Documenting the Change in Hemoglobin A1C after initiating Integrase Strand Transfer Inhibitors in Diabetic and Non- Diabetic HIV Patients compared to other antiretroviral drugs.

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Introduction

- With the introduction of integrase strand transfer inhibitors (INSTI) based combined antiretroviral therapy (ART), persons with HIV (PWH) have a well-tolerated and potent new treatment option, however metabolic effects including hyperglycemia and new onset diabetes mellitus have been reported with INSTI based ART [1-3]. The incidence of diabetes in PWH is higher than in the general population [4], but ART associated hyperglycemia remains incompletely defined in the era of newer ART. Further data is required on risk of hyperglycemia in diabetic and non-diabetic PWH on contemporary ART.

- The data from observational studies in North America and Europe associating INSTI use and new onset diabetes mellitus (DM) have been contradictory [5,6]. Both the North American and European studies have excluded patients with diabetes mellitus at baseline.

- In this study we analyzed the magnitude of the change in hemoglobin A1C (A1C) seen in diabetic PWH and non-diabetic PWH who start INSTI based ART and how this change compares to other HIV classes.

- DM is a condition with significant associated morbidity and mortality. DM is a leading cause of cardiovascular disease, blindness, end-stage renal disease, amputations, and hospitalizations. Investigating changes in A1C after initating ART or changing ART will help pharmacists and clinicians better understand hyperglycemia risk when selecting ART.

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Methods

- We conducted a retrospective cohort study of PWH at the Southern Alberta Clinic, Calgary AB, who started on a new ART regimen, including INSTI, protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI), between 2010-2020.

- We assessed the change in A1C pre and post-ART start. PWH with two A1Cs such that the first A1C was <18 months pre-ART start and the second A1C was >60 days after ART start and < 18 months post-ART start were included in the study. The A1C used in our study were the last A1C prior to ART start and the first A1C > 60 days post ART start.

- We included ART naïve PWH and experienced PWH who switched ART. PWH included were on ART regimen >90 days.

- PWH starting 2 or more ART classes (INSTI, PI, NNRTI) at one time were excluded.

- Diabetes diagnosis at ART start was determined using the Canadian Diabetes Guideline criteria (A1C ≥ 6.5%) or previous diagnosis of diabetes in patient chart.

- Diabetic PWH and non-diabetic PWH were stratified by ART class and then further stratified by INSTI medication.

- As per Canadian Diabetes Guidelines, in patients with A1C >8.5% (or >1.5% above target) it is recommended to add 1 or more antihyperglycemic medications. PWH with A1C >8.5% prior to ART initiation or change were more likely to have antihyperglycemic medications added making the A1C post ART switch difficult to interpret. Therefore we further compared diabetic PWH with an A1C of <8.5 prior to ART start versus A1C of ≥ 8.5.

- Diabetic PWH who were started on PIs were not included in analysis as n=5 was too small for proper analyses.

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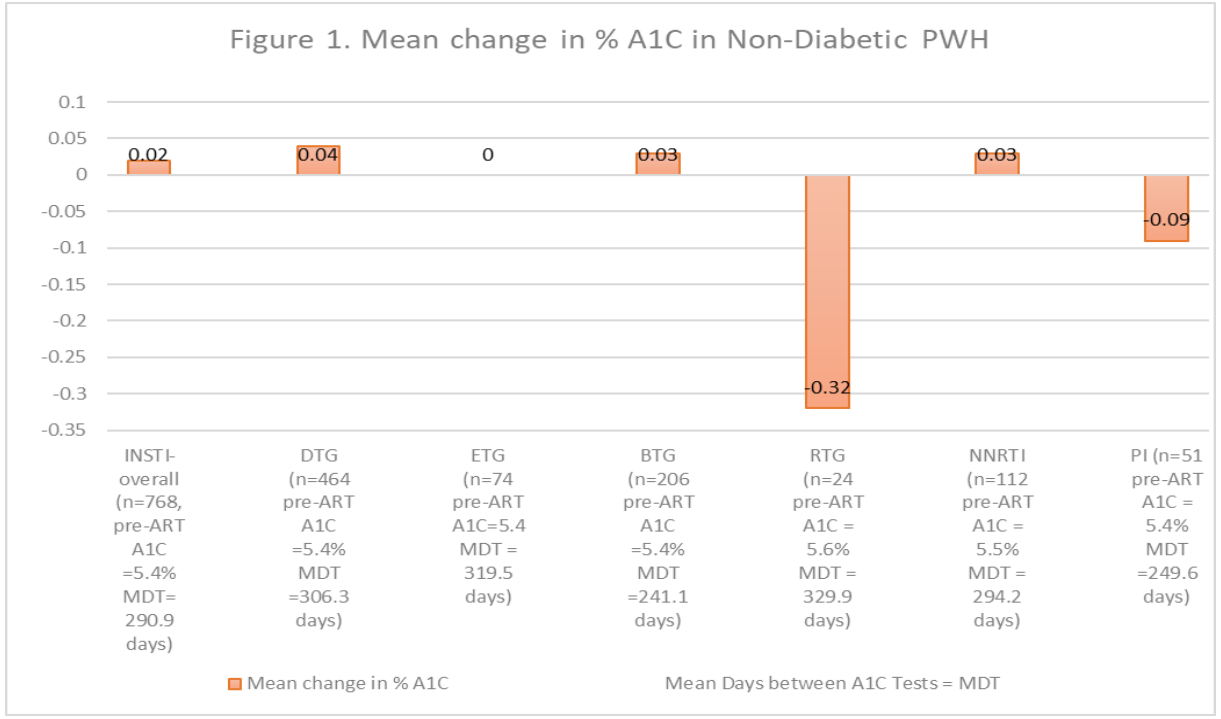
Results

