

Changing selection rates of resistance mutation K65R in antiretroviral-experienced HIV-1 infected patients

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RATIONALE

- We and others previously reported a rise and fall in K65R incidence between 2002 and 2005, despite a continuous increase in patients treated with cART including TDF
- The trend in K65R incidence significantly correlated over time with the number of patients failing TDF/ddI, which is no longer recommended by recent treatment guidelines
- Updated information on the impact of currently preferred NRTI regimens (TDF/FTC and ABC/3TC) on K65R selection at the population level is presently lacking

OBJECTIVES

- ✓ To evaluate changes in the population rate of K65R resistance mutation over time
- ✓ To identify factors associated with observed changes in K65R selection

DATA & METHODS

- A retrospective study of a Portuguese HIV drug resistance cohort between 2002 and 2010
 - 3820 viral isolates from 2736 HIV-1 infected patients failing cART containing a NRTI
 - only the first occurrence of K65R was considered
 - collecting information on treatment history and resistance profiles
- K65R incidence in a time period was defined as the number of unique treated patients with an incident case of K65R over the total number of unique treated patients with at least one resistance test.
- Statistical analysis included Fisher exact for categorical variables and non-parametric Spearman rank test for correlation coefficients. Odds ratios (OR) quantified direction and magnitude of the association. P-values of 0.05 or less were considered significant.
- Time trends were plotted using a sliding window approach (1 year with 1 month increase)

RESULTS

1) Drug regimens associated with K65R selection

- K65R mutation present in 144 patients (5.2%, CI: 4.5 - 6.2)
- 110 patients (76%) received TDF at time of detection, other NRTIs were 3TC (34%), FTC (32%), ddI (31%), ABC (14%), d4T (12%) and AZT (8%)
- Dual NRTI combinations (90%) were more accompanied by a NNRTI (84%) compared to a PI (15%) (p-value < 0.01)
- TDF/ddI and TDF/FTC accounted for most K65R cases (Contribution Rate, CR) (Table 1)
- Figure 1 shows the distribution of the regimens over time.
 - change in the NRTI accompanying TDF: decline of ddI and 3TC in favor of FTC
 - increasing contribution of ABC/3TC versus d4T/ddI

2a) Impact on K65R selection at the population level

- The population rate of K65R reflects the interplay between the prevalence of regimens among patients failing cART (Failing Rate, FR)
 - the proportion of K65R cases selected by each regimen (Selection Rate, SR) (Table 1)
- Experience with TDF among 2736 patients was high (41%)
 - continuous increase over time of patients failing cART including TDF, up to 60% and higher in 2010 (Figure 2a)

