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Tenofovir resistance and K65R

- K65R reduces viral susceptibility to most nucleosides; ZDV is an exception.
- Data suggest ZDV may prevent evolution of K65R.
- Impact of ZDV in patients who have already developed K65R.
- 3 cases reported in which ZDV added to failing regimens without switching the other drugs – patients achieve VL < 50 copies/mL.
- 3 cases shared the following traits:
  - Detectable VL while taking a regimen that provoked K65R and no TAMs.

Staszewski S et al. 3rd European HIV Drug Resistance Workshop, Abstract 89
<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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</thead>
<tbody>
<tr>
<td>Current regimen</td>
<td>ddl, 3TC, abacavir</td>
<td>ddl, TDF, abacavir</td>
<td>3TC, TDF, nevirapine</td>
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<tr>
<td>Past regimens</td>
<td>None</td>
<td>IDV, EFV, NVP, SQV, LPV/r</td>
<td>None</td>
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<tr>
<td>Viral load when</td>
<td>5300 copies/mL</td>
<td>48 000 copies/mL</td>
<td>1130 copies/mL</td>
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<tr>
<td>adding ZDV</td>
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<tr>
<td>Duration &lt; 50</td>
<td>8</td>
<td>15</td>
<td>6</td>
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<tr>
<td>copies/mL after adding</td>
<td></td>
<td></td>
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<td>ZDV (m)</td>
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Selection of K65R

- K65R can be selected under different NRTI pressure (TDF, ddI, ABC) – unclear what drugs or combinations exert a greater pressure
- 981 sequences analyzed (performed between 1996-2004)
- Rate of development of K65R significantly higher in patients that failed while receiving TDF containing regimen (13 of 97, 13.4%) than in those failed while on ddI (9 of 335, 2.7%) or ABC (9 of 144, 6.25%)
- Among TDF patients, K65R significantly more frequent among patients receiving three NRTIs than patients who received an NNRTI or PI-based regimen

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Virologic response with K65R

- High proportion of isolates with K65R have phenotypic resistance to TDF, ABC, ddI, and 3TC, especially if combined with the M184V mutation, the choice of NRTI analogues is limited.
- Few data exist on virologic response to the different NRTIs in patients with the mutation.
- Retrospective analysis of all patients infected with HIV-1 harboring the K65R mutation in the period 1996-2004.
- Evaluated regimens used after development of the mutation and virologic response obtained.

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Virologic response with K65R

- Total of 33 patients identified (11 patients on ABC, 17 on ddI, and 21 on TDF)
- % of patients with M184V mutation similar
- Only 2 patients had additional TAMs
- After development of the mutation, 8 patients received ABC: with NNRTI (n=2), PI (n=5), third NRTI (n=1)
- 16 patients received ddI: with NNRTI (n=6), PI (n=5), or third NRTI (n=5)
- 12 patients received TDF: with NNRTI (n=5) or a PI (n=3)
- After median follow-up of 12 weeks, VL ↓ from 4.4 log to 3.8 log
- No differences between drugs and whether patient had M184V
ddI/TDF/Efavirenz failure

- High rates of early virologic failure reported with ddI and TDF with an NNRTI
- Prospective randomized pilot study conducted in naïve patients with VL > 1000 copies/mL
  - ZDV+3TC+LPV/r (arm A), TDF+3TC+EFV (arm B), TDF+ddI+EFV (arm C)
- HIV RNA slope slower in arm C than B
- By week 28, 7/8 pts in arm A achieved VL<50, 10/10 in arm B, and 6/10 in arm C
- In 3 patients who failed to achieve 1 log ↓ in VL by week 4, NNRTI mutations K103N, Y188L, and G190E emerged first followed by K65R
- D67N and K219Q arose in one patient and L210F plus T215D in another
- Efavirenz levels (AUC 0-24hours) measured on day 7 were substantially lower in patients with early failure of ddI/TDF/efavirenz that patients who responded to that regimen