Table 1: Patient characteristic pre-ART start

Characteristic	Total n = 1109	Non-Diabetic PWH n= 933 (84.1%)	Diabetic PWH n =176 (15.9%)	P Value
Female n (%)	340 (30.4)	306 (32.8)	34 (19.2)	0.14
Median Age in years (range)	48.4 (17.2, 84.6)	46.9 (17.2, 84.6)	55.4 (24.1, 80.9)	0.20
CD4 ≥ 200 n (%)*	868 (85.7)	710 (84.9)	158 (89.3)	<.0001
VL <50 n (%)*	705 (66.6)	561 (63.6)	144 (81.4)	<.0001
ARV naive n (%)	214 (19.3)	196 (21)	18 (10.2)	0.00128
Self Reported Ethinicity n (%)	Caucasian 526 (47.6)	Caucasian 435 (46.6)	Caucasian 91 (52.0)	0.25
	Black 319 (28.7)	Black 263 (28.2)	Black 56 (31.6)	0.377
	Indigenous 40 (3.6)	Indigenous 32 (3.4)	Indigenous 8 (4.5)	0.61
	East Asian 40 (3.6)	East Asian 35 (3.8)	East Asian 5 (2.8)	0.708
	Indo Asian 52 (4.7)	Indo Asian 46 (4.9)	Indo Asian 6 (3.4)	0.498
	Hispanic 50 (4.5)	Hispanic 46 (4.9)	Hispanic 4 (2.4)	0.174
	Other 82 (7.3)	Other 76 (8.1)	Other 6 (3.4)	0.041

*CD4 and VL results used were last result prior to initiating ART or switching ART



