Do we need resistance testing?

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Thanks to: Regina Osih, Flavia Mugala-Mukungu, Doug Wilson, Carol Wallis, Francesca Conradie; Jo Eron; Clinical Care Options, Clinical Viewpoints, Helen Rees and others

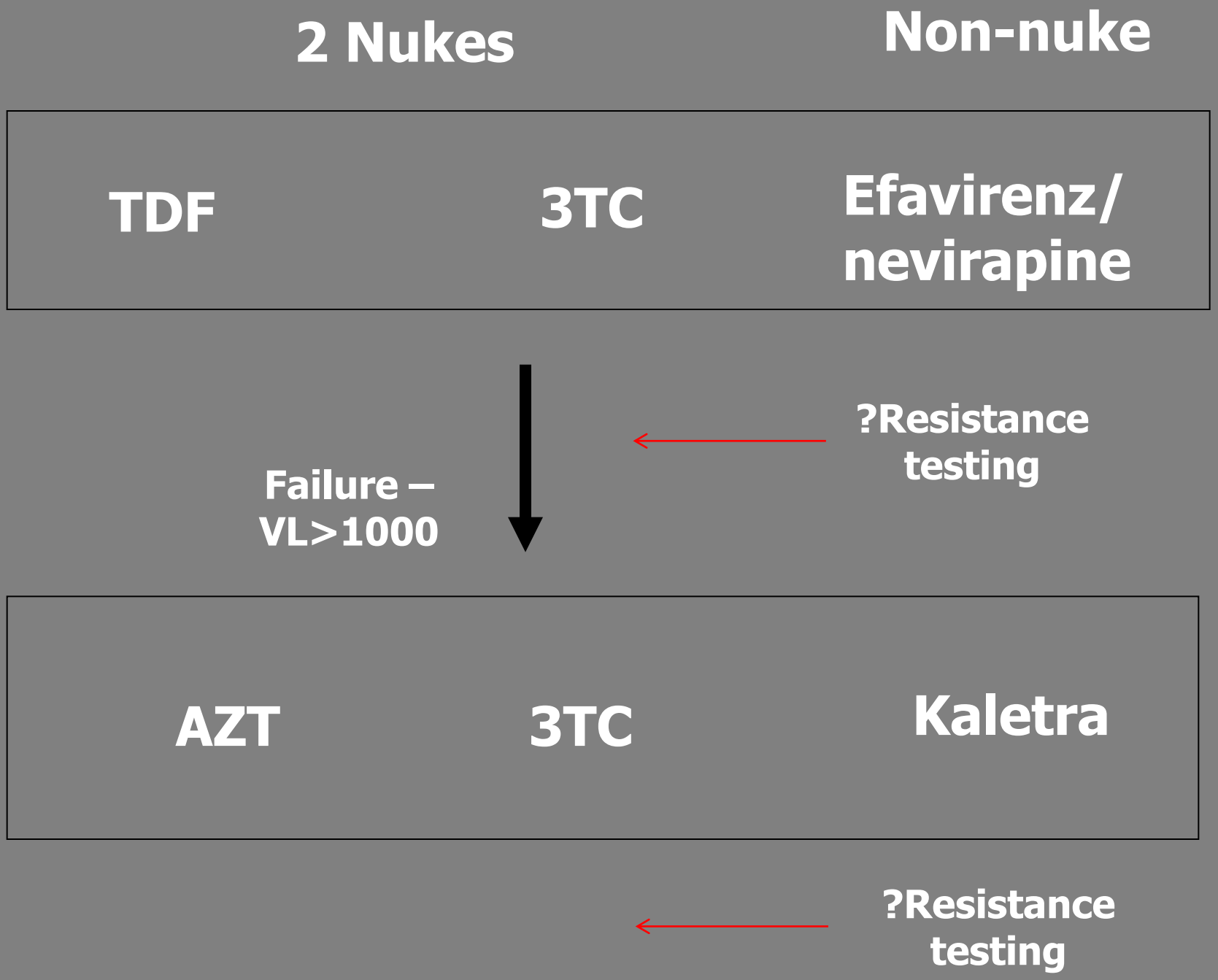
Answer: No

- Resistance is predictable
- Testing is expensive, distracting from toxicity management, and does not alter your choice of drugs

Some reflections…

- Definition of ‘2nd’ vs ‘salvage’ vs anything irrlevant
- Resistance = neurotic fear
- Resistance is ‘increasing’ but it isn’t
- Resistance is ‘irreversible’ but it isn’t
- Vested interests: Labs, HIV clinicians, researchers, pharma, researchers…
- Devastating for the rare patient

