Impact of Transmitted Drug Resistance on Clinical Outcomes in The VMVN Trial in Vietnam

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No conflicts of interest

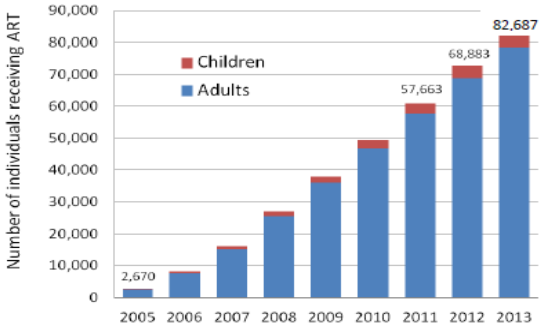
Background

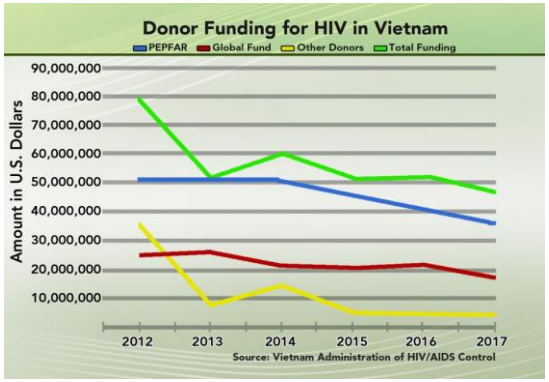
- Several studies from LMICs have recently documented an increased prevalence of HIVDR above 10%, in particular NNTRI resistance, among people starting first-line ART

- Pre-treatment drug resistance testing is not done in LMICs. Unidentified drug resistance → impair treatment outcomes → increased transmitted drug resistance → compromised ART programs

HIV statistics in Vietnam in 2017

- VN ranks 5th in HIV burden in the Asia Pacific region, 280,000 PLHIV
- Concentrated epidemic: 20% in IVDU, 10% in MSM, and 3-4% in FSW
- ARV coverage 50%
- TDR levels 5-10% as of 2009
- Major transition from international donor to national funding system → treatment default → increased HIVDR





National standardized ARV regimens since 2013

- 1st-line regimens: EFV based regimens
- 2nd-line regimens: 1. LPV/r based regimens
  2. ATV/r based regimens (2017)
- Monitoring: Clinical and 6-monthly CD4 counts
  VL and genotyping if suspected failure clinically and immunologically
  12-monthly viral load monitoring (2017)

Viral Load Monitoring in Vietnam (VMVN) RCT

Real-time viral load monitoring every 6 months + standard of care (N=325)

vs.

Standard of care: clinical and CD4 monitoring (N=325)

Follow up: monthly over three years

Primary Endpoints:

1. Death or new/recurrent stage IV AIDS events
2. Virological suppression over 3 years

Secondary Endpoints:

1. Time to treatment failure
2. Time to regimen switch
3. Drug resistance development
4. Cost effectiveness

PI: Todd Pollack, ClinicalTrials.gov: NCT01317498, complete follow up of 650 patients in December 2017

BỆNH VIỆN BẠCH MAI
BACH MAI HOSPITAL

Beth Israel Deaconess Medical Center
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Objectives

1. To investigate the prevalence, patterns and risk factors of transmitted drug resistance among ART-naïve patients starting first-line ART who enrolled in the VMVN RCT

2. To investigate the impact of transmitted drug resistance on virological and clinical outcomes

Study design

Study population 650 adult patients enrolled in the VMVN trial at Bach Mai Hospital from 04/2011 through 05/2017

