NUH HIV PROGRAMME

angsamerah.com klinik kesehatan pria dan wanita

HIV Therapy

managing treatment failure

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Scope of the presentation:

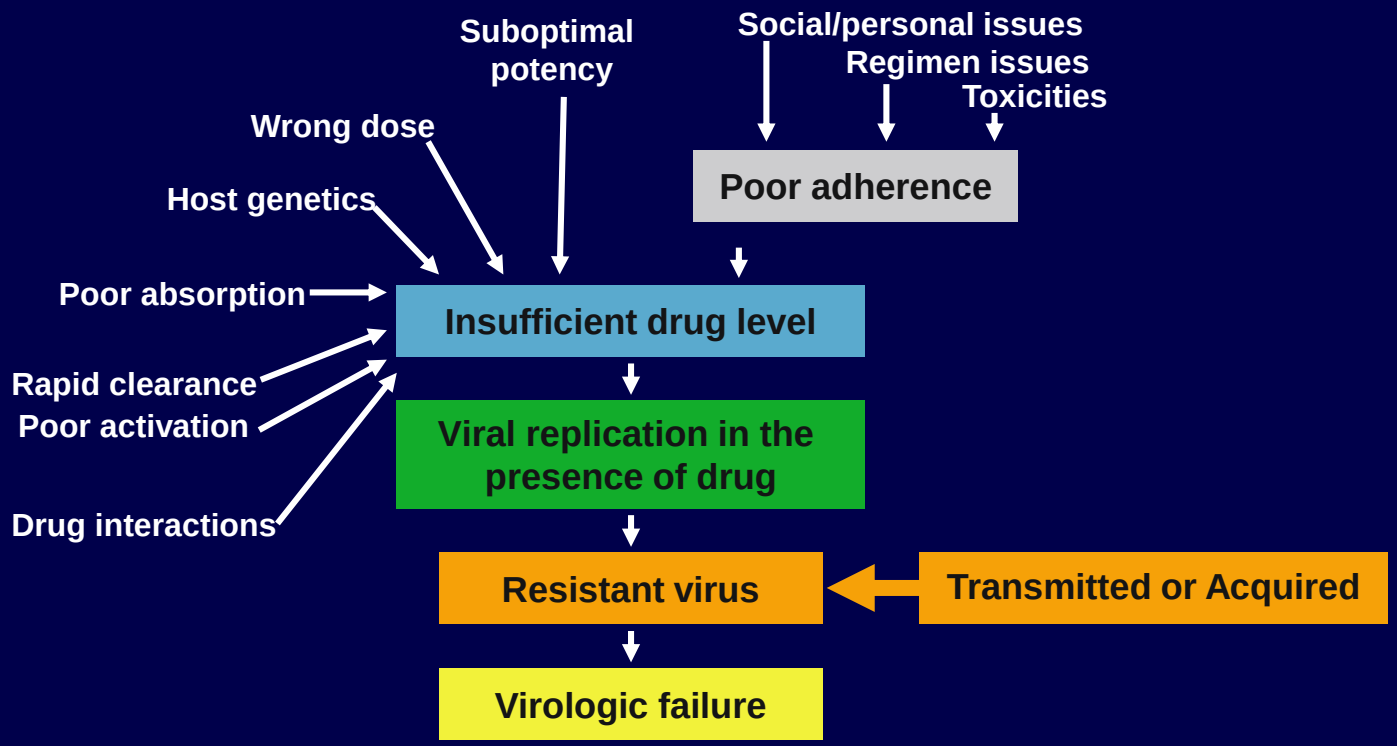
- Treatment failure in resource rich and limited setting
- Transmitted and acquired resistance
- Approach to treatment failure in Indonesia/Angsamerah
- Approach to treatment failure (WHO)
- Role of HIV resistance testing
- EARNEST trial
- SECOND-LINE trial

Introduction

Virologic suppression is the key to success of ART in controlling HIV infection and preventing HIV transmission

HIV Treatment Failure

Causes of Treatment Failure



DHHS Guidelines.