Torti et al. 3rd European HIV Drug Resistance Workshop, Abstract 58
TAM Pathways

TAMs tend to follow one of 2 pathways:
  - TAM-1 M41L, L210W, T215Y
  - TAM-2 D67N, K70R, T215Y, K219E/Q

TAM-1 associated with more cross-resistance to other NRTIs
Knowledge of prevalence and determinants of pathways is poor
Sequences with at least one TAM obtained from patients with genotype between 1993-2004
4035 sequences analyzed
Prevalence of TAM-1 increased from 20% before 1996 to peak of 59% in 2001
TAM-2 pattern decreased from 72% before 1996 to nadir of 30% in 2000
In multivariate analysis, TAM-1 pattern associated with a higher number of prior regimens (OR 1.08, 95% CI 1.02-1.15), d4T+3TC backbone in last regimen (OR1.37;1.01-1.88) and prior use of NVP (OR4.96;1.56-15.39)
Longer time on NRTI monotherapy was protective against TAM-1 pattern

DeLuca et al. 3rd European HIV Drug Resistance Workshop, Abstract 59
CCR5 Antagonists

- Acute HIV infection usually involves CCR5 coreceptor (“R5 tropic”)
- Advanced HIV – may involve CXCR4 (“X-4 tropic”) in ~1/2 of patients

Important Questions:

- How often does HIV switch from R5 to X4 in patients with drug resistance?
- Does pressure by CCR5 antagonists cause switch in co-receptor?
Coreceptor usage of HIV-1

- Longitudinal course of coreceptor usage in patients with repeated treatment failure has not been examined
- 42 patients with heavy treatment experience and multidrug-resistant HIV were assessed
- Median age 43 years, 84% male, 47% CDC Stage C, median CD4 240 and median VL 27 000
- Median time between two analyses was 1.37 years
- 25 people (59.5%) remained R5 tropic and X-4 tropic in 12 (28.6%)
- 2 went from X4 to R5, 1 from R5 to X4, 1 from X4 to R5 and back to X4, and 1 from R5 to X4 to R5

Kaiser et al. 3rd European HIV Drug Resistance Workshop, Abstract 60
Results of maraviroc monotherapy analysis presented
Among 63 patients who took maraviroc, X4 viral variants appeared in only two – one experienced 0.71 log decrease in viral load and the other 1.26-log
Roundtable discussion – emergence of X4-tropic virus is a possible threat during combination therapy
Resistance experiments with CCR5 antagonists have not revealed signature mutations
Not clear whether CCR5 resistant virus exists naturally in viral populations not exposed to these drugs
Enfuvirtide Resistance

Several reports from CROI that resistance to enfuvirtide occurs rapidly in failing regimen (mutations in gp41)

Investigators studied 11 heavily treated patients receiving T-20 who were not virologically suppressed

Substitutions in gp41 were analysed at baseline and every month over 96 weeks

Patients experienced VL decrease after starting T-20 (5.56 log to 3.58 log) at 2 weeks

Increase was observed shortly thereafter although did not reach baseline

Mutations associated with T20 resistance in gp41 were observed early in all patients

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Enfuvirtide Resistance

Mutations in HR1: G36V (n=2), V38A/M/E (n=6), Q40H (n=1), N42T (n=2), N43D/S (n=6), L44M (n=1), L45M (n=1)

Mutations at positions 36 and 38 were detected between weeks 1 and 4

Rapidly switched to other mutations

Mutations in HR2 and gp120 might occur simultaneously or subsequently to the selection of HR1 mutations and could contribute to increased resistance and improve viral fitness

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Enfuvirtide resistance

HIV env gene evolves very rapidly – particularly the part that encodes gp41

Genotyping virus from 53 HIV infected T-20 naïve Russians – 2 people with HIV-1 subtype A had virus bearing Q46M and N42T mutations and 2 with subtype F had R46M and V69I

41 of 53 (77%) had natural polymorphisms in HR1 positions

Vazquez de Parga et al. 3rd European HIV Drug Resistance Workshop, Abstract 8