Neuropsychiatric Adverse Events Associated With Integrase Strand Transfer Inhibitors

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ABSTRACT

Background
The increased use of INSTI based regimens over PI or NNRTI based regimens is largely due to the perceived safety and potency of INSTIs. Case reports of new-onset or worsening of neuropsychiatric conditions, particularly depression and suicidality, have emerged with INSTIs. These reports prompted FDA to investigate the relationship between INSTIs and neuropsychiatric adverse events (NPAE), and compare the frequency of NPAEs with INSTIs, PIs and EFV.

Methods
FDA conducted a meta-analysis of randomized, active-controlled Phase 3 trials in treatment-naïve subjects (TN) comparing raltegravir, dolutegravir or elvitegravir to: EFV, PIs (atazanavir or darunavir), or another INSTI. These trials were submitted by industry to FDA to support approval of the INSTIs. The frequency of NPAEs in each treatment group was assessed over 96 weeks. NPAEs were identified using the Standardized MedDRA Query (SMQ) Version 18.0. A broad search for terms in the Depression and Suicide/Self-Injury (DSS) SMQ and the Psychosis and Psychotic Disorders (PPD) SMQ was done. The event of highest toxicity grade was counted for each subject.
Overall risk difference for INSTI vs EFV and INSTI vs PI was computed based on fixed effects and random effects analyses using inverse variance weights in both models. In the random effects model (DerSimonian-Laird estimate), the study variable was included as a random effect. Analyses were also performed by demographic subgroups (age, sex, race, region, and IV drug use).

Results
The meta-analysis shows the risk of NPAE in TN patients was similar for INSTI vs EFV and INSTI vs PI. The risk difference (95% CI) for DSS AEs and PPD AEs was: INSTI vs EFV -3% (-5,0) and -1% (-2,1) and INSTI vs PI -1% (-2,4) and 0% (-2,1). Results were identical for the fixed and random effects analyses. Grade 3 and 4 events occurred in 1% of INSTI and PI subjects and 2% of EFV subjects. Subgroup analyses were not interpretable due to small sample size. *(Table 2)*

Conclusions
This meta-analysis shows the risk of NPAE when analyzed at the level of pooled DSS and PPD SMQs was similar between INSTIs vs EFV, with a trend toward lower risk with INSTIs compared with EFV. The risk for NPAEs is similar between INSTIs and PIs. Although NPAEs were infrequent and risk was not increased with INSTIs, providers should be aware of the association between HIV infection, ART, and NPAEs.

BACKGROUND

- There are currently 3 FDA approved Integrase Strand Transfer Inhibitors (INSTIs): raltegravir (RAL, approved 2007), elvitegravir (EVG, approved 2012 in a fixed dose combination tablet), and dolutegravir (DTG, approved 2013).
- INSTIs are a component of most Recommended ART regimens in The Department of Health and Human Services HIV Treatment Guidelines for adults and adolescents [1], primarily because of their potent anti-viral activity and favorable safety profile, as characterized in clinical trials.
- However, neuropsychiatric adverse events (NPAEs) were reported both pre- and post-marketing, including published reports in the medical literature describe new-onset or worsening of NPAEs among patients treated with INSTIs [2,3,4].
- FDA conducted a meta-analysis of clinical trial data to further evaluate the association between INSTIs and NPAEs.

METHODS

Trial Design and Population

- FDA conducted a meta-analysis of 5 randomized, double-blind, active-controlled Phase 3 trials in treatment-naïve subjects (TN) comparing INSTIS (RAL, EVG, DTG) to efavirenz (EFV) or ritonavir-boosted protease inhibitors: atazanavir or darunavir (ATV/r, DRV/r) [Table 1]
- Trials that did not have a head-to-head comparison of the treatments of interest were not included in the meta-analysis.
- NPAEs during the first 96 weeks of treatment were identified using a broad search for preferred terms in two Standardized MedDRA Queries (SMQs) Version 18.0:
  - 1) Depression and Suicide/Self-Injury (DSS SMQ)
  - 2) Psychosis and Psychotic Disorders (PPD SMQ)
- The adverse event of highest toxicity grade was counted for each subject.

Table 1: Summary of Trials

Trial	Treatment Groups	Total Subjects
STARTMRK (Protocol 021)	**RAL** + FTC/TDF (n=281) **EFV** + FTC/TDF (n=282)	563
GS-US-236-0102	**EVG**/COBI/FTC/TDF (n=348) **EFV** + FTC/TDF (n=352)	700
GS-US-236-0103	**EVG**/COBI/FTC/TDF (n=353) **ATV/r** + FTC/TDF (n=355)	708
SINGLE (ING 114467)	**DTG** + ABC/3TC (n=414) **EFV** + FTC/TDF (n=419)	833
FLAMINGO (ING 114915)	**DTG** + ABC/3TC or FTC/TDF (n=243) **DRV/r** + ABC/3TC or FTC/TDF (n=242)	485
SPRING-2† (ING 113086)	**DTG** + ABC/3TC or FTC/TDF (n=403) **RAL** + ABC/3TC or FTC/TDF (n=405)	808

†Data were not used in the meta analysis but included in the secondary analysis

Meta-Analysis

- The primary analysis is based on a meta-analysis with fixed effects. This model assumes a common effect size shared by all the studies (no heterogeneity across the studies). The estimate of the overall risk difference was computed as a weighted average of the study specific risk differences. Studies with smaller variance were given more weight.
- As a sensitivity analysis, a meta-analysis with random effects (DerSimonian-Laird method) was performed. The model estimates were adjusted to incorporate a measure of the variability across studies.