Slide credit: clinicaloptions.com

Some definitions first…

LLOD = Lower Limit of Detection

Wild Type (WT) virus / Resistant virus pool

Genotypic Resistance Testing

Transmitted HIV resistance

Acquired HIV resistance

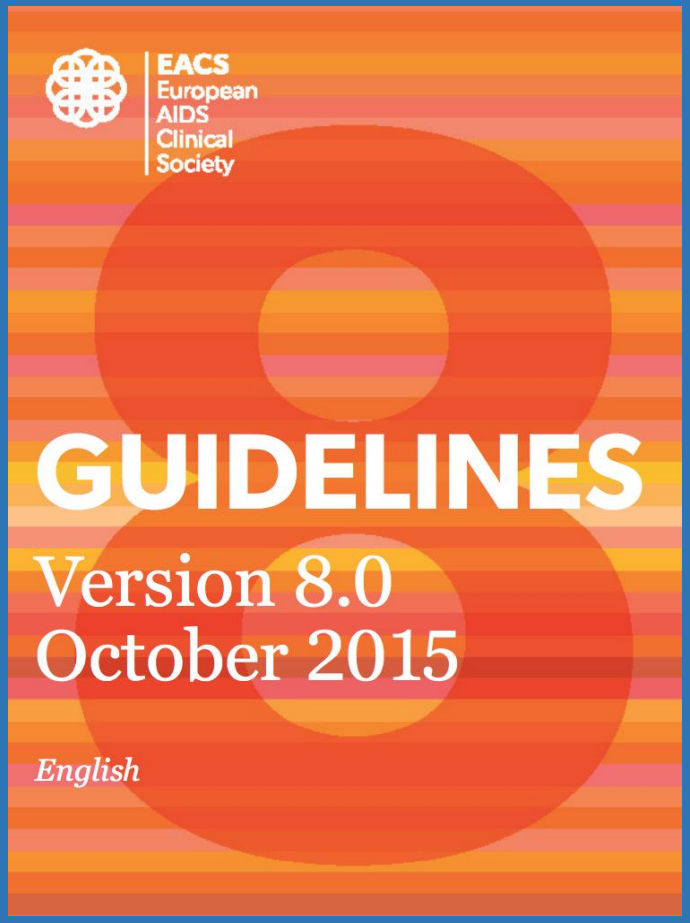
Selective drug pressure

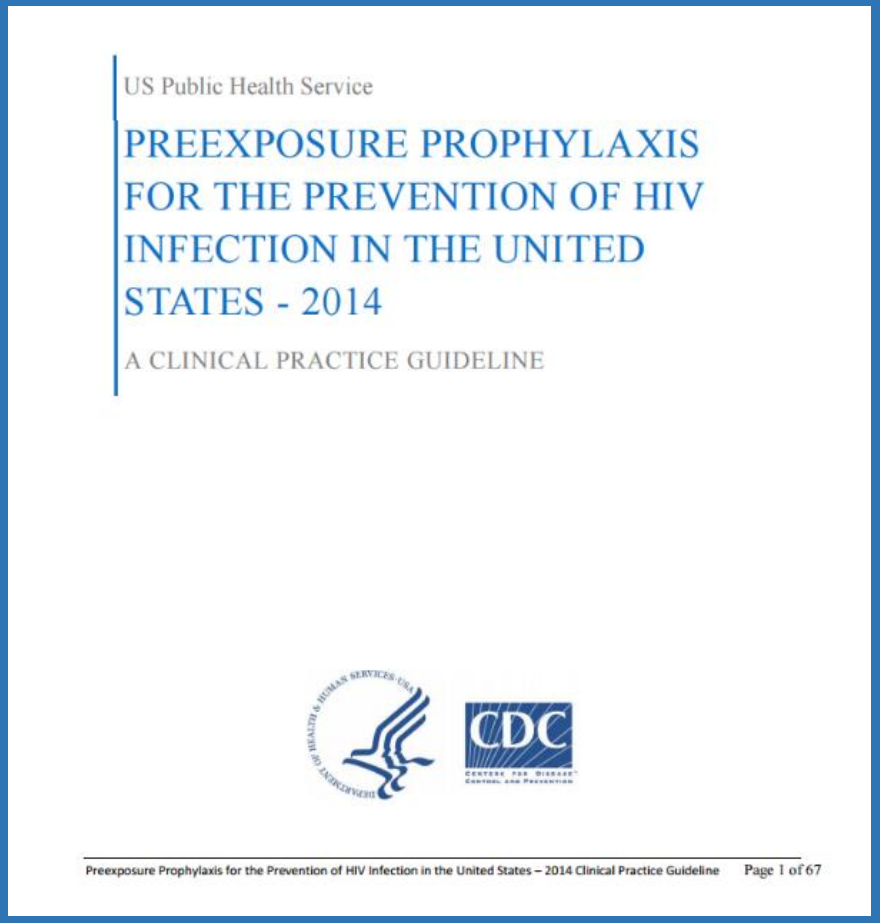
Archived mutations

First/Second/Third line ART

Treatment failure in resource-rich setting

Treatment Failure
resource-rich setting




US Public Health Service

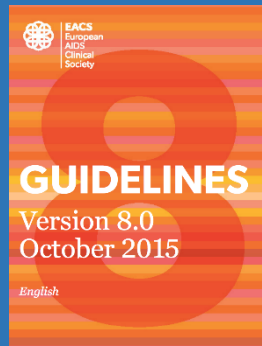
PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014

A CLINICAL PRACTICE GUIDELINE

CDC

Definition of viral failure
EACS

- HIV-VL > 50 cp/mL 6 months after starting/modifying therapy



Definitions of viral failure

DHHS

Virologic failure: when ART fails to suppress and maintain viral load to < 200 cp/mL

Virologic suppression: HIV-VL level below LLOD

…so what about patients with HIV-VL detectable, but below 200 cp/mL?

<50cp/mL ? 200 cp/mL Resistance

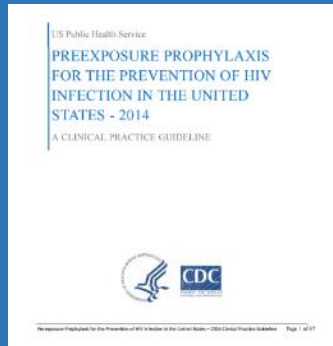
Approach to detectable HIV-VLs

HIV-VL (repeatedly) above LLOD and <200 cp/mL:

- assess adherence
- drug-drug interactions
- drug-food interactions
- no change of ART!
- monitor HIV-VLs every 3 months

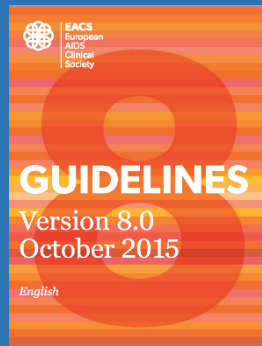
HIV-VL (repeatedly) above LLOD and ≥200 and <1,000 cp/mL:

- assess adherence, drug-drug interactions, drug-food interactions
- consider GRT
- what if no GRT available or cannot be sequenced:
  - **switch?**
  - **wait?**



Approach to treatment failure

- Review expected potency of regimen
