Impact of integrase inhibitor exposure on glucose homeostasis in patients living with HIV and diabetes mellitus

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INTRODUCTION

- Integrase strand transfer inhibitors (InSTI) are a highly effective class of anti-retroviral (ARV) therapy that demonstrate good tolerability, minimal drug interactions and lower resistance for people living with HIV (PLWH).[1, 2]
- There has been growing concern with an association of this class of medications with the development of diabetes mellitus (DM).[3, 4]
- Findings of recent observational studies are inconsistent. However, a case study published in February 2021 identified 3 PLWH with new or acutely worsening hyperglycemia after initiation of bictegravir-based ARV regimens.[5]
- As more patients in The Immunodeficiency Clinic at The Ottawa Hospital (TOH) have been treated with InSTIs over the last decade, increasing trends in hyperglycemia have been observed in this population.

OBJECTIVES

Primary Objectives:

1. Describe the proportion and characteristics of patients with HIV who have experienced a new diagnosis or worsening of DM following the initiation of InSTIs of interest.
2. Determine clinical characteristics associated with worsening DM and InSTI use.

Secondary Objective:

3. Describe the impact of our management strategies.

METHODS

Eligibility:

- Adult patients aged ≥ 18 years with DM followed at the Immunodeficiency Clinic at TOH
- Received regimens consisting of dolutegravir, bictegravir or elvitegravir for at least one month, between November 26, 2012, and March 1, 2021

Data collection:

- A retrospective chart review was conducted, and descriptive statistics were used to describe the patients who develop a new diagnosis or worsening of DM.
- A univariate analysis was conducted to assess patient factors associated with worsening DM in comparison to patients who remained stable.
- Management strategies of new or worsening DM were described with reported changes in HbA1c within a 2-year follow-up period.

Definitions:

Outcomes:

New diagnosis: HbA1c ≥ 6.5%, documented diagnosis and/or initiation of antihyperglycemics
Worsening: absolute increase in HbA1c by ≥ 0.5%, addition of new antihyperglycemics and/or metabolic decompensation.

Management:

- Change in ARV regimen
- Intensification of antihyperglycemics:
  - Started new or added agent
  - Increase in dose of previous agents

RESULTS

Objective #1: Proportions and Baseline Characteristics

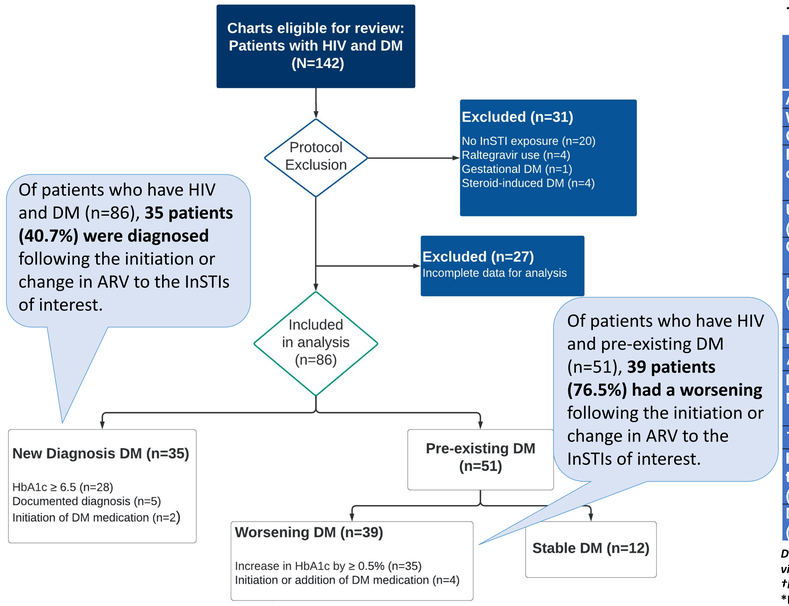

Figure 1. Patient Flow Diagram and proportions

Table 1. Baseline Characteristics†

		New diagnosis DM (n=35)	Pre-existing DM (n=51)	Total Population (n=86)
Age, mean ± SD (years)		53.3 ± 11.0	57.9 ± 10.6	56.1 ± 10.9
Weight, mean ± SD (kg)		86.6 ± 14.9	81.3 ± 14.8	83.5 ± 15
Gender, n (%)	Male	26 (74.3)	32 (62.7)	58 (67.4)
Region of origin, n (%)	Africa	20 (57.1)	21 (41.2)	41 (47.7)
	North America	10 (28.6)	19 (37.2)	29 (33.7)
	Caribbean	5 (14.3)	10 (19.6)	15 (17.4)
Undetectable HIV Viral Load, n (%)		21 (60)	31 (60.8)	52 (60.5)
CD4, median [IQR]		481 [200, 649]	529 [386, 761]	494 [303, 711]
HCV status, n (%)	HCV negative	35 (100)	43 (84.3)	80 (93)
	Treated HCV	0	4 (7.8)	4 (4.7)
	Chronic HCV	0	2 (3.9)	2 (2.3)
HbA1c, mean ± SD*		5.9 ± 0.6	7.4 ± 1.8	7 ± 1.7
ARV naïve, n (%)		6 (17.1)	4 (7.8)	10 (11.6)
InSTI Started at Baseline, n (%)	Dolutegravir	19 (54.3)	23 (45.1)	42 (48.8)
	Bictegravir	7 (20)	17 (33.3)	24 (27.9)
	Elvitegravir	9 (25.7)	11 (21.6)	20 (23.3)
TAF at InSTI start, n (%)		8 (22.9)	19 (37.3)	27 (31.4)
InSTI use prior to baseline, n (%)	Dolutegravir	3 (8.6)	6 (11.8)	9 (10.5)
	Elvitegravir	3 (8.6)	0	3 (3.5)
	Raltegravir	2 (5.7)	8 (15.7)	10 (11.6)
Mean ± SD follow-up time (years)		4.2 (1.9)	3.2 (1.7)	3.6 (1.7)