- NOT discussing surveillance


2 Nukes
Non-nuke
TDF
3TC
Efavirenz/
nevirapine
?Resistance
testing
Failure –
VL>1000
AZT
3TC
Kaletra
?Resistance
testing

Treatment Failure and Mortality Factors in Patients Receiving Second-Line HIV Therapy in Resource-Limited Countries

Mar Pujades-Rodríguez, MD, PhD
Suna Balkan, MD
Line Arnould, MD

Context Long-term antiretroviral therapy (ART) use in resource-limited countries leads to increasing numbers of patients with HIV taking second-line therapy. Limited access to further therapeutic options makes essential the evaluation of second-line regimen efficacy in these settings.

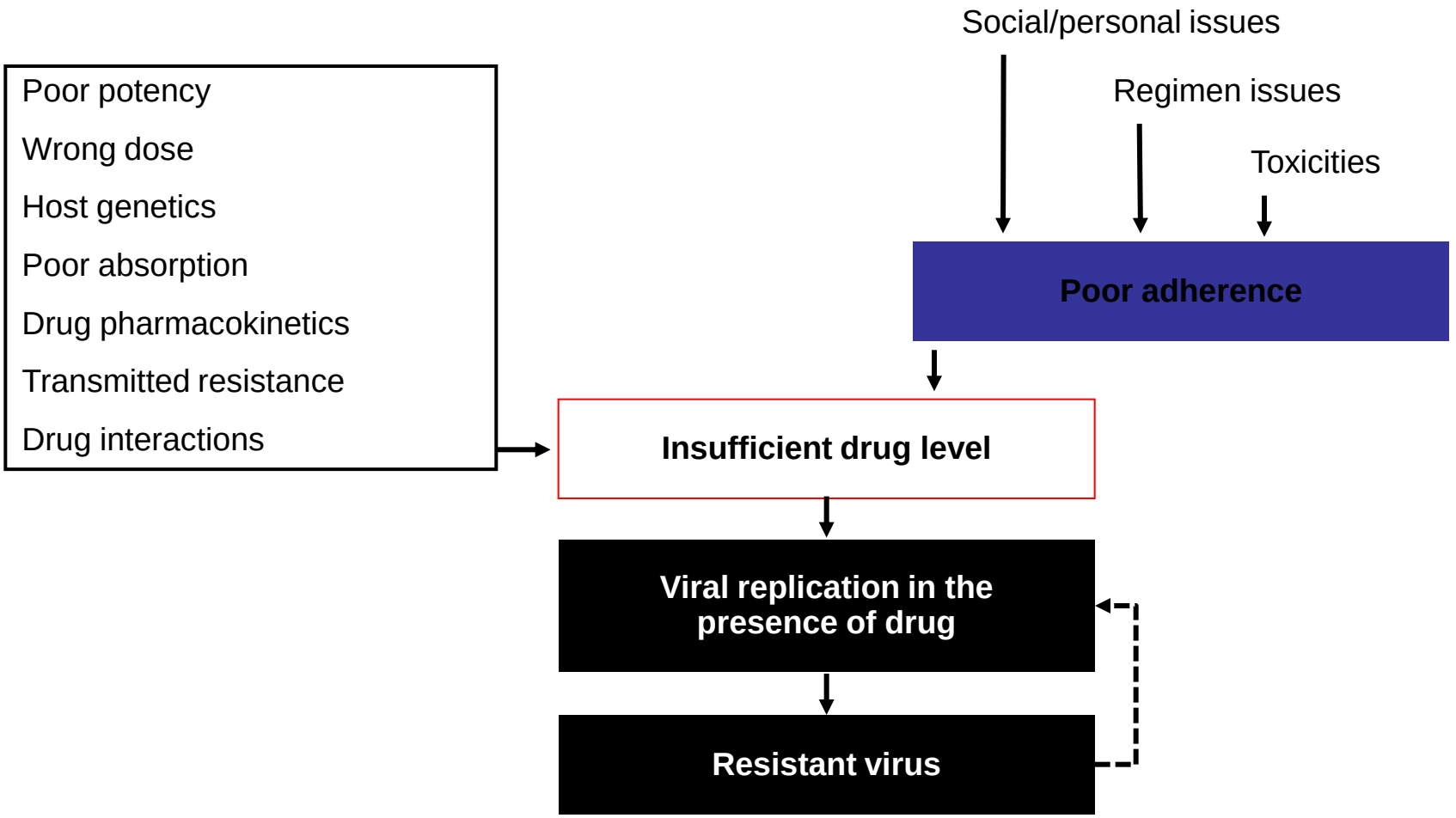
Conclusions Among patients in Africa and Asia receiving second-line therapy for HIV, treatment failure was associated with low CD4 cell counts at second-line therapy start, use of suboptimal second-line regimens, and poor adherence. Mortality was associated with diagnosed treatment failure.