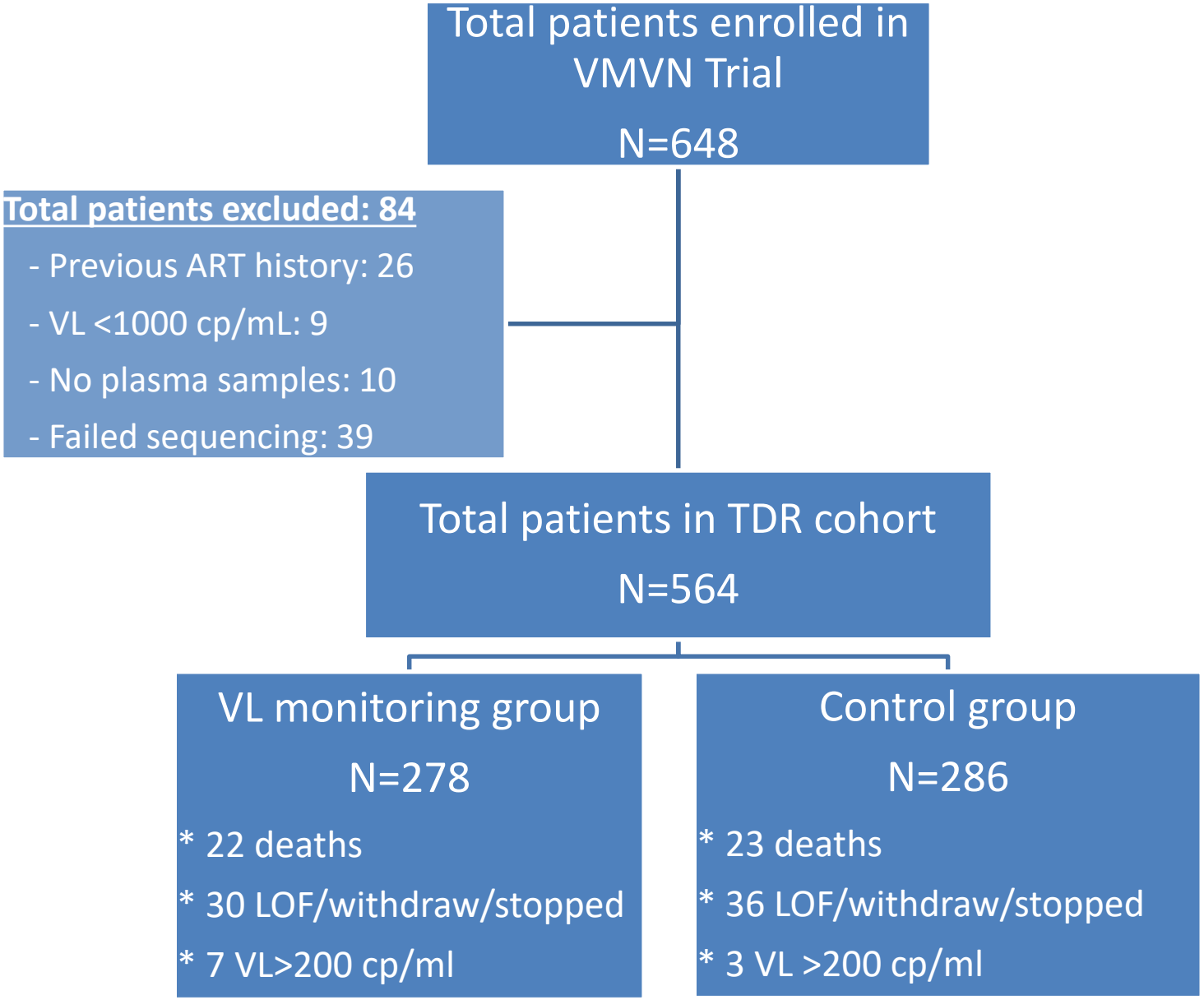
Resistance assessment and HIV subtyping

- Population sequencing
- 2009 WHO Surveillance of Drug Resistance Mutations
- REGA HIV-1 subtyping tool version 3.0

Statistical analyses

- Risk of TDR was evaluated using logistic regression modeling
- Impact of TDR on HIV RNA >200 copies/mL and/or death over 36 months using logistic regression analyses

