Early treatment failure with lenacapavir in HIV-2 infection

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BACKGROUND

In vitro data suggest efficacy of Lenacapavir (LEN) against HIV-2, although mean IC50 is 11-fold higher as compared to HIV-1.
We describe an early treatment failure after LEN initiation in an individuum infected with HIV-2 with so far unobserved mutations.

METHODS

A 65 old male was diagnosed with HIV-2 in 1991(WHO/CDC C2). ART was started in 2005 and adapted due to development of resistance. Previous (Feb. 2018) genotypic resistance analysis showed mutations against NRTIs (K65R, M184V), and PIs (I50V, I54M, I64V) without INI mutations. Last ART was Dolutegravir (DTG, BID), 3TC, AZT and Lopinavir/r. In June 2023 HIV-2 VL was 10.280 IU/ml, CD4 cells were 32/µl (2%). Salvage-ART was initiated with LEN, DTG (BID), 3TC and AZT. HIV-2-VL was measured with the Altona RealStar® HIV-2 RT-PCR Kit 1.0, mutations were identified by amplicon based nanopore sequencing of the gag, pol and env region. Plasma drug levels were determined with LC-MS/MS. HIV-2 drug resistance was interpreted with the HIV2EU tool.

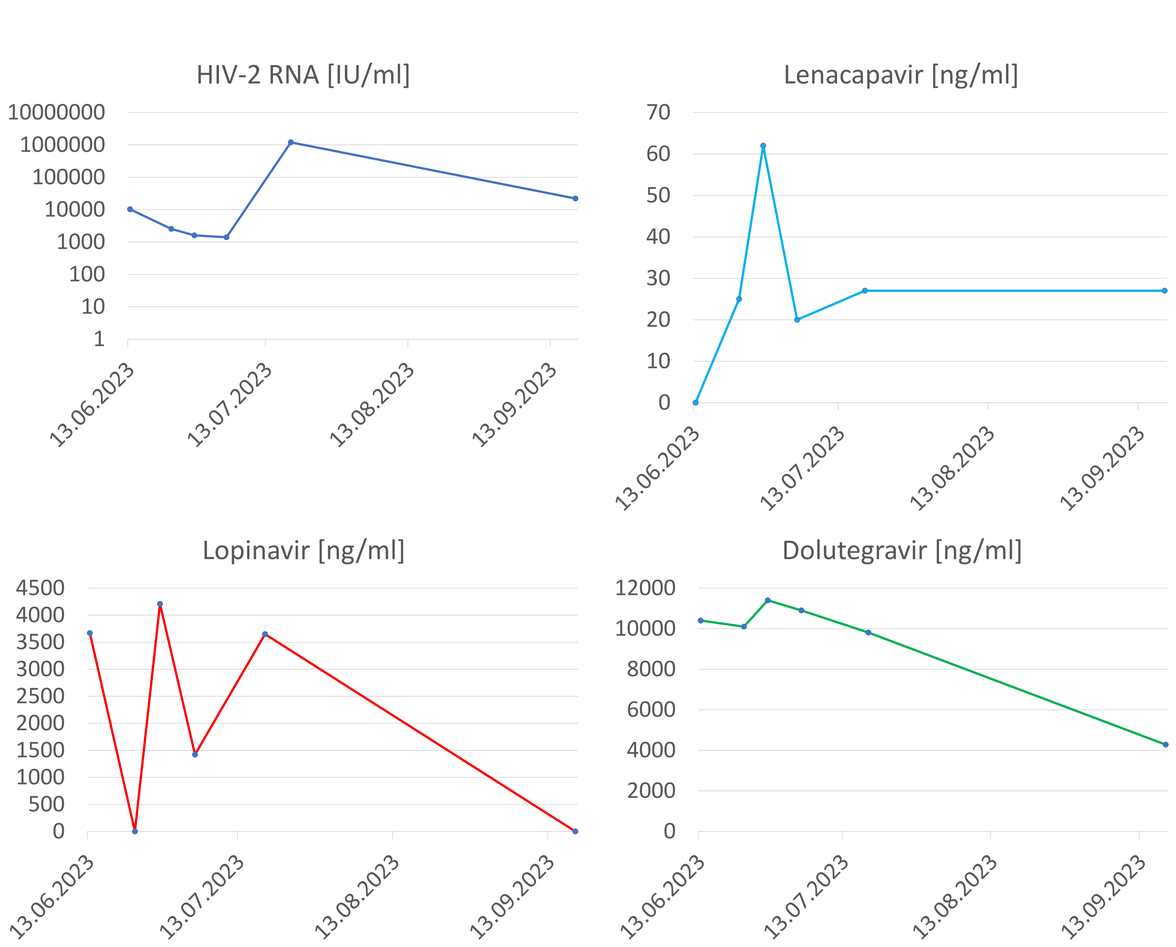

Figure 1: Viral load and pharmacokinetics

RESULTS

After 21 days a rapid decrease in HIV-2-VL from 10,280 IU/ml to 1,400 IU/ml was documented, followed by an increase at day 35 to 1,200,000 IU/ ml (CD4+ 84 cells/µl). LEN plasma levels were between 20 and 62 ng/ml (reference C(tau) CI: 19.8–52.6 ng/ml) and DTG 9810-11400 ng/ml (reference C(tau) CI: 790–4266 ng/ml) (figure1). Treatment was well tolerated with small lumps at the injection sites. In comparison to the baseline sequence a single amino acid change N73D (capsid position numbering HIV-2 BEN) at day 35 was observed (figure 2). Re-analysis of the pol region at baseline confirmed mutations in the Protease and Reverse Transcriptase with additional mutations D67N and V111I. Integrase mutations T97A, Y143A, N155S were observed, of which only the N155S was detected before (figure 3).

CONCLUSIONS

