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Prevalence and Incidence of Integrase Drug Resistance in BC, Canada 2009-2015

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Background

In British Columbia (BC), Canada, use of the integrase inhibitors (INI) in antiretroviral therapy (ART) regimens has increased rapidly in recent years.

The objective of this study was to characterize the evolution of incident and prevalent INI drug resistance mutations from 2009 to 2015, and test the hypothesis that prevalence of INI mutations has increased over time.

To provide context, the prevalence of drug resistance mutations to HIV protease inhibitors (PI) and reverse transcriptase inhibitors (RT) was examined during the same time period.

Methods

Inclusion criteria: HIV-1-infected persons age ≥19 years were included if they received ART through the BC Centre for Excellence in HIV/AIDS (BC-CfE) Drug Treatment Program between 01-Jan-2009 and 31-Oct-2015. In each year, persons were counted as "ART-treated" and the subset of "INI-treated" if they had at least one dispensed prescription for any ART or any INI (respectively) in the calendar year.

Drug resistance: The study included physician-ordered drug resistance tests analyzed at the BC-CfE Research Laboratory, with sample dates up to 31-Oct-2015. Persons with INI, PI or RT resistance were defined as those having at least one sample with score ≥30 (intermediate or high level resistance) by the Stanford HIV drug resistance algorithm v7.0.1.

Prevalence: ART-treated persons contributed INI, RT and PI resistance data in the first, and each subsequent year following identification of study-defined drug resistance. Annual prevalence/1000 ART-treated persons was calculated at year end (31-Oct in 2015). Changes in prevalent resistance over time were tested for trend (generalized additive model, R© v3.2.2).

Incidence: Incident cases of INI resistance were counted in the first year they appeared and were categorized by the INI temporally associated with new resistance: raltegravir, elvitegravir, dolutegravir, or unclassifiable (resistance pre-dated INI use in BC).

Results

Figure 1 shows the increase in INI use from 10% of ART treated persons in 2009 (540 raltegravir-treated) to 32% in 2015 (N= 978 raltegravir, 500 elvitegravir and 1011 dolutegravir).

While the majority of ART-treated persons have been tested for PI and RT drug resistance, physician-ordered INI resistance testing has lagged behind the uptake of INI therapy.

Fig. 1: Antiretroviral Therapy and Drug Resistance Testing

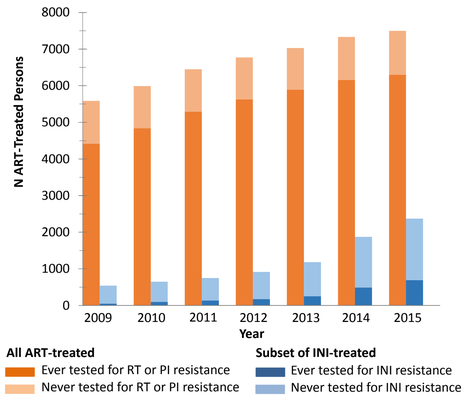
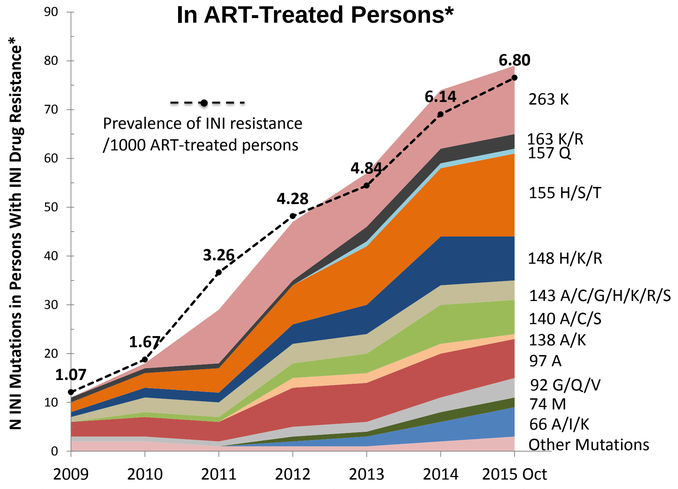