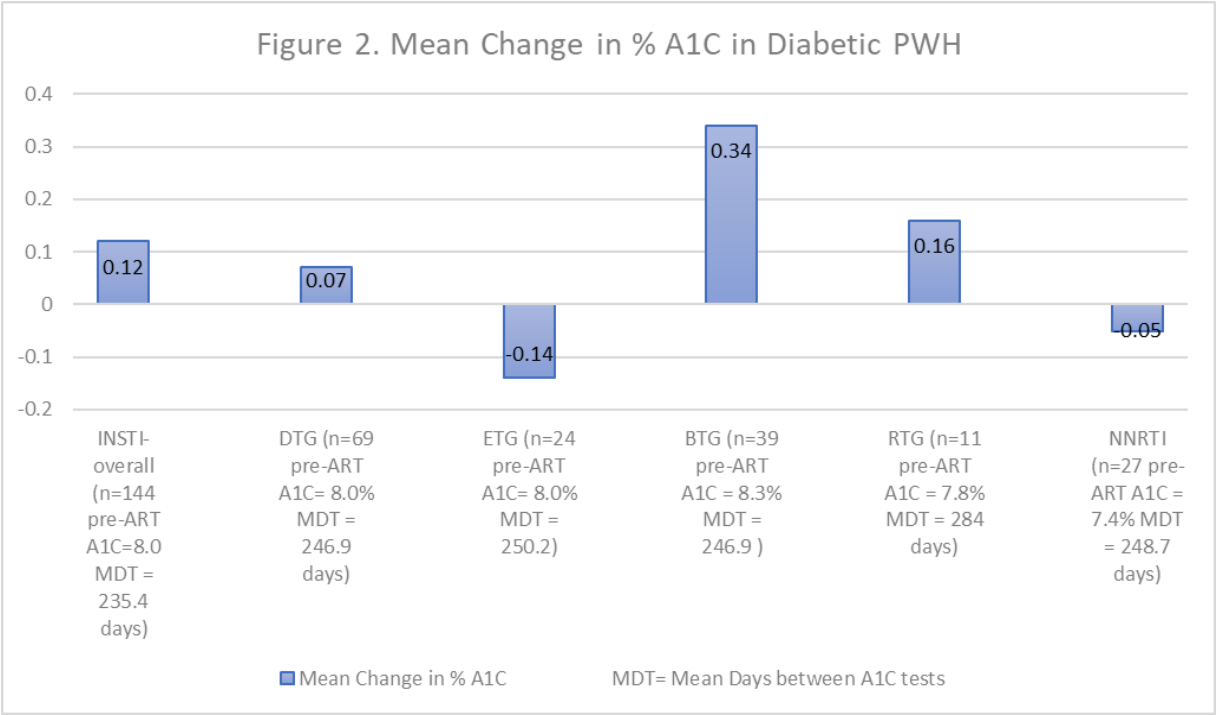
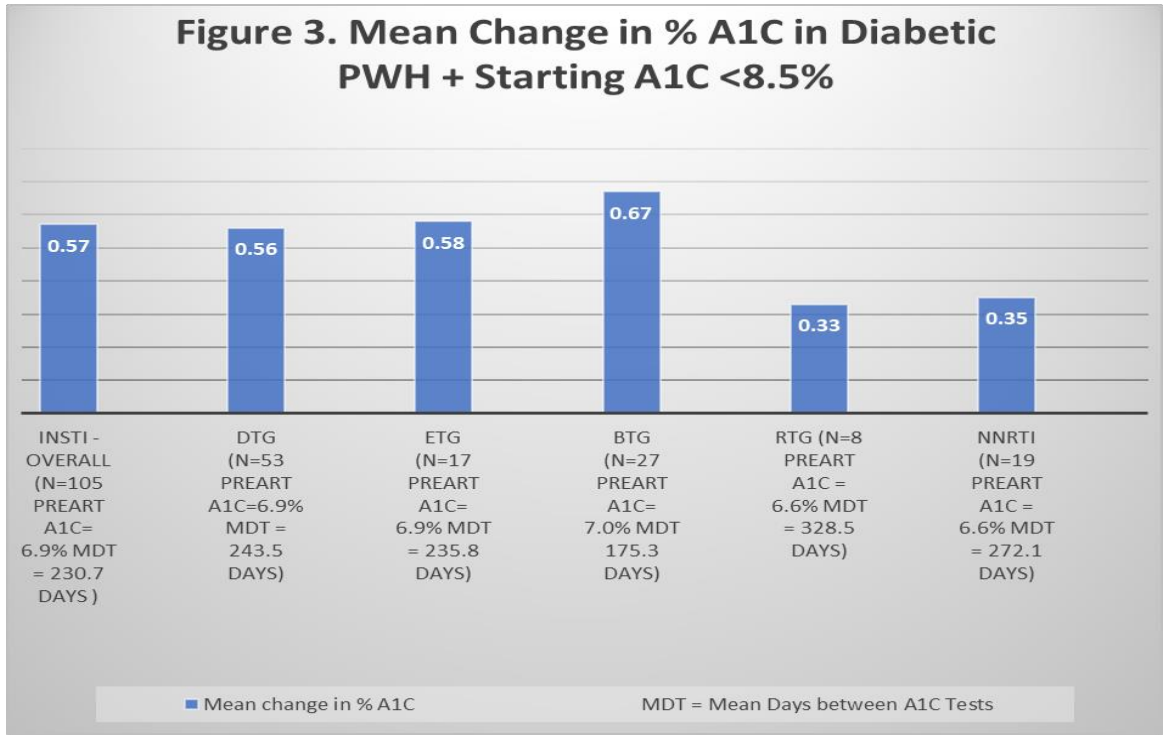


