Treatment-emergent resistance to bictegravir with minimal risk factors

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Introduction

- Bictegravir is a second generation integrase inhibitor (INSTI), administered in combination with emtricitabine/tenofovir-alafenamide as a single tablet regimen (BFTAF).
- It has demonstrated high rates of viral suppression and a high barrier to resistance when used first-line or in suppressed switch.
- To date, only five cases of resistance to bictegravir have been reported, three with first-line use and two in treatment-experienced people, all with risk factors for resistance development.
- We describe a case of treatment-emergent resistance to bictegravir in a person with minimal risk factors.

Case Report

HIV history

- A 33 year old male presented with constitutional symptoms, diarrhoea, joint pains and chest pain with shortness of breath.
- Following review and investigations by various specialists, Mycobacterium avium-intracellulare (MAI) infection was diagnosed.
- A HIV test was performed, confirming a new diagnosis of HIV, with a baseline viral load (VL) of 6 million copies/ml (wild-type) and CD4 count of 40 cells/mm3 (5%).
- Antiretrovirals (ARVs) commenced soon after diagnosis (see results).
- MAI treatment required four regimen modifications due to toxicities and side effects. MAI treatment was successfully completed with no evidence of recurrence.
- Possible TB IRIS was also treated shortly after starting antiretrovirals, and successfully treated.

Initial response to ARVs

- ARVs **commenced** soon after the HIV diagnosis with tenofovir disproxil fumarate/emtricitabine/dolutegravir.
- The ARVs were **switched** after three days to a tenofovir alafenamide/ emtricitabine /darunavir/cobicistat due to a transient paranoid reaction, acute kidney injury and for simplification.
- At month five the VL was 741, and at six months 4635 with an **isolated M184V detected**. The regimen was changed to tenofovir-AF/emtricitabine/bictegravir/darunavir/ritonavir.
- HIV **viral suppression** was achieved by month eight.

The emergence of R263K

- Subsequent VLs were 486, 112 and 589 with resistance testing showing **M184V and an emergent R263K**.
- Bictegravir was stopped, and tenofovir-AF/emtricitabine/darunavir/ritonavir continued.
- The VL remained **consistently in the thousands**.
- Resistance testing often **failed to amplify** or showed the same pattern (see table 1).

Interventions implemented

- Interventions included administration counselling, drug concentration measurement (therapeutic on two occasions), multi-disciplinary input including psychology, and two months of video-observed therapy which were satisfactory.
- Additionally the HIV sub-type remained unchanged.

Intensification

- The addition of maraviroc yielded no impact.
- The addition of dolutegravir twice a day resulted in HIV **viral suppression** with further readings pending.

Day	Antiretroviral regimen	Viral load copies/ml	CD4 count cells/mm3	Comment
0	TDF/FTC/DTG	6,000,000	40 (5%)	Resistance: Nil; Transient paranoid reaction
3	TDF/FTC/DRV/RIT			Acute kidney injury ?MAI treatment
14	TAF/FTC/DRV/RIT	600	105	Simplification
74	TAF/FTC/DRV/Cobi	851	150 (26.8)	Resistance: test failed to amplify
152		741		
195	TDF/FTC/DRV/Cobi	4635	230 (9.1)	Resistance including pro-viral: M184V
216	TAF/FTC/BIC/DRV/RIT	122		TDM1 normal
262		69		
277		<50	280 (12.8)	
307	TAF/FTC/BIC/DRV/RIT	486	220 (12.8)	Resistance: failed to amplify; Ferrous sulphate stopped
337		112		
367		589		Resistance: M184V, R263RK
369	TAF/FTC/DRV/Cobi		280 (12.9)	
375		110		
389		2630		
432		13804		Resistance: M184V, L74I
440	TDF/FTC/DRV/r	3631		TDM2 normal
464		3632		Resistance: M184V
491		2344		Resistance: M184V
580		7413		Resistance: M184V; Video observed therapy month 1
617		1698		Resistance: M184V; Video observed therapy month 2
644		1380		
657	TDF/FTC/DRV/r/MVC	2339		
693		1585		

Table 1 Summary of our patient's journey

Conclusion

- Bictegravir resistance emerged despite subjective and objective evidence of good adherence.
- Our case may represent expansion of clones originating in the viral reservoir.
- Better understanding of how bictegravir performs in the context of persistent viraemia is required.

Acknowledgements: Patient of which this case report is about.