

BHIVA 'BEST OF CROI' FEEDBACK MEETINGS  
*London | Manchester | Edinburgh*



## Resistance

*February 2008*

## Themes

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- ❖ Transmitted drug resistance (TDR)
- ❖ Treatment-associated resistance
- ❖ Entecavir and HIV
- ❖ Other news
- ❖ Viral load assays in non-B subtypes

## Themes

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- ❖ Viral load assays in non-B subtypes

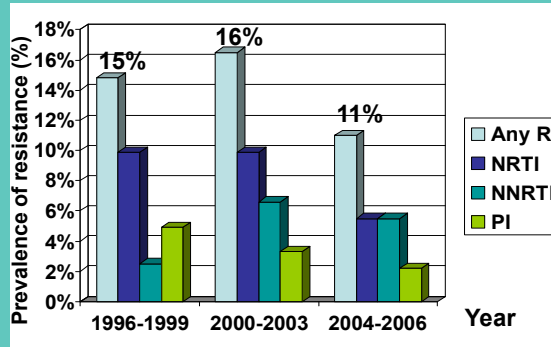
## Main findings

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- TDR rates stable in US and Europe at around 11-14%
  - UK rate currently around 8%
- TDR now reported in resource limited countries
  - Small numbers, selection criteria
- Ultrasensitive testing methods increase detection of TDR
- Clinical impact of low-frequency TDR to be established

## TDR in French seroconverters

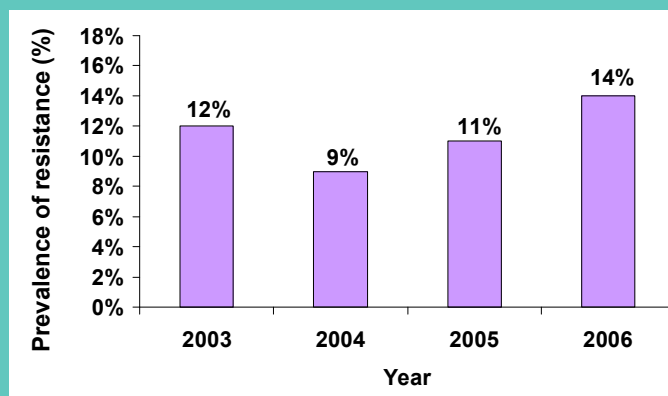
- Aquitaine cohort tested <18 months of seroconversion (n=265)
- 84% subtype B; 91% French-born; 67% MSM
- Overall prevalence of TDR 14% (subtype B 15% vs non-B 7%;  $p=0.15$ )
- Transmission clusters: subtype B 34% vs non-B 5% ( $p=0.0001$ )



Recordon-Pinson et al., Abstract 902, 15<sup>th</sup> CROI

## TDR in Californian drug-naïve patients

- Cohort from clinics in Northern California (n=942)
- Overall prevalence of TDR 12%



Fessel et al., Abstract 892, 15<sup>th</sup> CROI

## TDR in resource-limited countries

### Selection criteria:

- Burkina Faso, Thailand: Pregnant women
- Cameroon: Women aged 15-24 at 1<sup>st</sup> pregnancy
- Cambodia, Vietnam: Persons seeking VCT with presumed recent infection

Country	Number of Sequences (RT and PR)	Number of samples with resistant viruses (%)	95% Confidence Interval
Burkina Faso	51	0 (0)	0.0-7.0
Cambodia	58	1 (1.7)	0.3-9.2
Cameroon	52	1(1.9)	0.3-10.2
Thailand	56	0 (0)	0.0-6.4
Vietnam	63	2 (3.2)	0.9-10.9

Cambodia: RT K103N, M184V; Cameroon: RT K103N;  
Vietnam: RT G190A or PR M46I

*Ayoubu et al., Abstract 899, 15<sup>th</sup> CROI*

## TDR as low-frequency resistant mutants

- Subset cohort from CPCRA 058 FIRST study (n=258)
- Baseline plasma tested by standard genotype and Ultra Deep Sequencing