Despite the initial drop in HIV-2-VL and LEN plasma levels in the expected range, rapid resistance development was observed after 35 days of treatment. The found integrase mutations are most probably associated with resistance and were leading to subsequent LEN mono therapy. Further studies are needed to investigate the effectiveness and the use of LEN in salvage settings in HIV-2 patients. By now the observation could be confirmed by other groups and are now included in the capsid interpretation of the HIV2-EU Lenacapavir tool. (hosted at http://www.hiv-grade.de)

Alignment of amino-acid sequences:

Alignment of patient INT-gene sequence to Consensus A

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                              10         20         30         40         50         60
     INT-consensus A  FLEKIEPAQE  EHEKYHSNVK  ELSHKFGIPQ  LVARQIVNTC  AQCQQKGEAI  HGQVNAELGT
30489906 Patient seq  ..........  ...R.....R  ..C.......  ..........  P.........  ......D...
                              70         80         90        100        110        120
     INT-consensus A  WQMDCTHLEG  KIIIVAVHVA  SGFIEAEVIP  QESGRQTALF  LLKLASRWPI  THLHTDNGAN
30489906 Patient seq  ..........  ..........  ..........  .T...A....  ..........  ........T.
                             130        140        150        160        170        180
     INT-consensus A  FTSQEVKMVA  WWVGIEQSFG  VPYNPQSQGV  VEAMNHHLKN  QISRIREQAN  TIETIVLMAV
30489906 Patient seq  ...R.M....  ..........  ..A.....S.  ..S.SG....  ......D...  .V........
                             190        200        210        220        230        240
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Figure 3:Baseline Integrase Resistance

Gene	Differences from Consensus A	Drug Resistance Mutations
capsid	Q4K, G6A, T10V, L12V, N73D, L81T, E96D, Q119A, T147I, V152I, P159S, T176A, I190V, G224A	N73D

CAPI	HIV2EU 4.0			Final Rating
	Mutation List	Algorithm Result	SIR	
LEN	N73D	Resistant	R	

Scored mutations for Drugclass CAPI : N73D

Figure 4: HIV2EU Lenacapavir tool

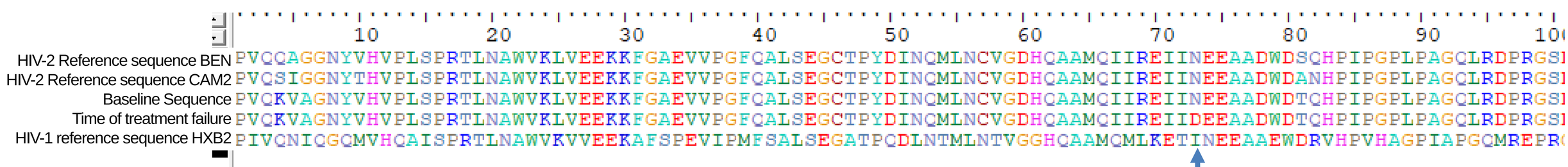

Figure 2 : Partial Capsid-Sequence

Mutation N73D occured at time of treatment failure
Mutation N74D in HIV-1 is a typical mutation for Lenacapavir resistance

Mutation N73D at time of treatment failure