- Evaluate
  - Adherence
  - Tolerability
  - Drug-drug interactions
  - Drug-food interactions
  - Psychosocial issues
- Perform resistance testing (usually available if HIV-VL > 500 cp/mL)
- Obtain historical resistance testing for archived mutations
- Tropism testing
- Consider TDM
- Review ART history
- Identify treatment options, active and potentially active drugs/combinations



Approach to treatment failure

- Review expected potency of regimen
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  - Drug-drug interactions
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- ~~Perform resistance testing (usually available if HIV-VL > 500 cp/mL)~~
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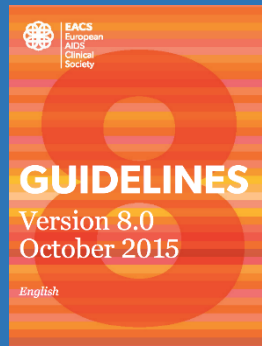


DHHS Guidelines for Virologic Failure

- Assess adherence, drug–drug or drug–food interactions, tolerability, HIV-1 RNA and CD4+ count trends, treatment history, and prior and current resistance data
- Perform resistance test while the patient is on failing ART, or within 4 wks of discontinuation; testing after this point may still provide useful information
- Goal of treatment for ART-experienced pts with drug resistance and virologic failure is to suppress HIV-1 RNA
- New regimen should include ≥ 2, and preferably 3, fully active agents, ie, agents with uncompromised activity based on treatment and resistance, and/or novel action

DHHS Guidelines. May 2015.

Case #1 – Mr TC

48 year old man on Atripla (TDF/FTC/EFV) for 7 years, with consistently suppressed viral loads comes for routine follow up.