Resistance mutations	Genotype		UDS		P
	n	%	n	%	
NNRTI	17	6.6	39	15.1	<0.001
PI	6	2.3	12	4.7	0.03
NRTI	16	6.2	36	14.0	<0.001
<b>Any</b>	<b>35</b>	<b>13.6</b>	<b>73</b>	<b>28.3</b>	<b>&lt;0.001</b>
K103N	4	1.6	4	1.6	
Y181C	0	0	2	0.8	
TAMs	15	5.8	25	9.7	
T215rev	7	2.7	13	5.0	

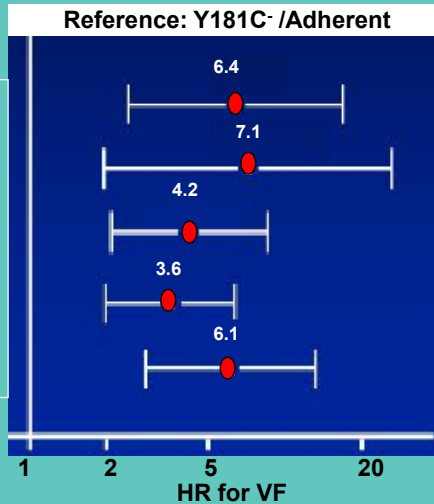
*Huppler Hullsiek et al., Abstract 878, 15<sup>th</sup> CROI*

## Low-frequency TDR & VF

- ZDV/3TC + ABC or EFV or ABC/EFV (ACTG 5095)
- ASPCR K103N, Y181C (sensitivity: 0.001-0.003% and 0.03%)
- K103N 4.4% Y181C 29.5%
- K103N + Y181C 6%

Resistant by bulk/Adherent	6.4
Resistant by bulk/Non-adherent	7.1
Sensitive/Y181C-/Non-adherent	4.2
Sensitive/Y181C+/Adherent	3.6
Sensitive/Y181C+/Non-Adherent	6.1

Sensitive = by bulk  
Y181C = by ASPCR



Paredes et al., Abstract 83, 15<sup>th</sup> CROI

## Low-frequency TDR & VF

- Patients starting 1<sup>st</sup> line Truvada + NNRTI or PI/r (n=220)
- Wild-type by standard genotyping
- ASPCR K65R, K103N, M184V (sensitivity: 0.4%, 0.01%, 0.2%)
- 27/220 (17.3%) showed TDR; 4 showed double mutants\*

RAM	% in cohort	% in quasispecies
K65R	4/219 (1.8%)	0.8-21.4%
K103N	10/216 (4.6%)	0.06-12.1%
M184V	17/215 (7.9%)	0.3-42.2%

\*K65R+M184V= 2; K65R+K103N=2

Metzner et al., Abstract 879, 15<sup>th</sup> CROI

## Outcomes

RAM (n)	VL at wk 24
K65R (2)	2 <50 [NVP]
K65R+ M184V (2)	1 <50 [LPV/r] 1 >50 [FPV/r]*
K103N (8)	2 <50 [NNRTI] 3 <50 [PI/r] 2 LTFU 1 d/c ART
K103N+ M184V (2)	2 <50 [PI/r]
M184V (13)	6 <50 [PI/r] 4 <50 [EFV] 1 >50 [LPV/r]* 2 LTFU