Fig. 2: Prevalence of Integrase Drug Resistance Mutations In ART-Treated Persons*



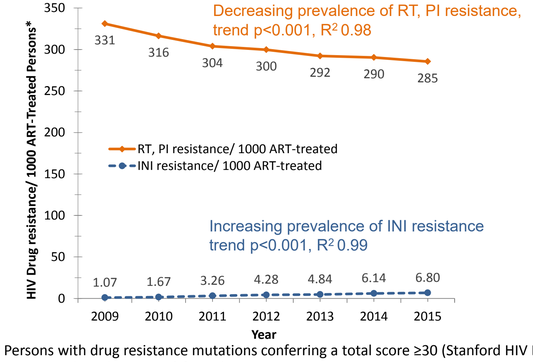
* Persons with drug resistance mutations conferring a total score ≥30 (Stanford HIV Drug Resistance Algorithm v.7.0.1) for at least one INI. For each person, cumulative INI mutations were reported in the first and each subsequent year following detection of drug resistance.

In BC, a total of 57 persons with intermediate or high level INI resistance were identified January 2009 to October 2015.

Figure 2, above, depicts the evolution of prevalent INI mutations, with an apparent increase in selection of mutations at integrase codons 66, 140, 148, 155 and 263.

Figure 3, below, shows that although the prevalence of INI resistance is increasing, INI resistance remains low in comparison to RT and PI resistance.

Fig. 3: Prevalence of Drug Resistance



* Persons with drug resistance mutations conferring a total score ≥30 (Stanford HIV Drug Resistance Algorithm v.7.0.1) for at least one INI, RT or PI.

Fig. 4: Incidence of Integrase Drug Resistance in the Context of Integrase Inhibitor Use

Fig. 4a: Integrase Inhibitor Use

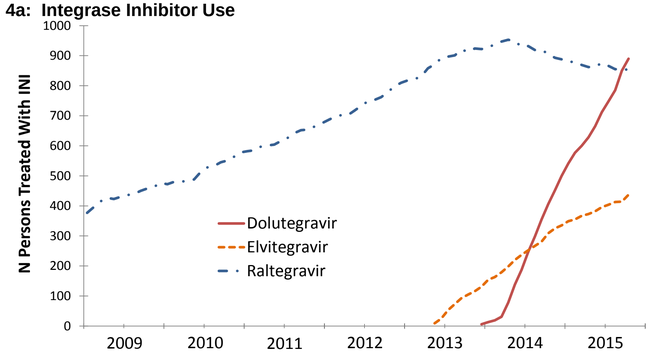


Fig. 4b: Newly Identified Cases of Integrase Resistance*

Year	2009	2010	2011	2012	2013	2014	2015
INI associated with resistance	N=6 n	N=4 n	N=12 n	N=8 n	N=8 n	N=11 n	N=8 n
Dolutegravir	-	-	-	-	-	-	3
Elvitegravir	-	-	-	-	-	2	3
Raltegravir	6	3	9	8	7	7	2
Unclassifiable	-	-	3	-	1	2	-

* ART-treated persons contributed data in the first year INI resistance mutations conferring a total score ≥30 (Stanford HIV Drug Resistance Algorithm v.7.0.1) for at least one INI were identified.

Until 2013, most new cases of INI resistance were associated with use of raltegravir, the only INI available in BC at that time (see Figures 4a and 4b).

In 2014 and 2015, 8/19 (42%) new INI resistance cases followed elvitegravir or dolutegravir use:

Five cases were associated with elvitegravir use in treatment-experienced persons (mutations: two 66A/I and one each 92Q, 145S, 147G).

Three cases of INI resistance emerged during dolutegravir therapy. Two were treatment experienced persons who developed mutation 263K. One treatment-naïve person treated with an initial ART regimen of dolutegravir-abacavir-lamivudine developed mutation 66I.

Conclusion

The prevalence of INI resistance remains low compared to RT and PI resistance, but is increasing with expanded INI use. Emergent INI resistance has been observed during treatment with raltegravir, elvitegravir and dolutegravir in ART naïve and experienced patients.

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