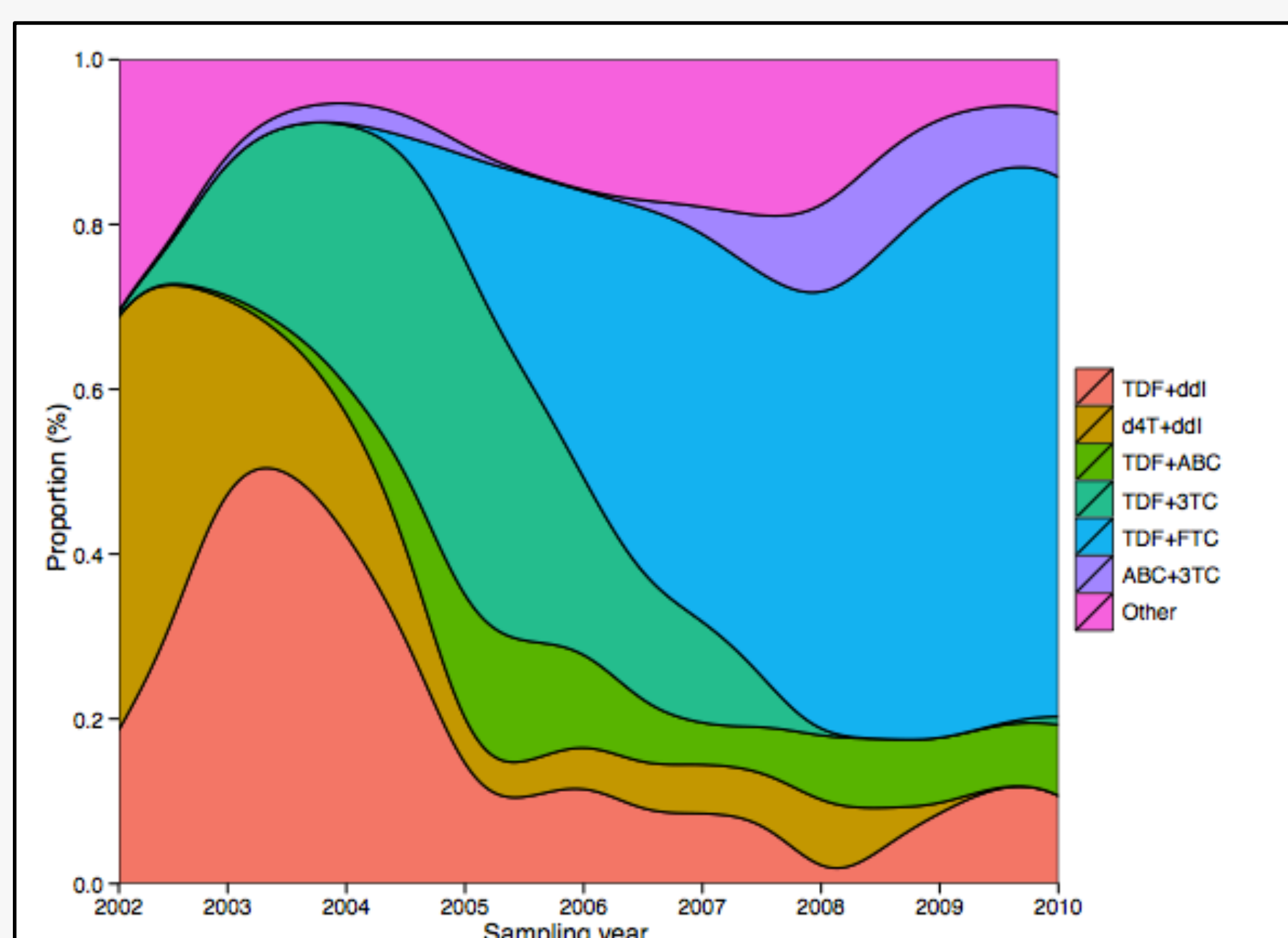


Figure 1: A density plot of the distribution of dual NRTI regimens over time among the 144 K65R patients, with the contributions to K65R plotted using a sliding window approach