\*non-compliant

Metzner et al., Abstract 879, 15<sup>th</sup> CROI

patient #	baseline viral load [HIV-1 RNA copies/ml plasma]	K65R mean ± SD	K103N mean ± SD	M184V mean ± SD	ART: Truvada plus...	24-weeks status viral load
1	317,000	<d.l.	<d.l.	3.4 ± 0.6 %	FPV/r	<50
2	36,500	<d.l.	0.17 ± 0.03 %	<d.l.	EFV	<50
3	271,000	<d.l.	2.86 ± 0.29 %	0.6 ± 0.1 %	SQV/r	<50
4	17,200	2.1 ± 0.5 %	<d.l.	<d.l.	NVP	<50
5	n.d.	<d.l.	12.14 ± 1.86 %	<d.l.	LPV/r	lost to F/U
6	76,300	<d.l.	0.22 ± 0.03 %	<d.l.	<d.l.	lost to F/U
7	>750,000	<d.l.	0.06 ± 0.02 %	<d.l.	LPV/r	<50
8	107,525	<d.l.	0.17 ± 0.03 %	<d.l.	NVP	<50
9	750,000	<d.l.	<d.l.	0.3 ± 0.0 %	FPV/r	<50
10	94,220	<d.l.	<d.l.	0.5 ± 0.1 %	ATV/r	<50
11	75,771	15.4 ± 3.4 %	<d.l.	<d.l.	NVP	<50
12	111,000	<d.l.	<d.l.	1.3 ± 0.3 %	<d.l.	lost to F/U
13	12,259	<d.l.	<d.l.	0.8 ± 0.2 %	EFV	<50
14	45,000	<d.l.	<d.l.	0.7 ± 0.1 %	SQV/r	<50
15	900,000	0.8 ± 0.0 %	<d.l.	27.6 ± 1.8 %	LPV/r	<50
16	110,000	<d.l.	<d.l.	42.2 ± 0.7 %	ATV/r	<50 (wk 38)
17	160,000	<d.l.	<d.l.	13.0 ± 1.8 %	EFV	<50
18	64,000	<d.l.	<d.l.	13.3 ± 0.3 %	EFV	<50
19	61,000	21.4 ± 0.9 %	<d.l.	4.5 ± 0.5 %	FPV/r	>50 (non compliance)
20	750,000	<d.l.	<d.l.	0.7 ± 0.1 %	LPV/r	>50 (non compliance)
21	400,000	<d.l.	<d.l.	0.3 ± 0.0 %	EFV	<50
22	85,000	<d.l.	0.13 ± 0.01 %	<d.l.	LPV/r	<50
23	240,000	<d.l.	0.12 ± 0.02 %	<d.l.	FPV/r	<50
24	359,794	<d.l.	0.06 ± 0.01 %	0.5 ± 0.1 %	LPV/r	<50 (wk 38)
25	48,564	<d.l.	<d.l.	0.9 ± 0.1 %	LPV/r	<50
26	23,288	<d.l.	<d.l.	2.9 ± 0.7 %	LPV/r	<50
27	128,000	<d.l.	0.09 ± 0.01 %	<d.l.	FPV/r	stopped ART (wk 8)

<d.l., below the detection limit of minority quasispecies; SD, standard deviation; F/U, follow-up.

## Impact of low-frequency TDR

- Frequency within quasispecies
- Drug affected within a regimen
- Genetic barrier
- Fitness
- Drug levels
- Adherence

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- ❖ Viral load assays in non-B subtypes

## Main findings

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- High degree of virological success and declining emergence of resistance in treated persons in North America and Western Europe
- There remains a risk of virological failure and resistance in patients starting HAART
  - Highest for patients receiving NNRTI-based therapy
  - No difference between NNRTI and PI/r regimens in the risk of developing NRTI resistance
- Historically, resistance testing not performed in all patients experiencing virological failure
- Current cohorts of NNRTI-experienced patients often show at least partial susceptibility to Etravirine

## Resistance in treated patients in Switzerland

### Swiss HIV cohort study

N = 5997 ART-exposed persons enrolled since 1999

In 2007: Always <50 cp/ml = 2459 (41%)

Virological failure or exposed to mono/dual therapy = 1345 (22%)

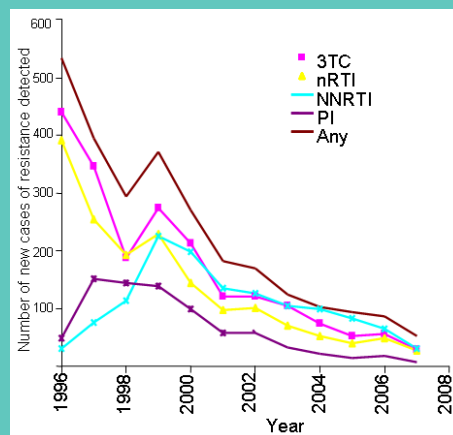
Unknown = 782 (13%)

