Dolutegravir and Insulin Resistance

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Introduction

- Insulin resistance (IR) is a condition in which a greater than normal amount of insulin is required to obtain a quantitatively normal glucose response and can be assessed by homeostasis model of assessment (HOMA)–IR as a surrogate marker
- HIV infection has been independently associated with IR, potentially through chronic immune activation/inflammation[1]
  - This effect is not necessarily mitigated through successful antiretroviral therapy (ART)[2]
- ART has been associated with IR through 2 principal mechanisms[3]
  - Interference with insulin signaling at the cellular level
  - Defects in lipid metabolism (eg, as seen with lipodystrophy)
- In the context of combination ART, increased obesity, and an aging population with HIV infection, potential associations of an individual antiretroviral with IR are difficult to evaluate

Objective

- Evaluate the association between baseline HOMA-IR and patient/disease characteristics
- Explore risk factors associated with IR post-baseline
- Evaluate any effect of DTG on IR over time compared with control

Methods

- 4 dolutegravir (DTG) clinical trials with fasting insulin and glucose measurements available were identified and included in the analysis: SPRING-1, STRIIVING, and SWORD-1/-2
- Participants with diabetes at baseline and those participants without results for glucose and insulin at either baseline or post-baseline timepoints were excluded from the analysis
- IR was determined by HOMA mathematical model calculated from the measurement of fasting insulin compared with fasting glucose using formula [insulin (μU/mL) × glucose (mmol/L)/22.5]
- There is no well-defined HOMA-IR cut-off established to be clinically relevant
  - For this analysis, a cut-off of 2 was used, with additional cut-offs of 3 and 4 used for sensitivity
- Analysis of relationship between baseline risk factors and HOMA-IR was completed
- Analysis of covariance (ANCOVA) calculated change from baseline for HOMA-IR by examining the ratio between log HOMA-IR value at Weeks 24 and 48 compared with baseline
- Relationship between potential risk factors and the proportion of participants with HOMA-IR cut-off >2, 3, or 4 was explored using a logistic regression model
  - Basic and multivariable logistic regression models were used

Results

- Table 1 shows the study details, treatment groups, participant numbers for analysis, and the timepoints of data available
  - SPRING-1 evaluated different doses of DTG; all doses were pooled for analysis of the DTG arm
- HOMA-IR data were available at baseline, Week 24, and Week 48 for 824, 304, and 543 DTG-exposed participants and 713, 219, and 460 controls, respectively
- Participants were mostly men (81%), white (76%), and from Europe or North America (92%), with a median age of 43 years (range, 20-80 years)
- Approximately 50% of the population were overweight or obese at baseline based on body mass index (BMI)
- Table 2 shows additional demographic and baseline characteristics
- Prevalence of IR at baseline based on different HOMA-IR thresholds is shown in Figure 1
  - Overall, 70% of participants had a HOMA-IR >2 at baseline
- An association between baseline HOMA-IR >2 and the following baseline factors was noted
  - Increasing age, geographic region (higher in participants in North America and Europe compared with the rest of the world), increased BMI and body weight, presence of a metabolic or cardiac disorder, lipid abnormalities, and abnormal liver function tests (alanine transaminase [ALT], albumin, and alkaline phosphatase)

Table 1. Treatment Groups, Participant Populations, and Data Timepoints by Study

Study number	Population	Actual treatment groups	No. of participants analyzed[a] DTG vs control	Baseline	Week 24	Week 48
ING112276 SPRING-1	ART naive	DTG (10, 25, and 50 mg once daily) vs EFV	137 vs 43	X	X	X
201636/ 201637 SWORD-1/-2	ART experienced, suppressed	DTG 50 mg + RPV 25 mg vs CAR	460 vs 453	X		X
201147 STRIIVING	ART experienced, suppressed	Early-switch DTG/ABC/3TC vs late-switch DTG/ABC/3TC	227 vs 217	X	X	

[a]Participants with available data at baseline (not all participants have data post-baseline).
ABC, abacavir; ART, antiretroviral therapy; CAR, current ART; DTG, dolutegravir; EFV, efavirenz; 3TC, lamivudine; RPV, rilpivirine.