JAMA. 2010;304(3):303-312 www.jama.com

Cost

- Second-line therapy was 2.4 times more expensive per year in care than first-line therapy (Long et al, The high cost of second-line antiretroviral therapy for HIV/AIDS in South Africa, AIDS. 2010 Mar 27;24(6):915-9.)

Causes of ARV Treatment Failure



ART resistance testing. AETC National Resource Center.

“We need to preserve drugs…”

Antiretroviral Agents Approved for Clinical Use and in Phase I, II & III Clinical Trials (by end 2010)

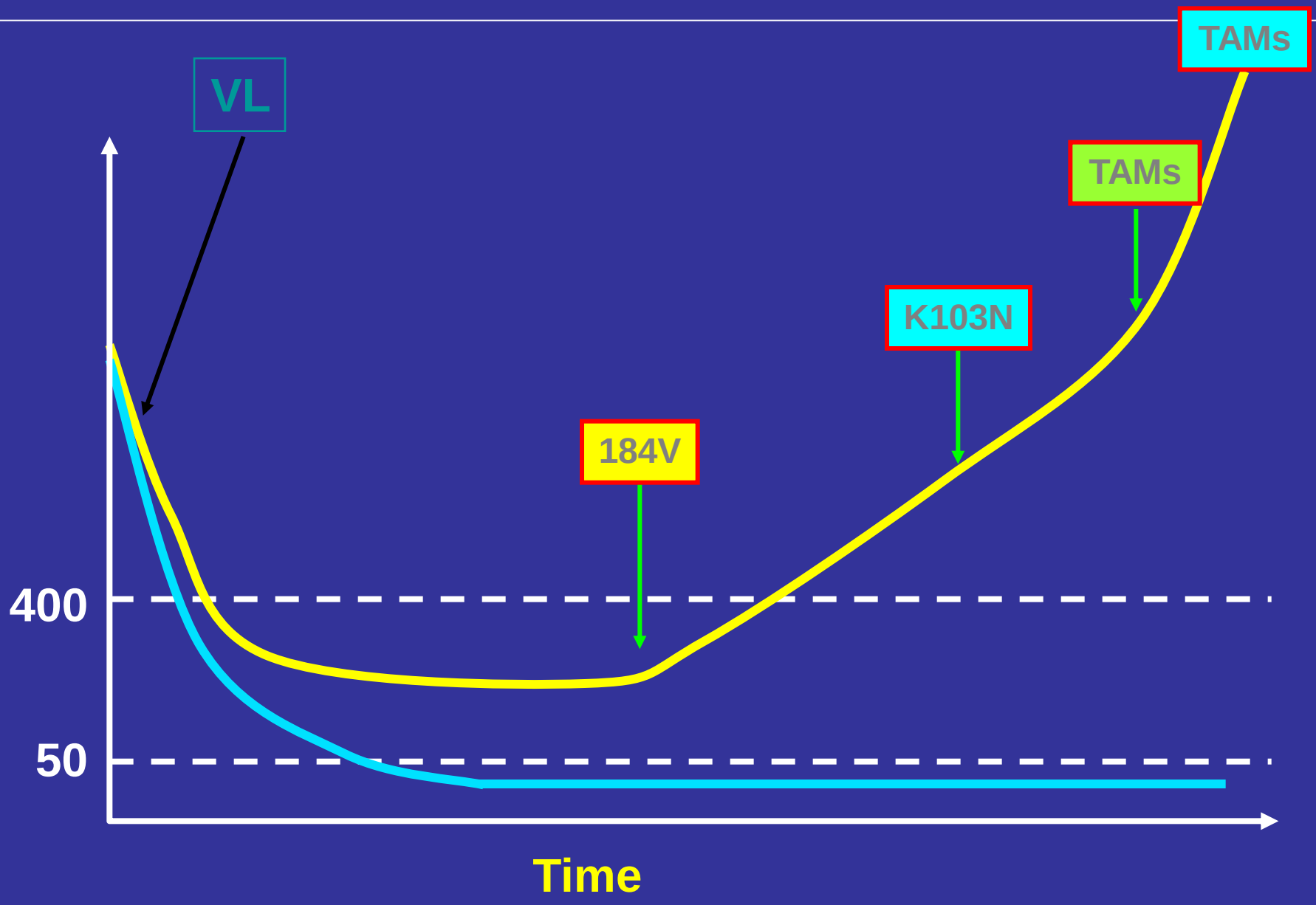
Approved Antiretroviral Agents						
NRTIs	**PIs**	**NNRTIs**	**Fusion Inhibitors**	**Entry Inhibitors**	**Integrase Inhibitors**	**Maturation Inhibitors**
Zidovudine	Saquinavir	Nevirapine	Enfuvirtide	Maraviroc	Raltegravir	
Didanosine	Ritonavir	Delavirdine				
Stavudine	Indinavir	Efavirenz				
Lamivudine	Nelfinavir	Etravirine				
Abacavir	Lopinavir/ ritonavir					
Tenofovir	Atazanavir					
Emtricitabine	Fosamprenavir					
	Tipranavir					
	Darunavir					
Major Investigational Antiretroviral Agents in Phase III Trials						
Apricitabine (AVX-201)		Rilpivirine (TMC-278)		Vicriviroc (SCH-D)	Elvitegravir (GS-9137)	
Major Investigational Antiretroviral Agents in Phase I/II Trials						
Elvucitabine (ACH-126443)	TMC-310911	Lersivirine (UK-453061)		Ibalizumab (TMB-355)	GSK-1349572	Bevirimat (MPC-4326)
Amdoxovir (DAPD)	CPT-518	GSK-2248761 (IDX-12889)		BMS-626529		PA-1050040
Racivir		RDEA-806		BMS-663068		
CMX-157				PRO-140		
				INCB-9741		
				TBR-652		

