ARV Therapies and Therapeutic Strategies

REPORTING ON IAS 2015

Comprehensive Expert Review and Discussion of Key Presentations

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Adverse Drug Reactions Associated with Integrase Stand Transfer Inhibitors (INSTI) in Clinical Practice: Post-Marketing Experience with Raltegravir, Elvitegravir-Cobicistat and Dolutegravir

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Abstract TUPEB256

Background

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

Methods

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

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 20-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

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Results

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)
Number (%) persons with ADR	26 (4.7)	30 (7.6)	25 (4.8)
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 naive	73 (13)	293 (74)	419 (81)
Treatment experienced	480 (87)	102 (26)	100 (19)
Co-prescribed ARVs, n(%)			
Tenofovir+3TC or FTC	197 (36)	340 (87)	111 (21)
Abacavir+3TC	114 (21)	0 (0)	306 (59)
Other regimen	242 (44)	50 (13)	102 (20)

- For each INSTI, treatment duration, ADR rates and proportion of patients experiencing and ADR are summarized on next slide
- ADR rates are presented as both unadjusted and adjusted (for sex, antiretroviral treatment experience and hepatitis C co-infection) rates

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.

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Results Continued…

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 Cumulative person-yr	 1.2 (0.6, 2.0) 742	 0.8 (0.4, 1.3) 341	 0.6 (0.4, 0.8) 331
Number (%) persons with ADR	26 (4.7)	30 (7.6)	25 (4.8)
Unadjusted ADR rate/100 person-yr (CI95)	3.5 (2.3-5.1)	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)

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)

*Poisson regression adjusted by sex, ARV treatment experience and hepatitis C co-infection.
Abbreviations: ADR: adverse drug reaction; INSTI: integrase strand transfer inhibitor; CI95: 95% confidence interval; yr: years

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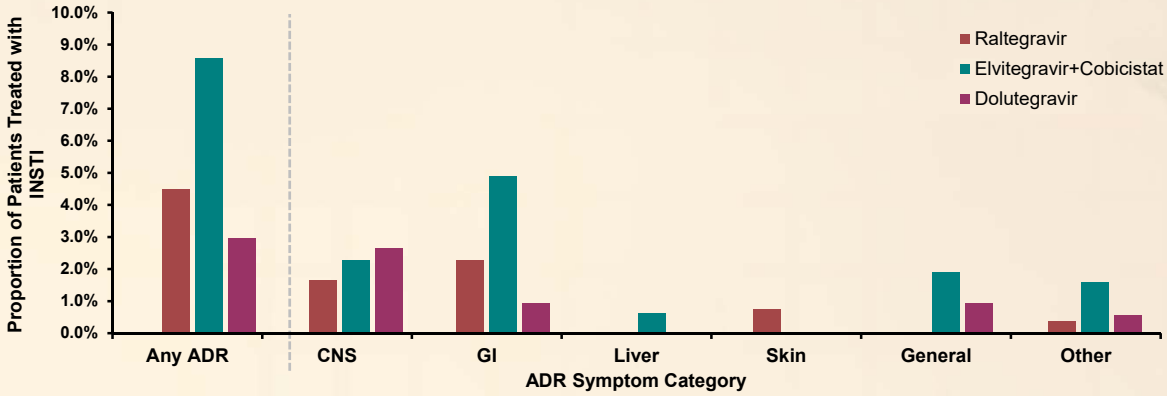
BC Experience: INSTI Adverse Drug Reactions

INSTI Adverse Drug Reactions by Symptom Category



- Adjusted ADR rates (CI 95) per 100 person-years were: Raltegravir 1.88 (0.72-4.93), elvitegravir-cobicistat 5.76 (2.14-15.49), and dolutegravir 3.34 (1.19-9.40).
- The adjusted RR (CI95) of ADR relative to raltegravir was 3.06 (2.97-3.14) for elvitegravir-cobicistat and 1.78 (1.65-1.91) for dolutegravir

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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 the interim analysis
- The planned 12 month follow-up of this cohort will continue until 21-Dec-2015

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