TUPEB256

Adverse drug reactions associated with integrase strand transfer inhibitors (INSTI) in clinical practice: Post-marketing experience with raltegravir, elvitegravir-cobicistat and dolutegravir.

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Background

- The **integrase strand transfer inhibitors (INSTI)** have demonstrated safety and efficacy in clinical trials.
- This observational study compares **adverse drug reactions (ADRs)** reported with raltegravir, elvitegravir-cobicistat (in a fixed dose combination) and dolutegravir during routine clinical use in British Columbia (BC) Canada.

Methods

NOTE: The interim analysis presented in this poster has been updated to include results from the completed enrollment period 01-Jan-2012 to 31-Dec-14 (previously to 31-Aug-14) and interim follow-up period (extended to 30-Apr-15).

Inclusion criteria

- HIV-1-infected persons, either antiretroviral treatment naïve or treatment experienced.
- Age ≥19 years at the time of INSTI initiation.
- Raltegravir, elvitegravir-cobicistat or dolutegravir initiated as a component of the antiretroviral regimen between 01-Jan-2012 and 31-Dec-2014.
- Patients could contribute data for more than one INSTI.

Data sources

- Clinical, demographic and ADR data: BC Centre for Excellence in HIV/AIDS (BC-CfE) Drug Treatment Program and BC-CfE Pharmacovigilance Initiative.

Follow-up

- All patients had ≥4 months follow-up opportunity until 30-Apr-2015. Planned ≥12 month follow-up opportunity will continue until 31-Dec-2015.

Primary outcome and data analysis

- Primary outcome was any ADR resulting in INSTI discontinuation, excluding suspected ADRs with causality classification assessed as "unlikely".
- ADR incidence density rates and 95% confidence intervals (CI_{95}) were estimated by robust Poisson regression (controlled for under-dispersion) and adjusted for covariates.
- Raltegravir was the reference category for adjusted relative ADR rates.

Results

- Of 1347 INSTI-treated patients, 115/1347 (8.5%) contributed data for ≥2 INSTIs.
- The cohort included 1467 distinct INSTI-patient records: 553 raltegravir, 395 elvitegravir-cobicistat and 519 dolutegravir-treated. See Table 1.

Table 1.

Baseline patient characteristics at time of INSTI initiation

Variable	Raltegravir	Elvitegravir-Cobicistat	Dolutegravir
	N=553	*N=395*	*N=519*
Age, median (IQR) years	50 (43,56)	43 (34,50)	48 (40,55)
Sex, n(%)			
Male	450 (81)	293 (74)	419 (81)
Female	103 (19)	102 (26)	100 (19)
CD4, median (IQR) cells/mm3	440 (230,640)	470 (270,672)	530 (360,740)
Viral Load <50 copies/mL, n(%)	307 (56)	175 (44)	348 (67)
Hepatitis C co-infection, n(%)	251 (45)	147 (37)	138 (27)
Previous ARV therapy, n(%)			
Treatment naïve	73 (13)	84 (21)	69 (13)
Treatment experienced	480 (87)	311 (79)	450 (87)
Co-prescribed ARVs, n(%)			
Tenofovir + 3TC or FTC	197 (36)	345 (87)	111 (21)
Abacavir + 3TC	114 (21)	0 (0)	306 (59)
Other regimen	242 (44)	50 (13)	102 (20)

Abbreviations and definitions: IQR: interquartile range; ARV: antiretroviral; INSTI: integrase strand transfer inhibitor; 3TC: lamivudine; FTC: emtricitabine; Co-prescribed ARVs: ARVs prescribed concurrently with INSTI at time of first prescription; Baseline viral load and CD4: most recent measurement within 6 months before INSTI start date.

- For each INSTI, treatment duration, ADR rates and proportion of patients experiencing an ADR are summarized in Table 2.
- ADR rates are presented as both unadjusted and adjusted (for sex, antiretroviral treatment experience and hepatitis C co-infection) rates.

Results continued

- For each INSTI, treatment duration, ADR rates (unadjusted and adjusted for sex, antiretroviral treatment experience and hepatitis C co-infection) and proportion of patients experiencing an ADR are summarized in Table 2.

Table 2.