DM, diabetes mellitus; SD, standard deviation; IQR, interquartile range; HCV, hepatitis C virus; ARV, antiretroviral; TAF, tenofovir alafenamide
†Baseline = at time of InSTI initiation.
*HbA1c at baseline for the new diagnosis group was only available in 21 patients.

Objective #1: Magnitude – Changes in HbA1c

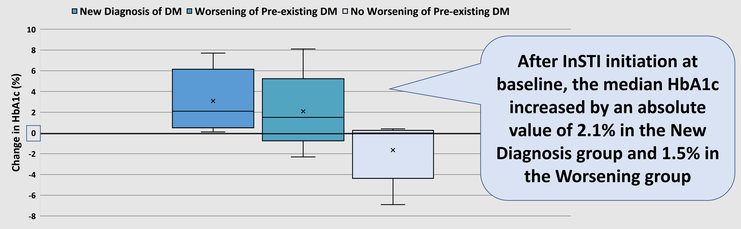

Figure 2. Median change in HbA1c from baseline (0) in the New Diagnosis, Worsening of DM and No Worsening of DM groups.

Objective #1: Magnitude – Changes in Weight

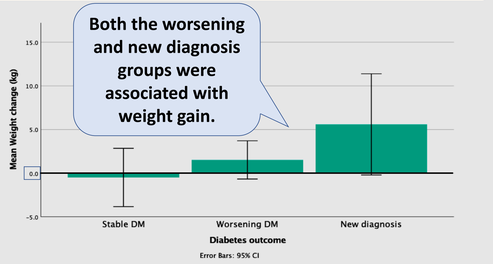

Figure 3. Mean weight change in all groups from baseline (0.0) to outcome.

Table 2. Variables included in univariate analysis between the worsening and no worsening DM groups

Variable	Effect Size	OR	P value
Gender (male vs female)	-0.243	0.784	0.718
InSTI:			
EVG	REF		
DTG	-0.677	0.578	0.453
BIC	0.036	4.5	0.971
TAF	1.352	3.864	0.107
Age	-0.008		0.809
Weight Change	2.246		0.382
Region of Origin:			
North America	REF		
Africa	-0.405	0.667	0.585
Caribbean	0.065	1.067	0.947

OR, odds ratio; EVG elvitegravir; DTG, dolutegravir; BIC, bictegravir; TAF, tenofovir alafenamide

Objective #2: Clinical characteristics for Worsening DM

When factors were compared between the worsening and stable DM groups (age, gender, region of origin, specific InSTI used, TAF use with InSTI, no significant differences were found.

Objective #3: Management and Impact

Of 74 patients who experienced an outcome, follow-up HbA1c was obtained in 53 patients (71.6%).

51 patients (96.2%) had an intensification of antihyperglycemic
- 8 patients (15.1%) had a new start of insulin

17 patients (32.1%) changed ARV regimens
10 patients (18.9%) discontinued the InSTI class

RESULTS CONT.

Objective #3: Management and Impact Cont.

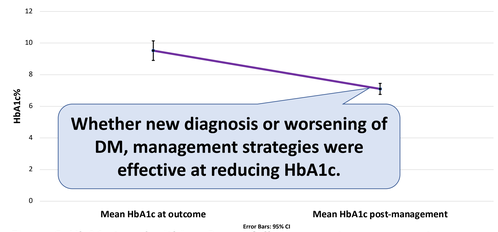

Figure 6. HbA1c trend within a 2-year follow-up post-management

DISCUSSION

- We report a total of 74 patients (86.0%) in our cohort of PLWH and DM who either had a new diagnosis (40.7%) or worsening (45.3%) of their DM following the initiation of an InSTI-based regimen.
- Increases in HbA1c and weight gain were clearly identified in patients who experienced an outcome.
- We were unable to identify specific risk factors that are associated with those who had a worsening of DM.
- Finally, management strategies that included changes in ARV and intensification of DM medications were successful in decreasing HbA1c.

Limitations:

1) We have no control group for those who experienced a new diagnosis (i.e patients on InSTI regimens who did not develop diabetes). Therefore, we were unable to calculate an incidence.
2) As this is an observational study, our participants were not randomized. Patients' lifestyles and family history were largely unknown and therefore, we cannot rule out contributing confounders such as physical activity, other drugs, diet, genetics, etc.
3) There were patients who had InSTI exposure prior to the defined baseline of the study. Therefore, there is uncertainty in these patients regarding which InSTI would correspond to the outcome.
4) There was a limitation in sample size to detect a significant difference in factors between the worsening (n=39) and stable DM (n=12) groups.

CONCLUSION

Given our observations, we encourage close monitoring of patients who are on InSTI-based ARV for impaired glucose homeostasis. Larger population studies with matched control groups would provide a better understanding of the risks related to specific InSTI agents, and the influence of known covariates (i.e., lifestyle, other drugs, genetics etc.) on metabolic conditions.

Disclosures:
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Click here for References.

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