- creatinine 89 µmol/L (N)
- LFT: N
- FBC: WBC 12.6 $x10^9$/L

HIV-VL: 626 cp/mL

TREATMENT FAILURE?

Case #1 – Mr TC

- ✓ adherence
- ✓ new medications
- ✓ supplements
- ✓ recreational drugs
- ✓ jamu

What to do next?

1. HIV Resistance testing
2. Switch ART regimen
3. Repeat HIV-VL in 2 months
4. No actions now, schedule routine follow up in 6 months

Case #1 – Mr TC

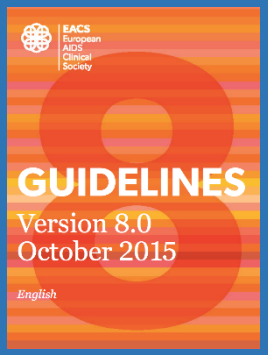
2 months later, HIV-VL: undetectable

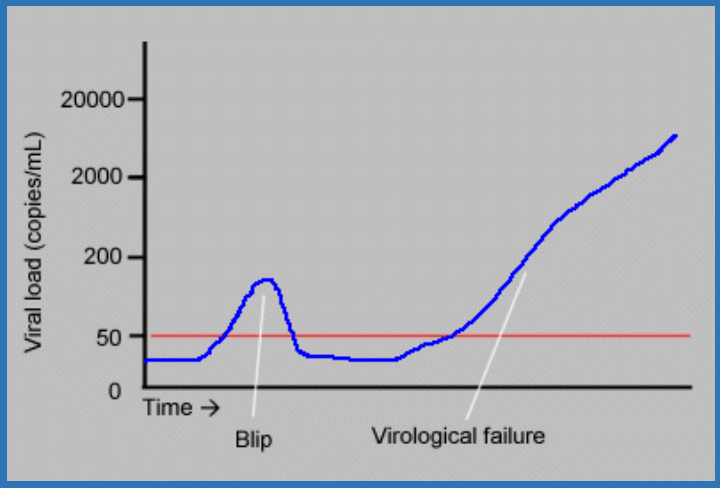
Patient shared that he had flu when taking bloods two months ago

VIRAL BLIP

HIV-VL >50 and < 500-1,000 cp/mL

- check adherence
- check HIV-VL again in 1-2 months
- usually viral blips
  - transient increases in HIV-VL (usually <2,000 cp/mL)
  - do not lead to development of resistance
  - often associated with intercurrent viral infections
  - implications for U=U / TasP?