Incidence of INSTI adverse drug reactions leading to therapy discontinuation

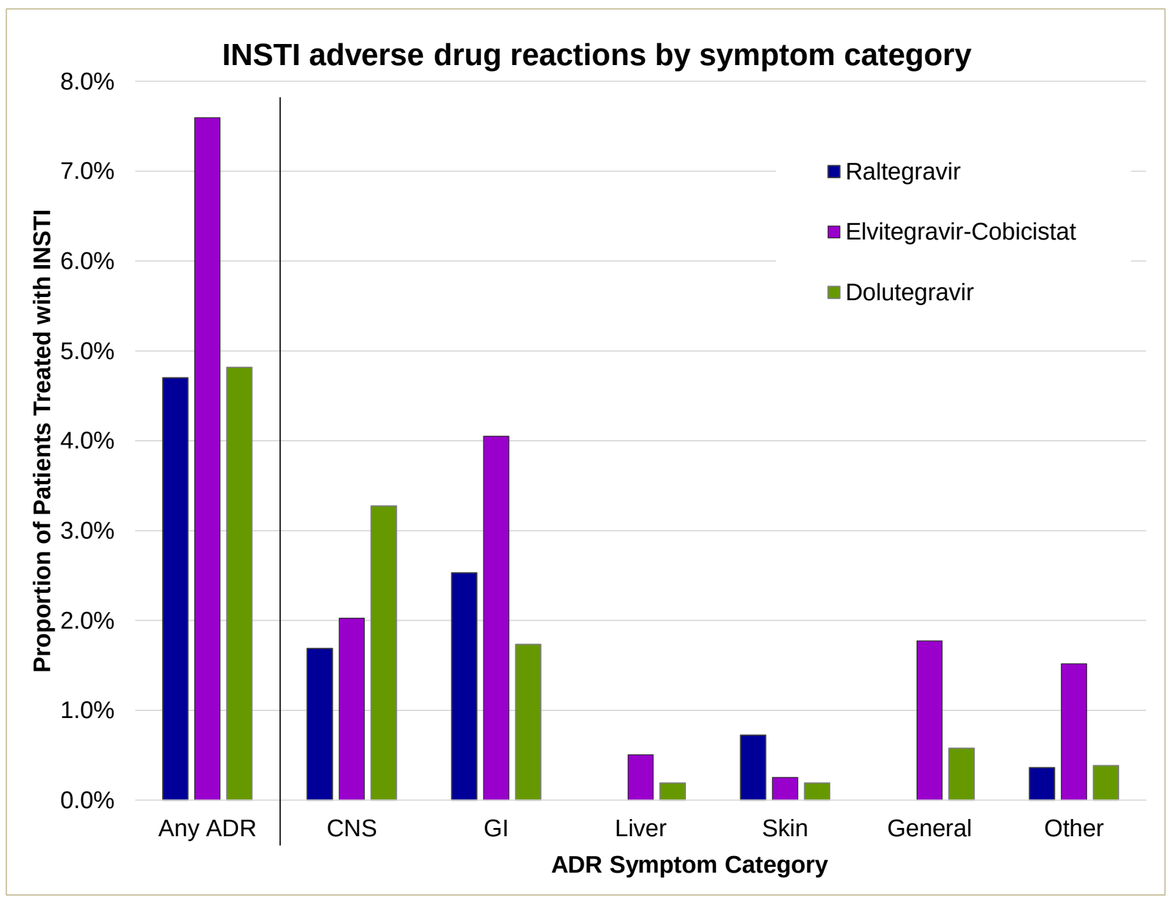
	Raltegravir	Elvitegravir-Cobicistat	Dolutegravir
	N=553	*N=395*	*N=519*
INSTI treatment duration			
Median (IQR) yr	1.2 (0.6,2.0)	0.8 (0.4,1.3)	0.6 (0.4,0.8)
Cumulative person-yr	742	341	331
Number (%) persons with ADR	26 (4.7)	30 (7.6)	25 (4.8)
Unadjusted ADR rate/100 person-yr (CI_{95})	3.5 (2.4-5.1)	8.8 (6.2-12.6)	7.5 (5.1-11.2)
Adjusted* ADR rate/100 person-yr (CI_{95})	1.6 (0.6-4.1)	4.5 (1.7-12.1)	2.9 (1.1- 8.0)

*Poisson regression adjusted by sex, ARV treatment experience and hepatitis C co-infection.

Abbreviations: ADR: adverse drug reaction; INSTI: integrase strand transfer inhibitor; CI_{95}: 95% confidence interval; yr: years

- Adjusted ADR relative rates (CI_{95}) were:
  - Raltegravir (reference category) 1.0
  - Elvitegravir-cobicistat 2.9 (2.8-3.0)
  - Dolutegravir 1.9 (1.8-2.0)

Figure 1.



Abbreviations and definitions: Any ADR: Any adverse drug reaction resulting in therapy discontinuation; INSTI: Integrase strand transfer inhibitor; ADR Symptom Category: Counting 1 symptom per category per patient INSTI-ADR record; CNS: central nervous system, GI: gastrointestinal, General: non-specific symptoms e.g. fatigue, malaise, pain.

- As shown in Figure 1, the most commonly reported ADR symptoms were:
  - Gastrointestinal tract: Nausea, diarrhea, gastrointestinal discomfort.
  - Central nervous system: Sleep disturbance, nightmares, headache.
  - General: fatigue/ malaise (more common with elvitegravir-cobicistat.
- No serious ADRs (grade IV severity or leading to hospitalization) were reported.

Conclusion

- All INSTI were generally well tolerated.
- The newer INSTIs elvitegravir-cobicistat and dolutegravir had shorter follow-up times than raltegravir, but had relatively higher rates of ADRs resulting in therapy discontinuation in this interim analysis.
- The planned 12 month follow-up of this cohort will continue until 31-Dec-2015.

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