Regimen	Failures	K65R	SR (%)	CR (%)	P-value	OR [CI]
TDF	1267	110	8,7	76,4	≤0,001	5,6 [3,8 - 8,1]
TDF/ddI	101	28	27,7	19,4	≤0,001	10,05 [6,33 - 16,04]
+ NNRTI	47	20	42,6	13,9	≤0,001	17,27 [9,67 - 30,88]
+ PI	33	2	6,1	1,4	0,640	1,46 [0,35 - 6,15]
+ 3TC/FTC	12	5	41,7	3,5	≤0,001	18,82 [5,91 - 60,15]
+ 3TC/FTC + PI	7	1	14,3	0,7	0,293	3,2 [0,40 - 25,80]
TDF/3TC	186	24	12,9	16,7	≤0,001	3,79 [2,38 - 6,03]
+ NNRTI	95	21	22,1	14,6	≤0,001	7,67 [4,59 - 12,81]
+ PI	80	1	1,3	0,7	0,264	0,27 [0,03 - 1,97]
TDF/FTC	561	43	7,7	29,9	≤0,001	2,17 [1,46 - 3,16]
+ NNRTI	250	37	14,8	25,7	≤0,001	5,01 [3,27 - 7,54]
+ PI	297	6	2,0	4,2	0,027	0,41 [0,15 - 0,93]
TDF/ABC	103	10	9,7	6,9	0,014	2,42 [1,11 - 4,76]
+ NNRTI	11	6	54,5	4,2	≤0,001	31,82 [7,98 - 133,40]
+ PI	50	2	4,0	1,4	0,650	0,87 [0,10 - 3,38]
+ 3TC/FTC	2	0	0,0	0,0	0,760	0 [-]
+ 3TC/FTC + PI	28	1	3,6	0,7	0,872	0,75 [0,02 - 4,54]
+ 3TC/FTC + NNRTI	6	1	16,7	0,7	0,206	5,12 [0,10 - 46,27]
ddI/d4T (no TDF)	260	14	5,4	9,7	0,340	1,29 [0,67 - 2,28]
+ NNRTI	109	9	8,3	6,3	0,043	2,18 [0,95 - 4,42]
+ PI	97	3	3,1	2,1	0,800	0,67 [0,14 - 2,07]
ABC/3TC (no TDF)	138	7	5,1	4,9	0,522	1,21 [0,47 - 2,64]
+ NNRTI	51	5	9,8	3,5	0,051	2,66 [0,81 - 6,79]
+ PI	84	2	2,4	1,4	0,586	0,53 [0,06 - 2,01]

Table 1: K65R selection by NRTI combinations including TDF, ABC or ddI is shown for 131 patients. For each regimen, the number of therapy failures, the number of K65R cases, the selection rate (SR) and the contribution rate (CR) are shown. P-values and odds ratios with confidence intervals indicate the significance and magnitude of the association of the regimen with K65R selection.