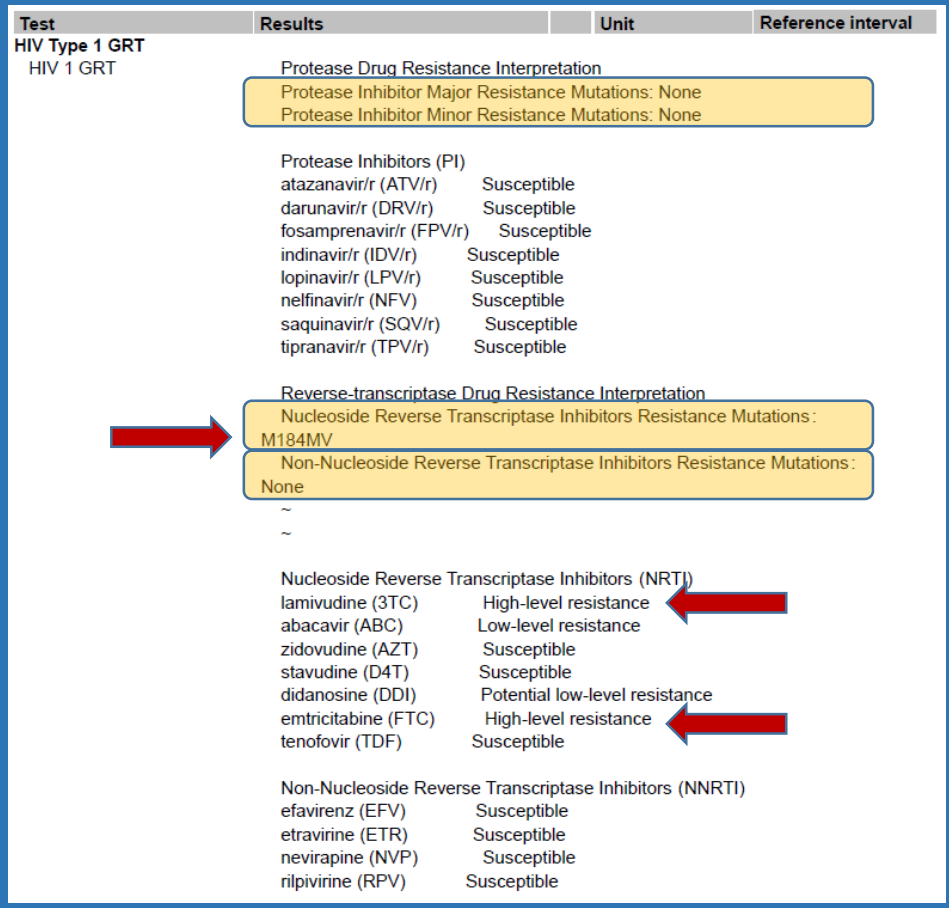
Source: i-base.info

Learning points from this case

- Not every rise in HIV-VL is treatment failure
- Important as it can lead to patient's anxiety

Case #2 – Mr JL

- Diagnosed in 2015 through voluntary testing
- Baseline GRT:
  - M184V mutation



Test	Results		Unit	Reference interval
HIV Type 1 GRT				
HIV 1 GRT				

Protease Drug Resistance Interpretation
Protease Inhibitor Major Resistance Mutations: None
Protease Inhibitor Minor Resistance Mutations: None

Protease Inhibitors (PI)

atazanavir/r (ATV/r)	Susceptible
darunavir/r (DRV/r)	Susceptible
fosamprenavir/r (FPV/r)	Susceptible
indinavir/r (IDV/r)	Susceptible
lopinavir/r (LPV/r)	Susceptible
nelfinavir/r (NFV)	Susceptible
saquinavir/r (SQV/r)	Susceptible
tipranavir/r (TPV/r)	Susceptible

Reverse-transcriptase Drug Resistance Interpretation
Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: M184MV
Non-Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: None
~
~

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

lamivudine (3TC)	High-level resistance
abacavir (ABC)	Low-level resistance
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
didanosine (DDI)	Potential low-level resistance
emtricitabine (FTC)	High-level resistance
tenofovir (TDF)	Susceptible

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

Case #2 – Mr JL

- Diagnosed in 2015 through voluntary testing
- Baseline GRT:
  - M184V mutation

ART started on 4 Dec 2015:

ZDV/3TC/TDF/DRV(r)

Test	Results		Unit	Reference interval
HIV Type 1 GRT				
HIV 1 GRT	Protease Drug Resistance Interpretation Protease Inhibitor Major Resistance Mutations: None Protease Inhibitor Minor Resistance Mutations: None Protease Inhibitors (PI) atazanavir/r (ATV/r) Susceptible darunavir/r (DRV/r) Susceptible fosamprenavir/r (FPV/r) Susceptible indinavir/r (IDV/r) Susceptible lopinavir/r (LPV/r) Susceptible nelfinavir/r (NFV) Susceptible saquinavir/r (SQV/r) Susceptible tipranavir/r (TPV/r) Susceptible Reverse-transcriptase Drug Resistance Interpretation Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: M184MV Non-Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: None ~ ~ Nucleoside Reverse Transcriptase Inhibitors (NRTI) lamivudine (3TC) High-level resistance abacavir (ABC) Low-level resistance zidovudine (AZT) Susceptible stavudine (D4T) Susceptible didanosine (DDI) Potential low-level resistance emtricitabine (FTC) High-level resistance tenofovir (TDF) Susceptible Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) efavirenz (EFV) Susceptible etravirine (ETR) Susceptible nevirapine (NVP) Susceptible rilpivirine (RPV) Susceptible			

Case #2 – Mr JL

- Diagnosed in 2015 through voluntary testing
- Baseline GRT:
  - M184V mutation

ART started on 4 Dec 2015:

ZDV/3TC/TDF/DRV(r)