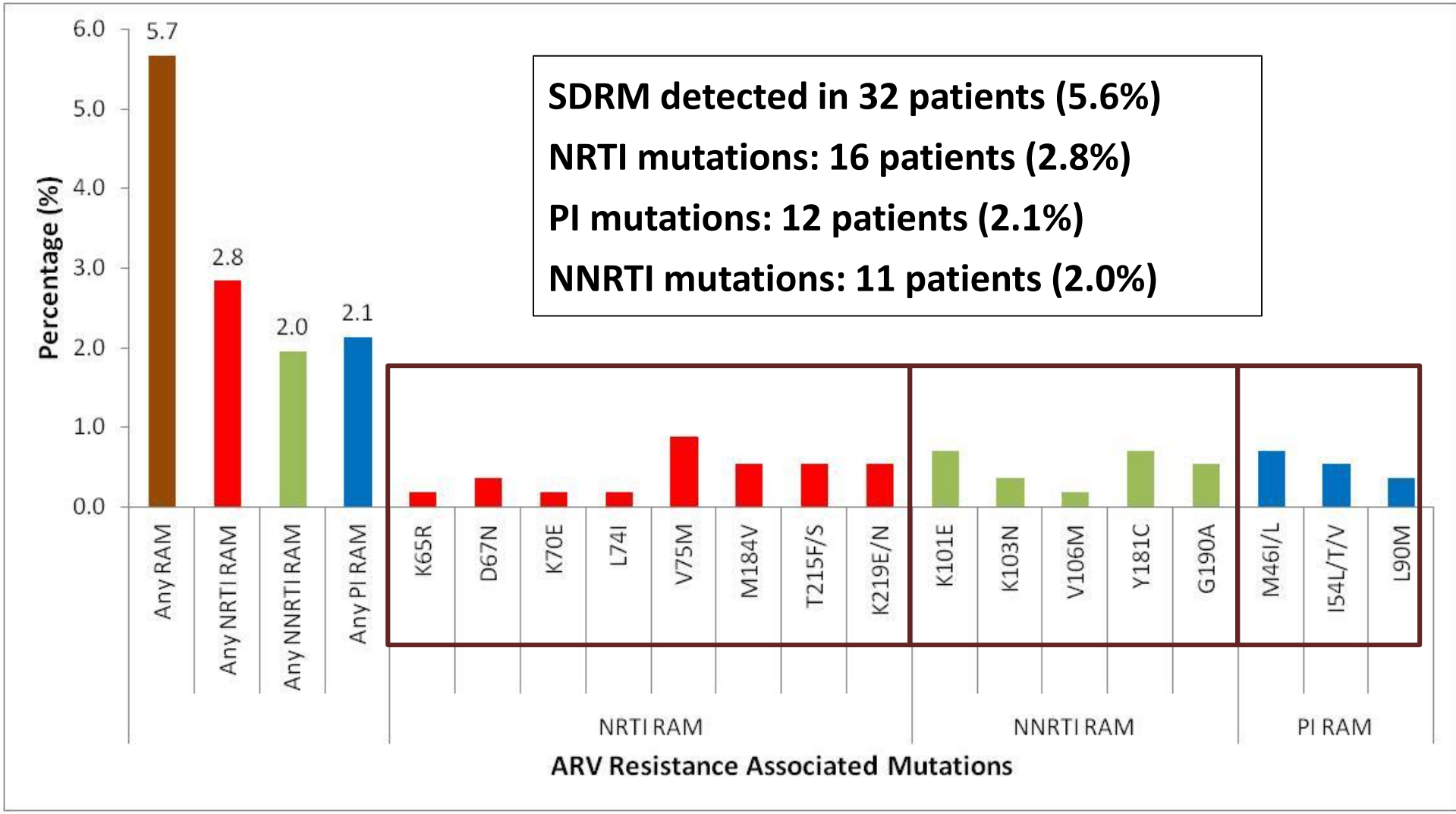
Study Flow


Total patients enrolled in VMVN Trial
N=648
Total patients excluded: 84
- Previous ART history: 26
- VL <1000 cp/mL: 9
- No plasma samples: 10
- Failed sequencing: 39
Total patients in TDR cohort
N=564
VL monitoring group
N=278
* 22 deaths
* 30 LOF/withdraw/stopped
* 7 VL>200 cp/ml
Control group
N=286
* 23 deaths
* 36 LOF/withdraw/stopped
* 3 VL >200 cp/ml