Failure of any line?

- Comes down to ONE question and one question only!
- ”Why are you not taking your drug?”

Mutations completely predictable…

Evolution of resistance - thymidine+NNRTI



1st line failures:

- 96 failures (clinical/immunologica.,
- Mainly M184V (81%) and NNRTI (93%) mutations; both and at least a single TAM (56%)
- High K65R/K70R rate (23%)

The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy

Mina C. Hosseinipour[a,b], Joep J.G. van Oosterhout[c,d], Ralf Weigel[e], Sam Phiri[e], Debbie Kamwendo[a], Neil Parkin[f], Susan A. Fiscus[b,g,h], Julie A.E. Nelson[b,g,h], Joseph J. Eron[b,g] and Johnstone Kumwenda[c,i]

AIDS, June 2009

Comparison of all HIVDR studies in SA

Site	JHB *(Wallis et al)*	KZN *(Marconi et al.)*	Cape Town (*Orrell et al.*)
Sample number **Clinic sites**	256 2	115 2	110 1
First line regimen	D4T, 3TC, EFV (54%) AZT, 3TC, EFV (21%)	D4T, 3TC, EFV (48.7%) AZT, 3TC, EFV (26%)	D4T, 3TC, EFV (67%) D4T, 3TC, NVP (15.5%)
% with failure with resistance	84%	83.5%	85%
HIV-1 subtype	96.5%	97.4%	97%
M184V	74%	64.3%	78%
NNRTI • K103N • V106M	78% 43% 26%	 51% 19.1% 39%	77% 55% 31%
TAMS • TAM-1 • TAM-2 • Both 1&2 > 3	33.5% 8% 17% 4% 11%	32.2% 7% 19.1% 6.1% 13%	23%
K65R	4%	0.3%	9%
NRTI + NNRTI	68%	64.3%	83%

- Cape Town model – if you act on detectable viral loads FAST, >1/2 will suppress!

Summary of 1st line failure:

- Resistance will occur predictably
- Viral load monitoring seem to protect from TAMS
- Can resuppress

Clinical question

- Can you actually get meaningful PI resistance to a boosted PI?
- If no – the only challenge is adherence, tolerability…