**Ever had resistance documented = 1411 (24%)**

*Von Wyl et al., Abstract 896, 15<sup>th</sup> CROI*

## Resistance in treated patients in Canada

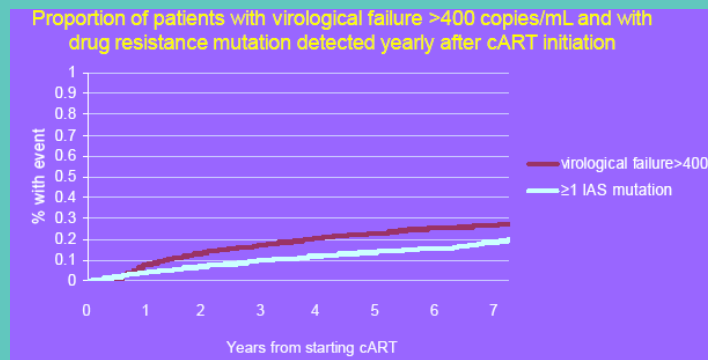
- British Columbia cohort on ART
- 1996-2007 (n=7363)
- Proportion <50 cp/ml
  - 65% in 2000
  - 86% in 2007
  - $p < 0.001$
- 21,300 resistance tests from 5216 individuals
- Significant decrease in incidence of resistance



*Lima et al., Abstract 895, 15<sup>th</sup> CROI*

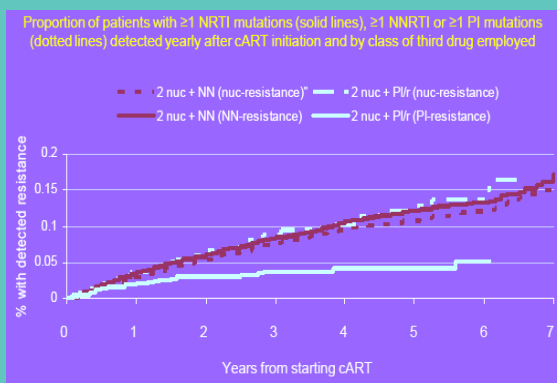
## Resistance in treated patients in the UK

- CHIC cohort, patient starting 1<sup>st</sup> line HAART from 1998 (n=6009)
- 2NRTIs + NNRTI (85%) or PI/r (15%)
- At 7 yrs: VF 27% (>400 x 2) - Resistance 20% (≥1 major IAS mutation)
- 47% tested for resistance at VF (MSM more likely than other groups)



Cozzi-Lepri et al., Abstract 894, 15<sup>th</sup> CROI

## Prevalence of resistance in CHIC study



Mutation	HAART	Proportion of patients
TAMs	NNRTI	5%
	PI/r	7%
M184V	NNRTI	11%
	PI/r	12%

- Patients on PI/r less likely to develop PI resistance than those on NNRTI to develop NNRTI resistance
- After 7 yrs: no difference in the proportion of patients with NRTI resistance in NNRTI- vs PI/r based regimens

Cozzi-Lepri et al., Abstract 894, 15<sup>th</sup> CROI

## Etravirine resistance mutations

\*ETV score: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S

Abstract	Place Year	n	% with ETV mutations*				Comments
			None	1	2	≥3	
865	Thailand 2004-2007	158	13%	62%		25%	Failing on 1 <sup>st</sup> line NNRTI-based regimen
867	Nigeria 2005-2007	210	31%	35%	23%	11%	Failing on 1 <sup>st</sup> line NNRTI-based regimen
866	Multiple 1999-2007	89,113	40%	37%	16%	7%	Virco database
868	Spain 1998-2006	1586	69%	22%		9%	Routine clinical samples

Most common ETV RAMs: Y181C and G190A

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## Entecavir monotherapy & HIV