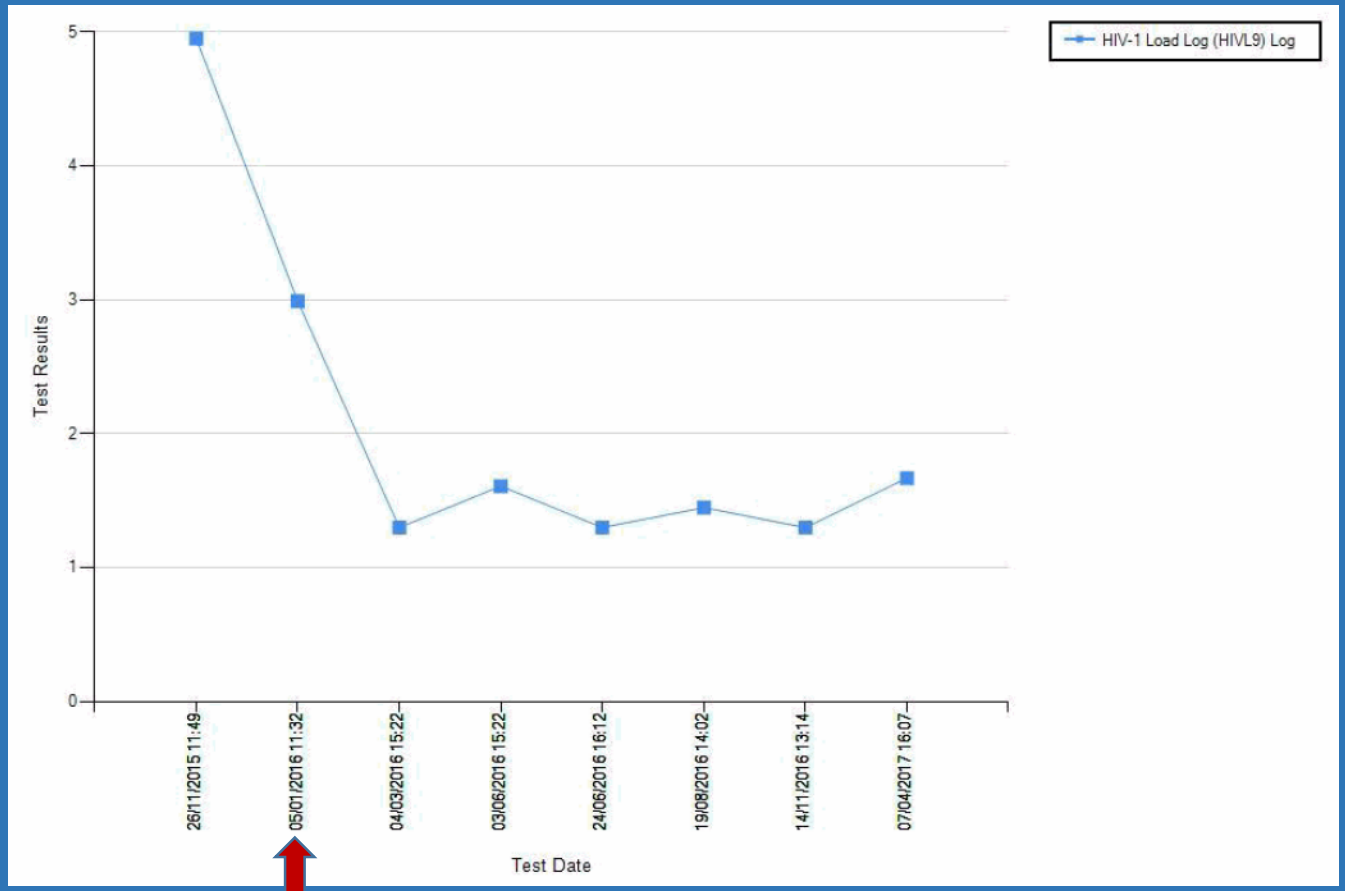
Jan 2016 ART switch to:

3TC/TDF/DRV(r)/RAL

(patient could not tolerate ZDV)

