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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

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	Case 1	Case 2	Case 3
Current regimen	ddI, 3TC, abacavir	ddI, TDF, abacavir	3TC, TDF, nevirapine
Past regimens	None	-IDV, EFV, NVP -SQV, LPV/r	None
Current (and archived mutations)	RT: K65R, L74V, Y115F, M184 V PR: L63P, V77I	RT: K65R, L74V, Y115 F, M184 V PR: L10V, M36I Archived RT: K103N Archived PR: L10I/V, M36I, I54V	RT: K65R, Y181C PR:L63P, G190S
Viral load when adding ZDV	5300 copies/mL	48 000 copies/mL	1130 copies/mL
Duration < 50 copies/mL after adding ZDV (m)	8	15	6

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

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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

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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

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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

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CCR5 Antagonist Overview – Maraviroc (Pfizer)

- 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 R46Mand V69I
- 41 of 53 (77%) had natural polymorphisms in HR1 positions

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