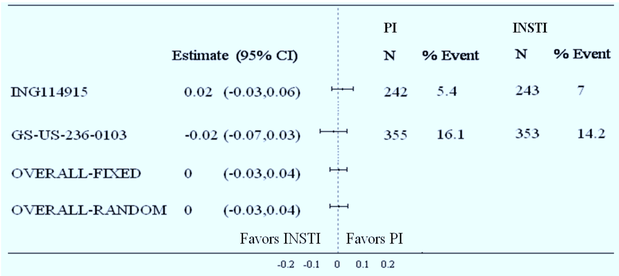
Supportive Analysis

- FDA conducted a supportive analysis comparing the proportion of subjects with NPAEs among the three treatment groups: INSTI, EFV, and PI.
- This analysis was performed with data from the 5 clinical trials included in the meta-analysis, plus SPRING-2.

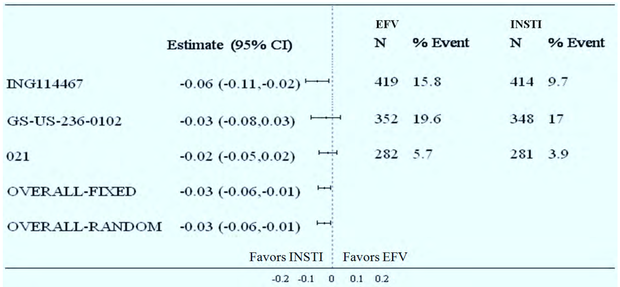
RESULTS

- Results of the meta-analysis are presented in forest plots below:

DSS + PPD SMQ Broad Search: PI vs INSTI



DSS + PPD SMQ Broad Search: EFV vs INSTI



- Risk Difference (95% CI) for NPAEs in the DSS and PPD SMQs:
  - DSS: INSTI vs EFV -3% (-5,0); INSTI vs PI -1% (-2,4)
  - PPD: INSTI vs EFV -1% (-2,1); INSTI vs PI 0% (-2,1)
- The majority of NPAEs were in the DSS SMQ. PPD events were infrequent:
  - Percent of Subjects with DSS events: INSTI 9.5%, PI 10.9%, EFV 13.1%
  - Percent of Subjects with PPD events: INSTI 0.4%, PI 0.9%, EFV 1.4%
- Results of the secondary analysis are summarized in Table 2.

Table 2: Summary of Frequently Reported NPAEs (Unweighted Totals)

	INSTI vs PI			INSTI vs EFV		
Pooled NPAEs (All Grades, All Cause)	**INSTI N=2447**	**PI N=597**	**Risk Difference (95% CI)**	**INSTI N=2447**	**EFV N=1053**	**Risk Difference (95% CI)**
Depression	174 (7.1%)	51 (8.5%)	-1.4% (-3.9%, 1.0%)	174 (7.1%)	101 (9.6%)	-2.5% (-4.5%, -0.5%)
Sleep Disorders	10 (0.4%)	0	0.4% (0.2%, 0.7%)	10 (0.4%)	12 (1.1%)	-0.7% (-1.4%, 0%)
Suicidal Thoughts and Behaviors	14 (0.6%)	1 (0.2%)	0.4% (0%, 0.8%)	14 (0.6%)	2 (0.2%)	0.4% (0%, 0.8%)
Memory Impairment	13 (0.5%)	5 (0.8%)	-0.3% (-1.1%, 0.5%)	13 (0.5%)	3 (0.3%)	0.2% (-0.2%, 0.7%)

- Grade 3 and 4 events were reported in 1% of subjects in the INSTI and PI cohorts and 2% of subjects in the EFV cohorts.
- Subgroup analyses included sex, age, race, geographic region, and history of intravenous drug use. These analyses were not interpretable due to small sample size in some groups.

CONCLUSIONS

- Results of the meta-analysis demonstrate that the risk of NPAEs is similar for subjects treated with INSTIs compared to EFV, with a trend toward lower risk with INSTIs relative to EFV.
- The risk for NPAEs is similar between INSTIs and PIs.
- Depression was the most frequently reported NPAE in all three ARV classes and accounts for the majority of NPAEs observed overall.
- Severe and life threatening events were infrequent across all trials and treatment groups.
- The analyses were unable to identify subgroups at increased risk for NPAEs.
- The relationship between ART and NPAEs remains confounded by numerous factors that were not evaluated, including exposure to concomitant medications, presence of pre-existing neuropsychiatric illness, and social stressors.
- In conclusion, although NPAEs were infrequent and risk was not increased with INSTIs, providers should be aware of the association between HIV infection, ART, and NPAEs.

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