Test	Results		Unit	Reference interval
HIV Type 1 GRT				
HIV 1 GRT	Protease Drug Resistance Interpretation			
	Protease Inhibitor Major Resistance Mutations: None			
	Protease Inhibitor Minor Resistance Mutations: None			
	Protease Inhibitors (PI)			
	atazanavir/r (ATV/r)	Susceptible		
	darunavir/r (DRV/r)	Susceptible		
	fosamprenavir/r (FPV/r)	Susceptible		
	indinavir/r (IDV/r)	Susceptible		
	lopinavir/r (LPV/r)	Susceptible		
	nelfinavir/r (NFV)	Susceptible		
	saquinavir/r (SQV/r)	Susceptible		
	tipranavir/r (TPV/r)	Susceptible		
	Reverse-transcriptase Drug Resistance Interpretation			
	Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: M184MV			
	Non-Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: None			
	~			
	~			
	Nucleoside Reverse Transcriptase Inhibitors (NRTI)			
	lamivudine (3TC)	High-level resistance		
	abacavir (ABC)	Low-level resistance		
	zidovudine (AZT)	Susceptible		
	stavudine (D4T)	Susceptible		
	didanosine (DDI)	Potential low-level resistance		
	emtricitabine (FTC)	High-level resistance		
	tenofovir (TDF)	Susceptible		
	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)			
	efavirenz (EFV)	Susceptible		
	etravirine (ETR)	Susceptible		
	nevirapine (NVP)	Susceptible		
	rilpivirine (RPV)	Susceptible		

Case #2 – Mr JL



3TC/TDF/DRV(r)/RAL

Transmitted HIV resistance

- Resistant mutations transmitted with the virus to the patient
- Not associated with noncompliance of the patient
- First line ART must be adjusted if such transmitted mutations are present
  - role of genotypic resistance testing (GRT)
- Prevalence varies across the world

Prevalence of Transmitted MDR HIV in the US: Selected Studies

- Transmission of HIV resistant to a single class of ARV more common than HIV resistant to multiple classes[1,3]
  - 13.6%, 2.1%, and 0.5% of transmitted HIV resistant to 1, 2, and 3 ARV classes, respectively[3]

Prevalence of Transmitted Drug-Resistant HIV (2009-2013), %[1-3]	
Overall	12.6-16.2
▪ NRTI	3.7-6.7
▪ NNRTI	8.1-8.4
▪ PI	2.0-4.5

1. Baxter JD, et al. HIV Med. 2015;16:77-87. 2. INSIGHT START Study Group. N Engl J Med. 2015;373:795-807. 3. Kim D, et al. CROI 2013. Abstract 149.

Current Status of INSTI Resistance in the US

- Transmitted INSTI resistance remains rare and rates of on-treatment INSTI resistance continue to be low[1-3]

Study	Key Findings
CDC National HIV Surveillance System[1]	▪ Prevalence of INSTI resistance for HIV diagnoses through 2014: 65/14,468 (0.4%) ▪ Pre-ART prevalence of INSTI resistance (ie, transmitted): 2/4631 (0.04%)
UNC CFAR HIV Clinical Cohort[2]	▪ 2015 INSTI resistance prevalence in 685 pts who began ART in 2007 or later: 1%
Modeling study[3]	▪ Assuming 0.1% rate of transmitted INSTI resistance and $250 cost per test: pre-ART INSTI resistance testing correlated with worse outcomes, higher costs vs no test

1. Hernandez AL, et al. CROI 2017. Abstract 478. 2. Davy T, et al. CROI 2017. Abstract 483.
3. Koullias Y, et al. CROI 2017. Abstract 493.

Learning points from this case

- Patients starting ART may have transmitted resistance
- Prevalence of transmitted resistance varies across the world (highest in U.S., low in Asia Pacific Region)
- M184V mutation:
  - most common mutation selected by 3TC
  - cross resistance to FTC
  - hypersensitivity to ZDV and TDF
  - less fit virus (this patient started on 3TC despite lack of activity based on GRT)

Case #3 – Mr LH

- MSM, diagnosed in Sep 2014 after an episode of herpes zoster
- CD4 nadir 274 (13%)
- Baseline HIV-VL: 1.59E+04 copies/mL