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- Retrospective multicentre study of 17 HIV/HBV co-infected patients
- ARV-naïve = 10
- 3TC-experienced = 7
- Median HIV VL reduction 1.2 log<sub>10</sub> copies/ml
  - ARV-naïve: -1.0 (0.5-2.0) after median 113 days (17-291)
  - 3TC-experienced: -1.1 (0.1-2.3) after median 96 days (75-215)
- 4 persons had a HIV VL rebound ≥0.5 after initial suppression
- M184V in 6 persons: 3 ARV-naïve + 3 3TC-experienced

### **Limitations**

- Small study, different VL tests, key data points missing, variable time points of assessments, no in depth virological analysis

*Audsley et al., Abstract 63, 15<sup>th</sup> CROI*

## Entecavir monotherapy & HIV

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### **Unanswered questions**

- Some did not show HIV VL reductions despite HBV VL responses
- Some did not develop M184V despite prolonged ETV exposure
- Pre-exposure to 3TC not apparently required for selection of M184V, but presence of low-level M184V as TDR cannot be excluded

### **Main conclusion:**

***HIV/HBV co-infected persons should not receive ETV monotherapy***

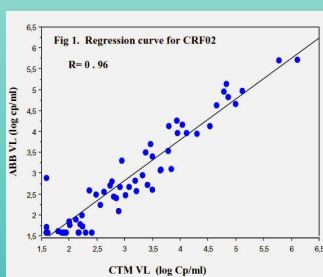
*Audsley et al., Abstract 63, 15<sup>th</sup> CROI*

## Other news on resistance

- ❖ Two main mechanisms of resistance to MVC confirmed<sup>1,2</sup>
  - gp 120-mediated virus entry through occupied CCR5 co-receptor
  - Tropism switch at the quasispecies level
- ❖ VircoTYPE clinical cut-offs for etravirine proposed<sup>3</sup>
  - DUET + 4 Phase IIb trials - wk 8 decline in viral load
  - Lower CCO 1.6 (drop in response by 20%)
  - Upper CCO 27.6 (drop in response by 80%)
- ❖ Large set of worldwide *integrase gene* sequences from IN-inhibitor naïve persons shows no natural occurrence of major resistance mutations for RAL or ELV<sup>4</sup>
  - 1265 persons in Africa, Asia, Europe, Middle East, and America
  - 121/288 amino acids (42%) polymorphic at a level of  $\geq 1\%$
  - Residues 148 and 155 highly conserved

<sup>1</sup> Heera et al., Abstract 40LB, <sup>2</sup>Lewis et al., Abstract 871; <sup>3</sup>Winters et al., Abstract 873; <sup>4</sup>Hackett et al., Abstract 872, 15<sup>th</sup> CROI

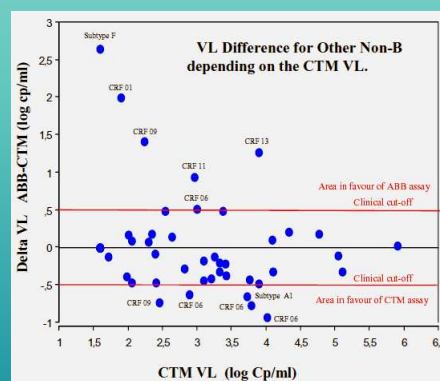
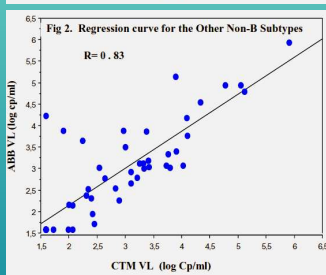
## HIV viral load assays in non-B subtypes: Abbott Real Time vs Roche TaqMan



N=122

71 CRF02

51 other non-B (G, CRF01, CRF06, others)



Wirden et al., Abstract 913, 15<sup>th</sup> CROI

## Conclusions

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- Strong correlation between the two VL assays for CRF02
  - Abbott assay tends to quantify CRF02 below Roche assay values with differences  $>0.5$  in 20% of cases, but most discrepancies  $<1$  log
- For other non-B subtypes, the assays are less correlated
  - Differences sometimes in favour of Abbott assay and sometimes in favour of Roche assay
- Ongoing vigilance required