BRITISH COLUMBIA CENTRE for EXCELLENCE in HIV/AIDS
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Pharmacovigilance Initiative
SAFETY ALERT
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Drug resistance emerging during therapy with dolutegravir and other integrase inhibitors

Safety signal

At least three B.C. patients have developed new integrase resistance mutations affecting dolutegravir and/or raltegravir and elvitegravir which emerged during treatment with dolutegravir 50 mg daily plus abacavir-lamivudine. Two of the three patients also developed new resistance to lamivudine and abacavir. One patient was treatment naïve and two were treatment experienced. None had previously documented drug resistance. Two of these patients achieved virologic suppression followed by rebound, while one never achieved a viral load <40 c/mL. Drug resistance emerged within 8-12 months after starting the dolutegravir-based regimen. Incomplete medication adherence appeared to be a contributing factor.

Background

- The integrase inhibitors include:
  - Raltegravir, (Isentress™).
  - Elvitegravir (in Stribild™ with booster cobicistat and tenofovir-emtricitabine).
  - Dolutegravir (Tivicay™, and in Triumeq™ with abacavir-lamivudine).
- Raltegravir and elvitegravir have a relatively moderate genetic barrier to developing drug resistance and there is high potential for cross-resistance between these two drugs. Emergent integrase resistance has been reported in clinical trials and during post-marketing use.
- Dolutegravir has a relatively higher genetic barrier to drug resistance than raltegravir and elivitegravir. Pre-marketing dolutegravir clinical trials reported no emergent major integrase mutations in treatment naïve persons and low incidence in treatment experienced persons; however, there is limited long-term, post-marketing experience in clinical practice.
- Baseline integrase resistance remains uncommon; however, cases of mutations conferring low-level resistance have been identified in BC.
- Clinical interpretation of integrase resistance mutations is evolving. The latest version of the Stanford database has upgraded the interpretation of resistance associated with certain integrase mutations.

Recommendations to reduce risk of developing drug resistance to integrase inhibitors

Please note: BC Centre for Excellence in HIV/AIDS Therapeutic Guidelines consider integrase inhibitors to be an **alternative therapy option** which may be requested if a preferred agent cannot be used.

- **Use a regimen of ≥3 fully active drugs:** All integrase inhibitors should ideally be prescribed in combination with two additional, fully active antiretroviral drugs. If integrase mutations are present, dolutegravir may be an option, but a dose of 50 mg twice daily is advised in this setting.
- **Caution if drug resistance history is incomplete:** Avoid switching patients from suppressive antiretroviral therapy to an integrase inhibitor-based regimen if drug resistance history is incomplete. Prior to therapy change, request drug resistance tests (including integrase resistance) for viral load samples at pre-treatment baseline and during previous episodes of virologic rebound. Obtain an updated BC-CfE laboratory interpretation of previous resistance test results (see p.2).

- **Monitoring:** Integrase inhibitor regimens typically achieve rapid virologic suppression. If viral load <40 c/mL is not achieved within 3-4 months, assess the patient for medication adherence, possible drug interactions and new or previously unrecognized drug resistance.
- After starting a new regimen, monitor HIV viral load monthly until virologic suppression <40 c/mL is achieved. See Therapeutic Guidelines at www.cfenet.ubc.ca for monitoring guidelines.
- **When and how to order drug resistance testing:** Integrase resistance is not presently included in the standard drug resistance test. Please check both "standard" and "integrase" sections of the requisition if an integrase inhibitor is considered as a treatment option. Downloadable form: www.cfenet.ubc.ca/publications/centre-documents/laboratory-requisition-form-british-columbia
- Drug resistance testing is best performed on viral load samples >250 c/mL. The BC-CfE laboratory will test samples 50-250 c/mL if there is clinical concern of treatment failure.
- Routine *genotypic* testing identifies viral genetic mutations and predicts drug resistance based on an evolving database of known mutations. The interpretation of resistance may change over time. To request a re-interpretation of a previous test: Submit a drug resistance requisition and write "re-interpret" beside the viral load sample date(s) requiring re-interpretation.
- The BC-CfE laboratory also performs case-specific *phenotypic testing* (growing virus in the presence of drug) on a "research use only" basis. Results take at least one month.
  Contact Dr. Richard Harrigan 604-788-0998 for information.

Selected references

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- Molina JM, LaMarca A, Andrade-Villanueva J, et.al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. Lancet Infect Dis 2012; 12: 27–35.
- Cahn P, Pozniak AL, Mingrone H, et.al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet 2013; 382: 700–08.
- Raffi F, Jaeger H, Quiros-Roldan E, et.al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis 2013; 13: 927–35.
- Harrigan PR, Hogg RS, Dong WWY, et.al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. J Infect Dis 2005; 191:339-47.

Thank you for reporting suspected adverse reactions to antiretroviral drugs

The BC Centre for Excellence in HIV/AIDS (BC-CfE) Pharmacovigilance Initiative conducts ongoing monitoring of adverse reactions to antiretroviral drugs in order to identify drug-related problems and alert health care providers and patients regarding safety concerns.

How to report: Complete the adverse reaction section on the HIV drug prescription request (at time of drug therapy change) or ADR form at http://www.cfenet.ubc.ca/hiv-drug-safety/report-drug-reaction.

Contact the BC-CfE Pharmacovigilance Initiative:
Telephone: 604-806-8663 Fax: 604-806-9044 E-mail: ADR@cfenet.ubc.ca

***SAFETY ALERT* editors:**
Ms Katherine Lepik BSc(Pharm), MSc; Research Coordinator, Pharmacovigilance Initiative
Dr. Rolando Barrios MD; Principle Investigator, Pharmacovigilance, Assistant Director BC-CfE

Acknowledgement: Dr. Richard Harrigan, Director, BC-CfE Laboratory Program