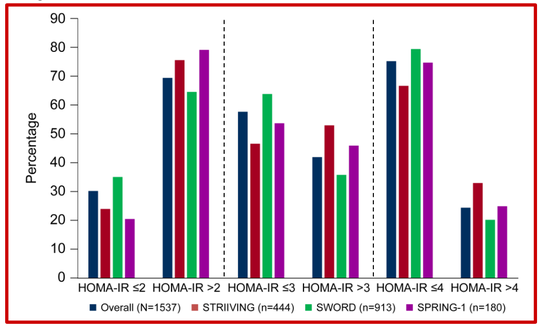
Table 2. Demographic and Baseline Characteristics

Variable	Participants, n (%) N=1537
Previous exposure to antiretroviral therapy	
Experienced (from SWORD and STRIIVING studies)	1357 (88.3)
Naive (from SPRING-1)	180 (11.7)
Third agent class[a]	
Integrase strand transfer inhibitor	301 (19.6)
Non-nucleoside reverse transcriptase inhibitor	623 (40.5)
Protease inhibitor	433 (28.2)
Body mass index category 1, kg/m^2	
Underweight: <18.5	28 (1.8)
Normal: 18.50-24.99	739 (48.1)
Overweight: 25.00-29.99	504 (32.8)
Obese: ≥30	260 (16.9)
Smoking history	
Current	475 (30.9)
Former	276 (18.0)
None	786 (51.1)
High blood pressure, mm Hg	
<140/90	1449 (94.3)
≥140/90	88 (5.7)
Cardiovascular treatment	
Yes	383 (24.9)
No	1154 (75.1)

[a]SWORD and STRIIVING studies only (N=1357).

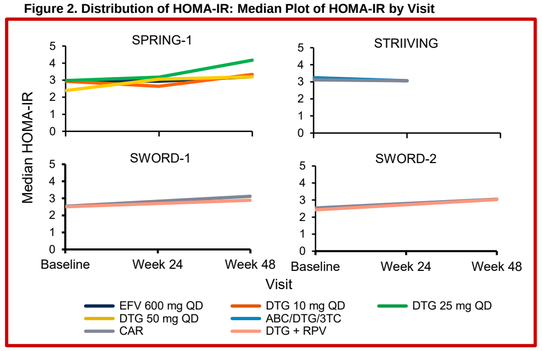
- Unadjusted median HOMA-IR by study and timepoint are shown in Figure 2
  - There are no clear shifts in median HOMA-IR over time that are consistent across all 4 studies
  - In SPRING-1, in which 3 different doses of DTG were given (10, 25, and 50 mg), a modest increase was observed in median HOMA-IR from baseline to Week 48 with the 25-mg dose that was not apparent in the other 2 dose groups or the control group
    - Median HOMA-IR in this dose group decreased from Week 48 to Week 96, tending toward the baseline value

Figure 1. HOMA-IR Assessments at Baseline



HOMA, homeostasis model of assessment; IR, insulin resistance.

Figure 2. Distribution of HOMA-IR: Median Plot of HOMA-IR by Visit



ABC, abacavir; ART, antiretroviral therapy; CAR, current antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; HOMA, homeostasis model of assessment; IR, insulin resistance; 3TC, lamivudine; QD, once daily; RPV, rilpivirine.

- Table 3 shows results for changes in HOMA-IR over time (logistic regression) and relative to controls (ANCOVA)
  - ANCOVA of HOMA-IR demonstrated no statistically significant difference between DTG and control treatment groups at Week 48 using either the basic or full multivariate model
  - Both groups showed a similar modest increase in HOMA-IR from baseline by Week 48 (least squares means estimated)
  - No statistically significant difference was observed between the study examined and IR or between DTG and control treatment groups or study at Week 24
  - Consistent with the ANCOVA, logistic regression analysis showed no association between treatment (DTG vs control) and HOMA-IR >2, >3 or >4 at Week 48; proportion of participants with IR was similar between DTG and control groups irrespective of the HOMA-IR cut off used
    - Same observations were made for Week 24 analysis
    - Treatment-emergent changes in HOMA-IR were not assessed
- Risk factors for HOMA-IR >2 at Week 48: baseline HOMA-IR, female sex, higher BMI, AIDS Centers for Disease Control and Prevention category, smoking history, and elevated ALT