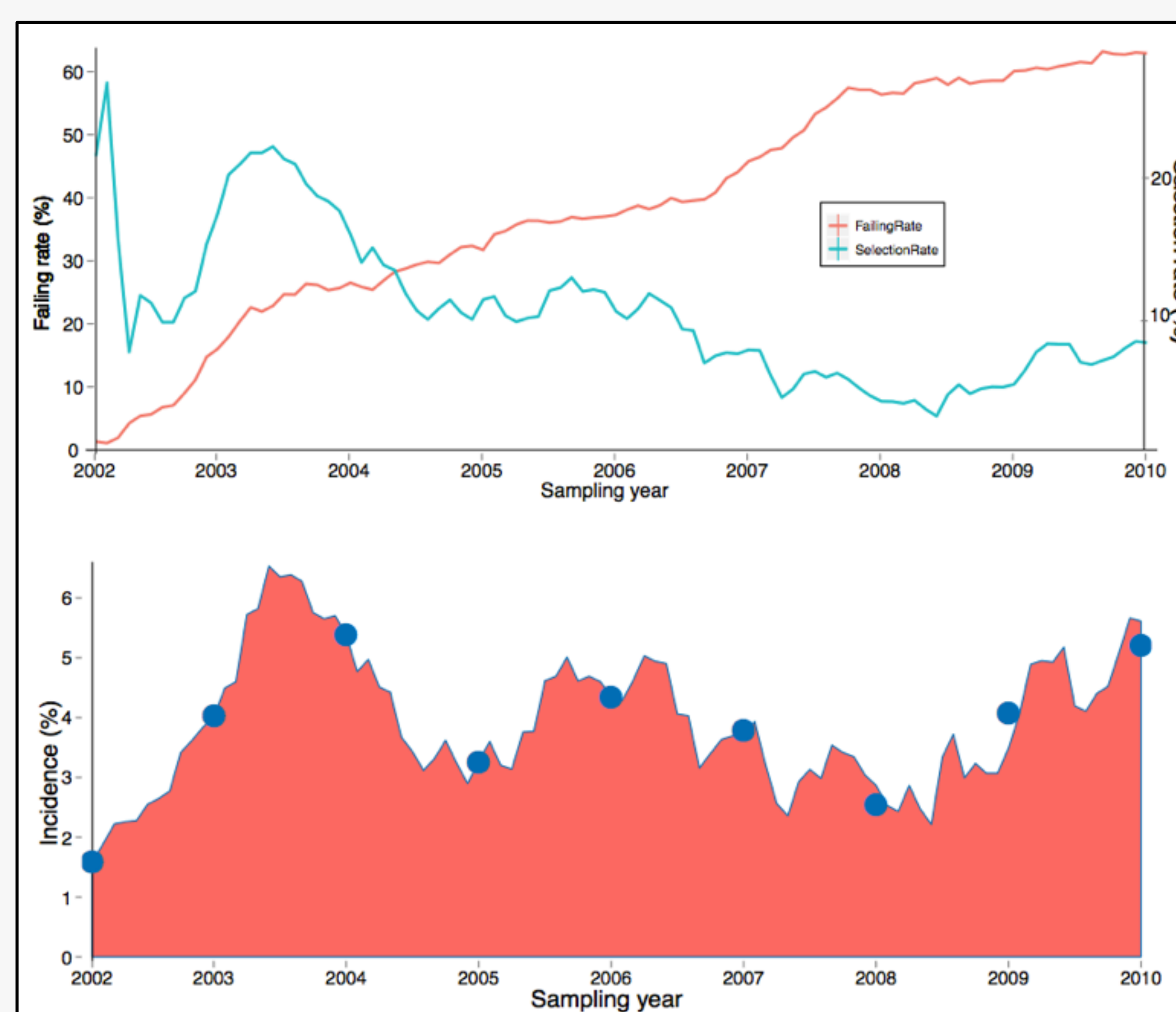


Figure 2: a) Rate of K65R selection by TDF-based regimens (green) and the proportion of TDF among patients failing cART (red) b) Incidence of K65R over calendar year (blue dots) and sliding window (blue line)

2b) Impact on K65R selection at the population level

- No clear increase in K65R incidence over time (Figure 2b)
 - persistent reduction in selection rate over time (Figure 2a)
- Explained by changes in the co-administration of TDF
 - increasing failing rate of widely used TDF/FTC (Figure 3)
 - TDF/FTC associated with low probability of K65R selection (Table 2)
- For dual NRTI regimens including TDF, higher selection rates were observed with a NNRTI (18.1%) versus PI (2.2%) (p-value < 0.001)
- Comparable K65R selection rates for d4T/ddI and ABC/3TC
 - increase in patients treated with ABC/3TC in recent years

3) Changing characteristics of patients showing K65R

- Co-occurrence of M184V increased up to 77% in 2010.
- Major NNRTI mutations (K103N, Y181C) occurred in 67% of K65R cases with no clear trends over time
- Inverse correlation between K65R incidence trend and trend in AZT accompanying TDF (p-value = 0.039, r = -0.27)
- Time on therapy before K65R detection increased with 49 days with every additional calendar year (p-value = 0.003)
- No difference in K65R prevalence between subtype B (2.9%) and G (4.1%) (p-value = 0.24)

