500LB

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

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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 regimens 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 (EVG) 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

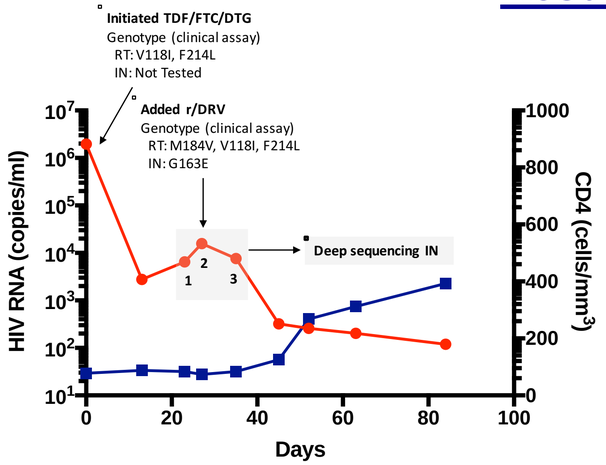

Figure 1. Time course of HIV-1 viremia and CD4 T cells. HIV RNA copies and CD4 T cell counts from clinical labs are plotted from the time of diagnosis and initiation of ART. Time points designated "1, 2, and 3" indicate those used for paired end deep sequencing analysis (Figure 2).

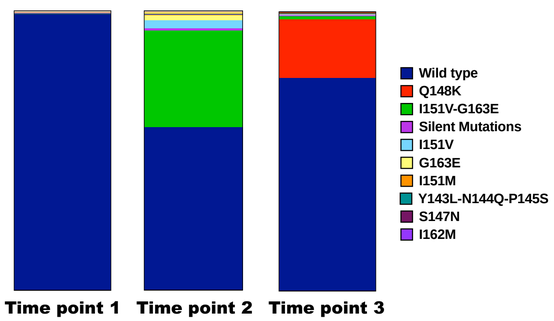

Figure 2. Paired end deep sequencing of IN amino acid region 142-165. Deep sequencing analysis was performed on pre-amplified region of IN from three time points during the period of virologic inflection (Figure 1). Graph shows distribution of genotypes as portion of whole population. Rapid evolution from wild type to Q148K genotype can be seen from time point 1 (0.0015%) to time point 3 (20.9%).

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, V77I
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, V77I
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 erythroderm 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 inflection 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

Acknowledgments

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