Absence of Major PR Mutations at VF of First-line Therapy With Boosted PIs

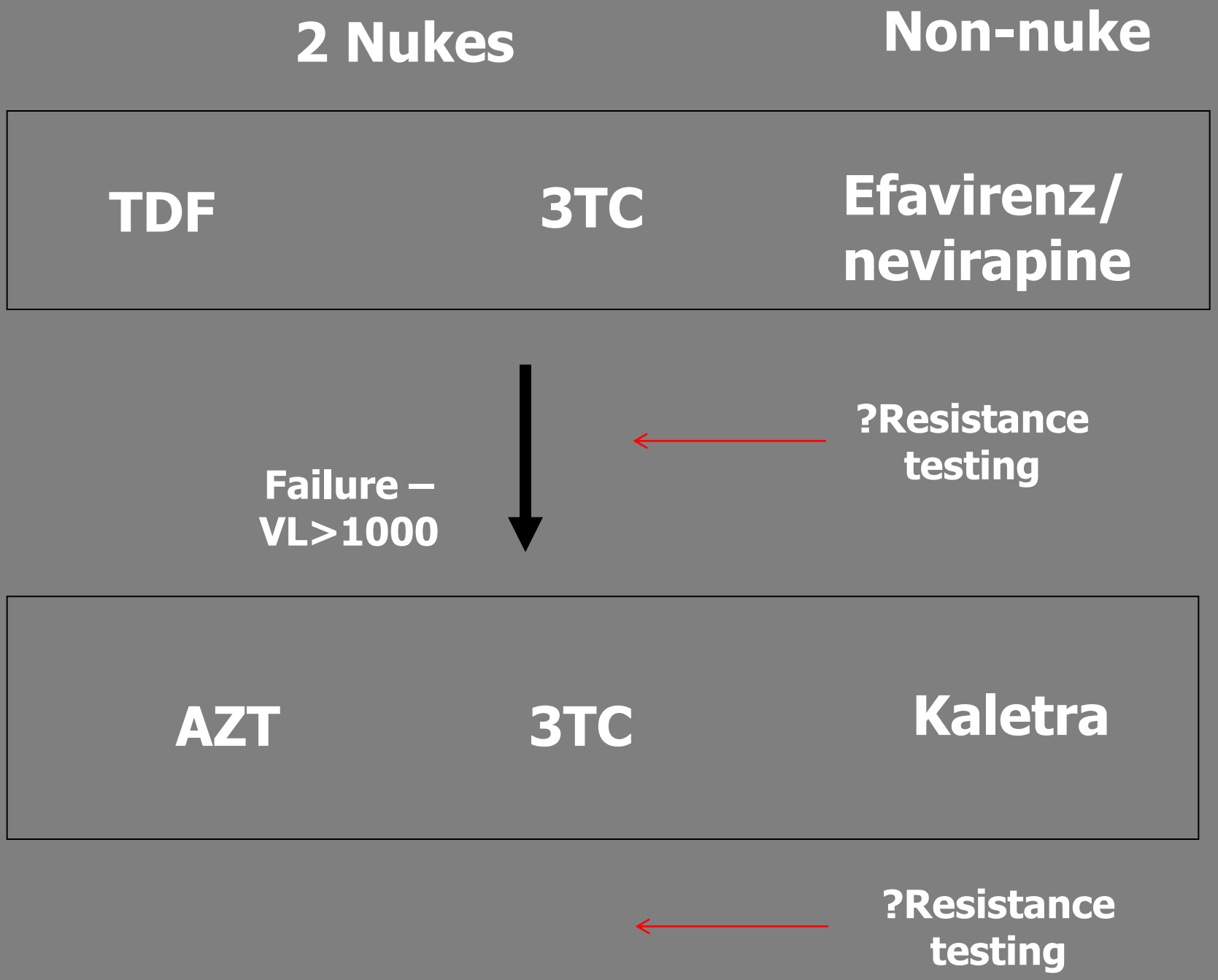
Study	N	NRTI backbone	PI/RTV	Wk	Genotypes	Primary PI Mutations
720[1]	100	d4T + 3TC	LPV	360	28	0
KLEAN[2]	878	ABC/3TC	FPV or LPV	48	35	0
BMS 089[3]	95	d4T-XR + 3TC	ATV	48	2	0
ARTEMIS[4]	689	TDF/FTC	DRV or LPV	96	NR	0
CASTLE[5]	881	TDF/FTC	ATV or LPV	96	52	1*
GEMINI[6]	337	TDF/FTC	SQV or LPV	48	16	1†

*In pt with ATV/RTV. †In pt with SQV/RTV.

1. Murphy R, et al. HIV Clin Trials. 2008;9:1-10. 2. Eron JJ Jr, et al. Lancet 2006; 368: 476-482. 3. Malan DR, et al. J Acquir Immune Defic Syndr. 2008;47:161-167. 4. Mills T, et al. ICAAC/IDSA 2008. Abstract H-1250c. 5. Molina JM, et al. ICAAC/IDSA 2008. Abstract H-1250d. 6. Walmsley SL, et al. J Acquir Immune Defic Syndr. 2009;50:367-374.

Which nukes?

- WHO – cycle thymidines and TDF
- ABC? ddI?
- Does it matter if you have a good PI?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Finally

- Good clinician=adherence expert
- Good clinician can’t fix bad patient
- Resistance testing adds next to nothing
- Caveat: detection of non-adherence…