Emergence of Integrase Resistance Mutations During Initial Therapy with TDF/FTC/DTG

Jennifer A. Fulcher¹, Yushen Du², Ren Sun², Raphael J. Landovitz¹,³

¹Division of Infectious Diseases, Department of Medicine, ²Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, CA ³UCLA Center for Clinical AIDS Research and Education (CARE), Los Angeles, CA

Background

- Dolutegravir (DTG) has become increasingly recommended as part of first-line HIV treatment regimens due to its tolerability, safety, high-barrier to resistance and paucity of drug-drug interactions
- Most recent DHHS guidelines for treatment of acute or primary HIV infection recommend DTG or a r/PI based regimen due to their robust antiviral activity in the face of high viral load
- The prevalence of INSTI resistance mutations remains low, with most common mutations associated with raltegravir (RAL) and elvitegravir (EVI) as shown below:
  - Q148K ➔ RAL and EVG resistance; DTG resistance >10-fold in combination
  - N155H ➔ RAL and EVG resistance
  - G140S ➔ RAL (100-fold), EVG (100-fold), DTG (10-fold) resistance in combination with Q148
  - E138K/A ➔ RAL (100-fold), EVG (100-fold), DTG (10-fold) resistance with Q148
  - To date, drug resistance to DTG has only been reported in treatment-experienced individuals

Methods

- Clinical laboratory testing (HIV viral load, CD4 count, HIV genotype) were performed in the context of clinical care
- Specimens: Plasma was obtained longitudinally over a one week period during which the patient experienced virologic failure
- Deep sequencing:
  - Viral RNA isolated and cDNA was generated using random hexamers
  - Nested PCR performed for pre-amplification generating a 70 bp amplicon
  - Paired end deep sequencing was performed using Illumina Hiseq 2000

Results

Clinical Course

45 year old man with no past medical history admitted with *Pneumocystis jirovecii* pneumonia and new HIV-1 diagnosis.

- New HIV-1 diagnosis made; initial CD4 T cells 78 (12%) and HIV RNA 1,970,000 copies/ml with genotype:
  - RT gene mutations: V118I, F214L
  - PR gene mutations: E35D, L63P, A71T, A77I
  - IN gene mutations: not tested

- Initiated ART with TDF/FTC plus DTG and discharged home; however, he was readmitted to ICU days later with worsened hypoxia
- HIV RNA upon readmission initially 2,770 copies/ml but then increased to 15,700 copies/ml (Figure 1) despite medication compliance and no co-administered divalent cations
- r/DRV added to ART regimen with repeat genotype:
  - RT gene mutations: M184V, V118I, F214L
  - PR gene mutations: E35D, L63P, A71T, A77I
  - IN gene mutations: G163E

- Pneumonia improved and discharged home with repeat HIV RNA decreased to 320 copies/ml after two weeks
- Currently remains virologically suppressed on TDF/FTC, DTG, RPV (switched from r/DRV to RPV for development of diffuse erythrodern on r/DRV)

Summary

- A unique case of a 45 year old man with new HIV diagnosis who was started on initial therapy with TDF/FTC + DTG
- At start of therapy HIV RNA was 1,970,000 copies/ml followed by expected 3 log decline; however HIV RNA then increased despite medication compliance including directly observed therapy while in hospital (Figure 1)
- Initial HIV genotype (RT and PR) showed polymorphisms only; repeat HIV genotype at time of rising viremia showed emergence of M184V but no IN resistance (Figure 1)
- Paired end deep sequencing analysis of IN 142-165 during the time of virologic infection revealed rapid evolution of mutations associated with INSTI resistance; most notably prevalence of Q148K (20.9%) at time point 3 (Figure 2)
- Further sequencing of other IN regions to investigate mutations (e.g. G140, E138) which confer DTG resistance in combination with Q148K are ongoing

Conclusions

- Rapid emergence of known integrase inhibitor resistance mutations during failure of virologic suppression suggest that INSTI resistance may have contributed to failure on the initial regimen in this case
- To our knowledge, this is the first description of potential DTG resistance emerging on initial therapy

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