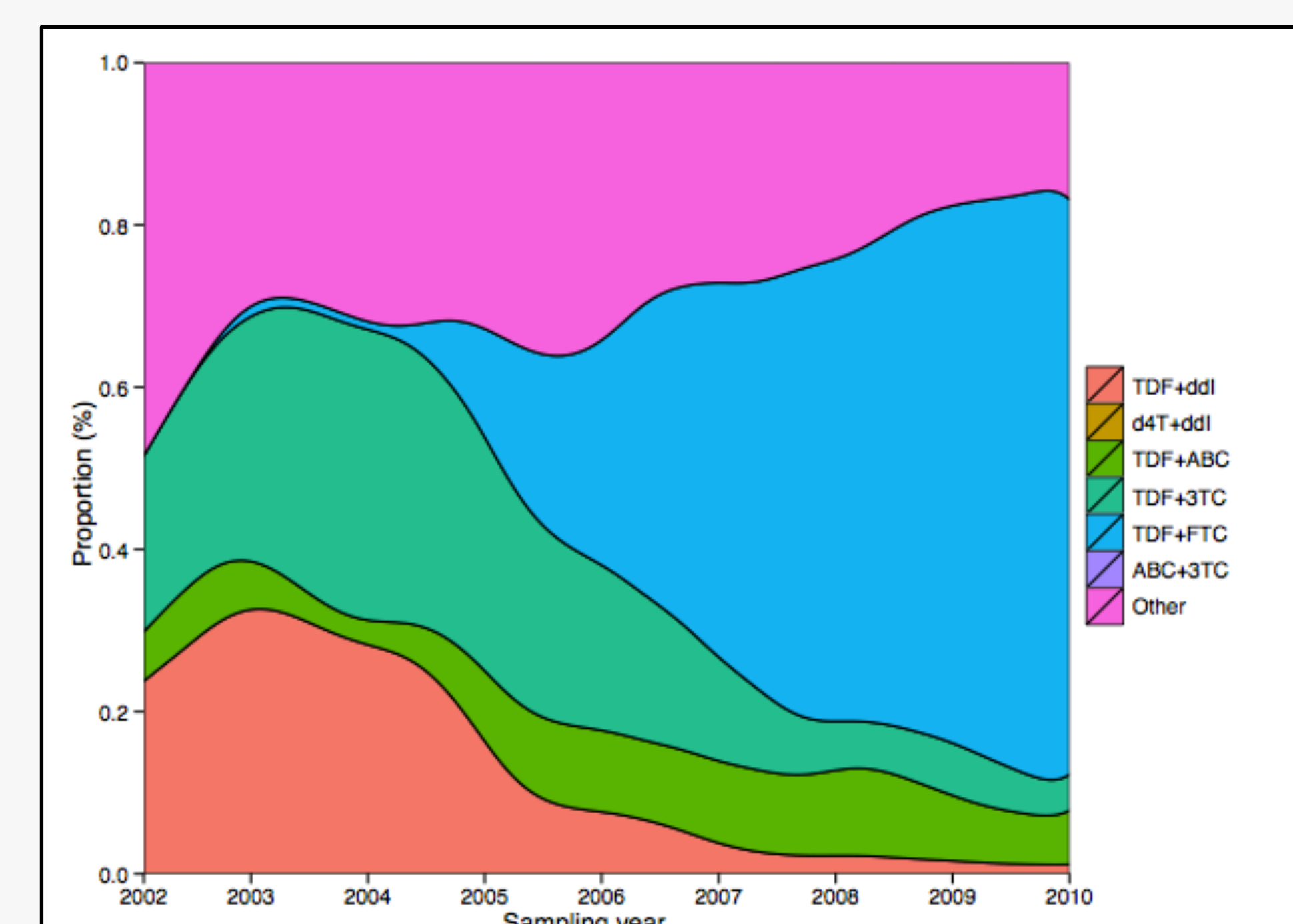


Figure 3: A density plot of the distribution of the accompanying backbone NRTI over time among patients failing cART including TDF

CONCLUSIONS

- ✓ The use of TDF accounted for the majority of K65R cases observed, with an increasing role for ABC in K65R patients naive to TDF
- ✓ K65R incidence trend remained relatively stable despite elevated rates of TDF and ABC use
- ✓ TDF/FTC predominantly prevailed among K65R cases in recent years, but this widely used co-formulation displayed very low selection rates of K65R
- ✓ These findings illustrate increased potency of current TDF regimens for HIV-1 treatment

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