Table 3. Changes in HOMA-IR Over Time and Relative to Controls

			ANCOVA analysis			Logistic regression analysis		
Study timepoint	Arm	n	LS means estimates (SE)[a]	Geometric LS mean ratio (95% CI)[b]	*P* value	HOMA-IR >2/n	Odds ratio (95% CI)	*P* value
Overall Week 48[c]	Control	460	1.18 (0.024)			360/460		
	DTG	543	1.16 (0.022)	0.98 (0.92-1.04)	0.497	413/543	0.81 (0.57-1.14)	0.222
SPRING-1 Week 24	Control[d]	35	1.07 (0.090)			29/35		
	DTG	125	1.02 (0.047)	0.95 (0.77-1.16)	0.583	98/125	0.46 (0.12-1.45)	0.215
SPRING-1 Week 48	Control[d]	38	1.06 (0.092)			29/38		
	DTG	123	1.13 (0.050)	1.07 (0.86-1.32)	0.546	99/123	0.20 (0.03-1.16)	0.086
STRIIVING Week 24[e]	Control[f]	184	0.97 (0.046)			131/184		
	DTG	179	1.05 (0.046)	1.07 (0.95-1.22)	0.273	147/179	1.86 (1.08-3.23)	0.027
SWORD-1/-2 Week 48	Control[f]	422	1.21 (0.024)			331/422		
	DTG	420	1.15 (0.024)	0.95 (0.89-1.02)	0.161	314/420	0.78 (0.55-1.11)	0.167

HOMA-IR formula: [insulin (μU/mL × glucose (mmol/L)/22.5]. [a]Geometric LS mean ratio estimates the LS ratio at the analysis timepoint over baseline values. The following baseline characteristics were selected from the final ANCOVA model as potential risk factors for the development of IR at Week 48: baseline HOMA-IR, female sex, bodyweight, immune disorder, and increased triglycerides, ALT, and viral load. [b]Baseline characteristics selected from the final logistic model as potential risk factors for developing IR at Week 48: baseline HOMA-IR, female sex, body mass index, smoking history, immune disorder, elevated ALT, and increased viral load. [c]Includes SPRING-1 and SWORD studies. [d]Efavirenz. [e]Only Week 24 data are presented as all participants switched to DTG after this timepoint. [f]Current antiretroviral therapy (boosted protease inhibitor, integrase strand transfer inhibitor, NRTI, non-NRTI).
ALT, alanine transaminase; ANCOVA, analysis of variance; CI, confidence interval; DTG, dolutegravir; HOMA, homeostasis model of assessment; IR, insulin resistance; N, number of participants with evaluable HOMA-IR data at baseline and analysis time point; LS, least squares; NRTI, nucleoside reverse transcriptase inhibitor; SE, standard error based on log scale.

Limitations

- These results should be interpreted with caution because the studies were not primarily designed to assess effects of DTG exposure on IR
  - These analyses are exploratory, and logistic regression and ANCOVA were not adjusted for multiplicity
- In SWORD-1/-2, 33 participants (6%) in the early-switch group and 29 participants in the late-switch group were taking a DTG-containing regimen prior to baseline; in STRIIVING, 1 patient was already taking a DTG-containing regimen
  - These patients were not excluded from the analysis, but it is not anticipated that these small numbers should impact the interpretation of the results

Conclusions

- High prevalence of IR (70% with HOMA-IR >2) at baseline was observed and consistent across the 4 studies
- Numerical increase in HOMA-IR was observed for DTG and control groups, but differences between groups were not statistically significant, with no evidence of a treatment effect over 48 weeks
  - Increase in HOMA-IR over time is not surprising in this population, because many participants had elevated HOMA-IR at baseline and were at increased risk of worsening IR
- Incidence of IR was similar in DTG and control arms irrespective of HOMA-IR threshold
- In general, potential risk factors identified as being associated with IR at Week 48 were consistent with known risk factors for diabetes and IR

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References: 1. Brener et al. *Am Cardiol.* 2018;117:993-1000. **2.** Hunt et al. *J Infect Dis.* 2016;214:S44-S50. **3.** Feeney et al. *Best Pract Res Clin Endocrinol Metab.* 2011;25:443-458.