.37 - 5.70	0.005
Intravenous heroin use	1.64	1.09 - 2.48	0.02

Table 3: Multivariate Analyses of Relationship between STR use and Blood Glucose Control (n = 784)

Covariate	Adjusted odds ratio	95% confidence interval	P-value
Use of single tablet regimen	1.02	0.66 - 1.15	0.95
Baseline glucose value	1.03	1.01 - 1.04	<0.001
Prior diagnosis of diabetes	2.77	1.83 - 4.19	<0.001

Table 4: Multivariate Analyses of Relationship between STR use and Lipid Control (n = 388)

Covariate	Adjusted odds ratio	95% confidence interval	P-value
Use of single tablet regimen	0.95	0.5 - 1.88	0.92
Concomitant comorbidities	1.03	1.00 - 1.05	0.03

CONCLUSIONS

- Use of STR was not significantly associated with maintenance of BP, glucose or lipid control after adjustment for other confounding factors.
- Prior diagnoses, concomitant comorbidities, intravenous heroin, polypharmacy and baseline laboratory values were predictive of maintenance of cardiometabolic comorbidity control