Table 2. Diabetic PWH patient characteristic pre ART start

Characteristic	Diabetic PWH n =176 (15.9%)	Diabetic PWH starting A1C >8.5 n=44 (25%)	Diabetic PWH starting A1C <8.5 n=132 (75%)	P Value
Female n (%)	34 (19.2)	6 (13.6)	28 (21.2)	0.38
Median Age in years (range)	55.4 (24.1, 80.9)	52.2 (34.2, 74.9)	56.3 (24.1, 80.9)	0.33
CD4 ≥ 200 n (%)*	158 (89.3)	38 (86.4)	120 (90.1)	0.28
VL <50 n (%)*	144 (81.4)	32 (72.7)	112 (84.8)	0.11
ARV naive n (%)	18 (10.2)	8 (18.1)	10 (7.6)	0.08
Self Reported Ethinicity n (%)	Caucasian 91 (52.0)	Caucasian 25 (56.8)	Caucasian 66 (50)	0.54
	Black 56 (31.6)	Black 8 (18.2)	Black 48 (36.4)	0.04
	Indigenous 8 (4.5)	Indigenous 5 (11.4)	Indigenous 3 (2.3)	0.02
	East Asian 5 (2.8)	East Asian 1 (2.3)	East Asian 4 (3.0)	0.63
	Indo Asian 6 (3.4)	Indo Asian 0 (0)	Indo Asian 6 (4.5)	0.33
	Hispanic 4 (2.4)	Hispanic 3 (6.8)	Hispanic 1 (0.7)	0.05
	Other 6 (3.4)	Other 3 (6.8)	Other 3 (2.3)	0.17



Summary:

Non-diabetic PWH:

Non-diabetic PWH started on INSTI showed an average change in % A1C of 0.02 (SD 0.37, average days between A1C test = 291) (n=769) versus 0.03 (SD 0.26, average days between A1C tests = 294) with NNRTI start (n=115) p=.881

We found no significant difference in mean change in % A1C between INSTI and NNRTI p=.881.

There were 5 new onset diabetes mellitus cases observed in patients started on dolutegravir and 2 new onset diabetes mellitus cases observed in patients started on bictegravir. No other new onset diabetes mellitus cases were observed.

Diabetic PWH with starting A1C <8.5%:

Diabetic PWH started on INSTI showed an average change in % A1C of 0.57 (SD 1.24, average days between A1C tests= 230) (n=105) versus 0.35 (SD 0.75, average days between A1C test =280) with NNRTI start (n=19) p=.461.

Age, sex, CD4 >200 , VL<50 were not associated with higher increases in % A1C in diabetic patients.

Discussion

- In our **non-diabetic** PWH patients there was no significant or clinically relevant change in HbA1C in patients started on INSTI vs NNRTI.
- In our non-diabetic PWH patients, the raltegravir group had the largest decrease in A1C. There were a small number of patients in the raltegravir group (n=24) and 2 of these patients had a drop in A1C >1.0%. If these 2 patients are removed the decrease in A1C is -0.19. Further investigations would be required to determine the effect of raltegravir on hyperglycemia.
- In our **diabetic** PWH patients, the increase in A1C was greatest in the INSTI group. The increase in A1C was 1.63 times greater after initiating INSTI versus initiating NNRTI (0.57 vs 0.35) but the difference not statistically significant p =.461.
- In pharmacy practice an increase of 0.57 vs. 0.35 would be considered clinically important as meeting the A1C targets in diabetes mellitus has been shown to lower risk of diabetic nephropathy, retinopathy and cardiovascular complications [7-9].
- For PWH on an INSTI, bictegravir showed the highest increase in A1C = 0.67 and raltegravir showed the lowest increase in A1C =0.33. Further investigations are needed with larger cohorts to determine if the differences in A1C PWH on an INSTI are significant.
- There were many confounding factors which were not accounted for such as changes in antihyperglycemic medication, backbone ARVs in regimen and changes in diet and exercise. Additional studies on the effect of integrase inhibitors on A1C are recommended for diabetic and non-diabetic PWH.
- A high A1C is shown to be directly correlated with severe diabetes complications. In today's practice an increase in A1C of >0.5% as seen with our diabetic PWH taking bictegravir, dolutegravir and elvitegravir is clinically relevant and important to pharmacists and clinicians initiating ART or making changes to ART.

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