

HIV-1 RESISTANCE
against authentic
INTEGRASE INHIBITORS

VALERY FIKKERT

Chemotherapy & Immunology
Department of Microbiology & Virology
Rega Institute, KULeuven

HIV INHIBITORS

HIV resistance to currently used antiviral compounds → Target alternative steps: INTEGRASE (IN)

Only recently authentic IN inhibitors (effective in cell culture) were identified

<u>Diketo compounds:</u>	L- 708,906	DKA
	S-1360	clinical candidate (phase I/II) <i>GSK-Shionogi</i>
<u>Pyranodipyrimidines:</u>	V-165	<i>in house</i> inhibitor

HIV RESISTANCE TO INHIBITORS

- ON VIRAL LEVEL Selection of HIV- 1(III_B) in the presence of L- 708,906

Mutations T66I, L74M and S230R emerged successively in *IN*.

The third mutation renders this virus resistant to L- 708,906, while the single and double mutant only showed a slight decrease in susceptibility.

The mutation T66I was sufficient to cause cross-resistance to S- 1360

T66I showed reduced sensitivity to V-165, but L74M and S230R appear to reverse the resistance phenotype

IN-Chimeric Virus Technology:

IN-Recombination into WT background of a proviral clone provided evidence that IN mutations on their own are sufficient to reproduce the resistance phenotype

- **ON ENZYMATIC LEVEL** **Generation of mutant IN enzymes & analysis of their susceptibility**

All 3 mutations were required for reduced sensitivity to **L- 708,906** and **S-1360** in this assay

(other mutants did not lose their susceptibility for these compounds)

complete resistance towards the diketo compounds in cell culture could not be reproduced at this level

As in cell culture, the single mutant T66I was partially resistant to inhibition by **V-165**, whereas the double- and triple- mutants remained fully sensitive

the DKA- resistant strain remained sensitive to inhibition by V-165

ONGOING STUDIES: **Selection of HIV-1 in the presence of S-1360 and V-165**

Once resistance is phenotypically observed, this methodology will be used to examine mutations associated with reduced sensitivity

SPECIAL THANKS !!!

GSK....

Myriam Witvrouw

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