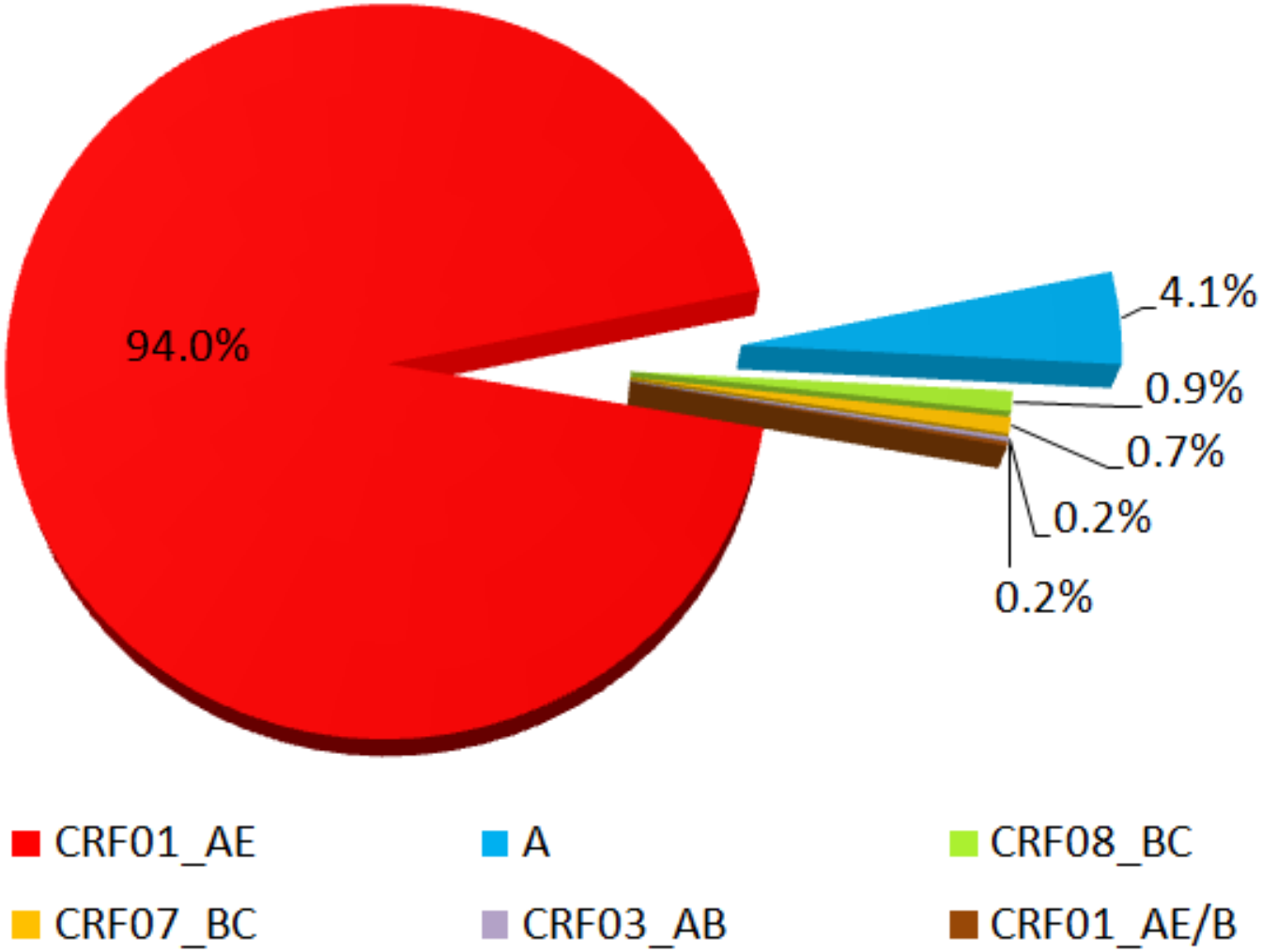
Baseline characteristics of 564 patients

Characteristics		**N=564**
Male (%)		367 (65%)
Median age (years)		33 (29-38)
Median CD4 count (cells/mm^3)		119 (29-273)
Median HIV RNA (log_{10} copies/mL)		5.1 (4.6-5.6)
Transmission risk (%)		
transmission	IVDU	99 (18%)
	Sexual	445(79%)
	Others	20(3%)
Hepatitis co-infection (%)		
	HBSAg pos	72(13%)
	Anti HCV	210 (37%)

Identified TDR mutations by ARV class



Circulating HIV subtypes in 564 patients



Risk factors of TDR

Covariates	Patients without TDR (N=532)	Patients with TDR (N=32)	Univariate effect		Multivariate effect	
			OR (95% CI)	P value	OR (95% CI)	P value
IDU (yes)	94 (18%)	5 (16%)	0.86 (0.29-2.12)	0.768	0.69 (0.21-1.93)	0.504
CD4 (median)	120 (29-275)	76 (24-246)	0.98 (0.86-1.10)	0.711	0.97 (0.84-1.11)	0.716
Median $\log_{10}$ HIV RNA	5.1 (4.6-5.6)	5.1 (4.5-5.7)	0.95 (0.60-1.53)	0.828	0.90 (0.55-1.52)	0.683
HBSAg pos or AntiHCV pos	232 (44%)	16 (50%)	1.19 (0.63-2.66)	0.480	1.43 (0.63-3.15)	0.380

Impact of TDR on HIV RNA >200 copies/mL and/or death at 36 months

Covariates	Patients with successful treatment (N=443)	Patients with death/virological failure (N=55)	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Any TDR mutation (Yes/No)	23 (5.2%)	4 (7.3%)	1.43 (0.41 – 3.89)	0.582	1.45 (0.41 – 3.98)	0.506
VL monitoring vs. Control group	218 (49.2%)	29 (52.7%)	0.88 (0.49 – 1.54)	0.645	0.87 (0.49 – 1.52)	0.617

A sensitivity analysis of the risk of treatment failure in patients barboring NRTI and NNRTI mutations was conducted. The difference in risk was not statistically significant, adjusted OR=0.108, 95% CI: 0.17-3.99, P=0.917

Conclusions

- TDR in treatment-naïve adults initiating first-line ART in Hanoi remains stable at <10%
- The emergence of PI resistance mutations raises a concern as PI drug class is currently the last treatment option in Vietnam
- The increase in number and diversity of non-CRF01_AE subtypes raises a need for surveillance of circulating HIV strains to understand transmission networks in the region
- TDR does not impact virological failure or death at 36 months. Our data suggest that baseline HIV drug resistance testing does not impact treatment outcomes in Vietnam

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