Case #3 – Mr LH

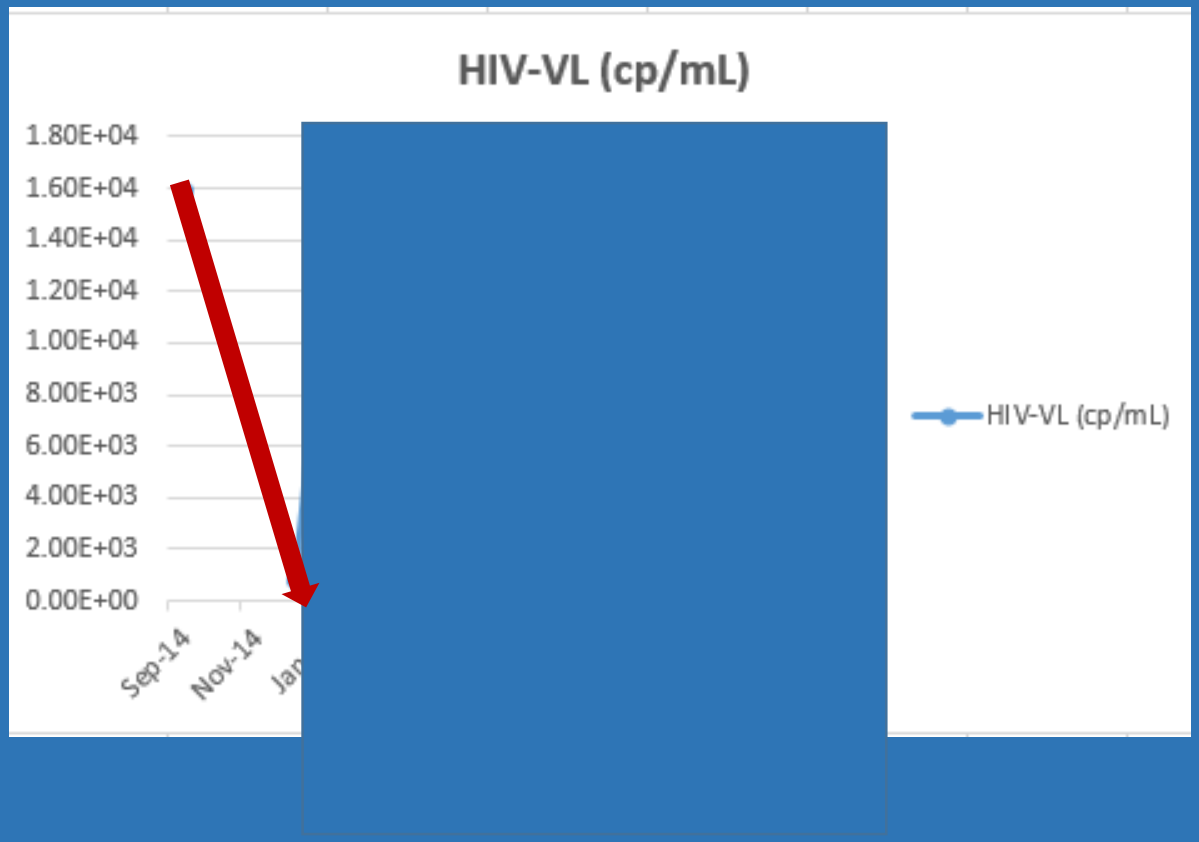
GRT September 2014

Test	Results		Unit	Reference interval
HIV Type 1 GRT				
HIV 1 GRT	Protease Drug Resistance Interpretation			
	Protease Inhibitor Major Resistance Mutations: None			
	Protease Inhibitor Minor Resistance Mutations: None			
	Other Mutations: L63P, I72IV, V77I, I93L			
	Protease Inhibitors (PI)			
	atazanavir/r (ATV/r)	Susceptible		
	darunavir/r (DRV/r)	Susceptible		
	fosamprenavir/r (FPV/r)	Susceptible		
	indinavir/r (IDV/r)	Susceptible		
	lopinavir/r (LPV/r)	Susceptible		
	nelfinavir/r (NFV)	Susceptible		
	saquinavir/r (SQV/r)	Susceptible		
	tipranavir/r (TPV/r)	Susceptible		
	Reverse-transcriptase Drug Resistance Interpretation			
	Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: None			
	Non-Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: V106I			
	Other Mutations: E6EK, K122E, S162AT, K173EK, Q174R, I178M, T200I, Q207D, R211K, V245E, A272P, I293IV, P313T, Q334L, P345PQ, V365I, K385R, K390R			
	Nucleoside Reverse Transcriptase Inhibitors (NRTI)			
	lamivudine (3TC)	Susceptible		
	abacavir (ABC)	Susceptible		
	zidovudine (AZT)	Susceptible		
	stavudine (D4T)	Susceptible		
	didanosine (DDI)	Susceptible		
	emtricitabine (FTC)	Susceptible		
	tenofovir (TDF)	Susceptible		
	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)			
	efavirenz (EFV)	Susceptible		
	etravirine (ETR)	Susceptible		
	nevirapine (NVP)	Susceptible		
	rilpivirine (RPV)	Susceptible		

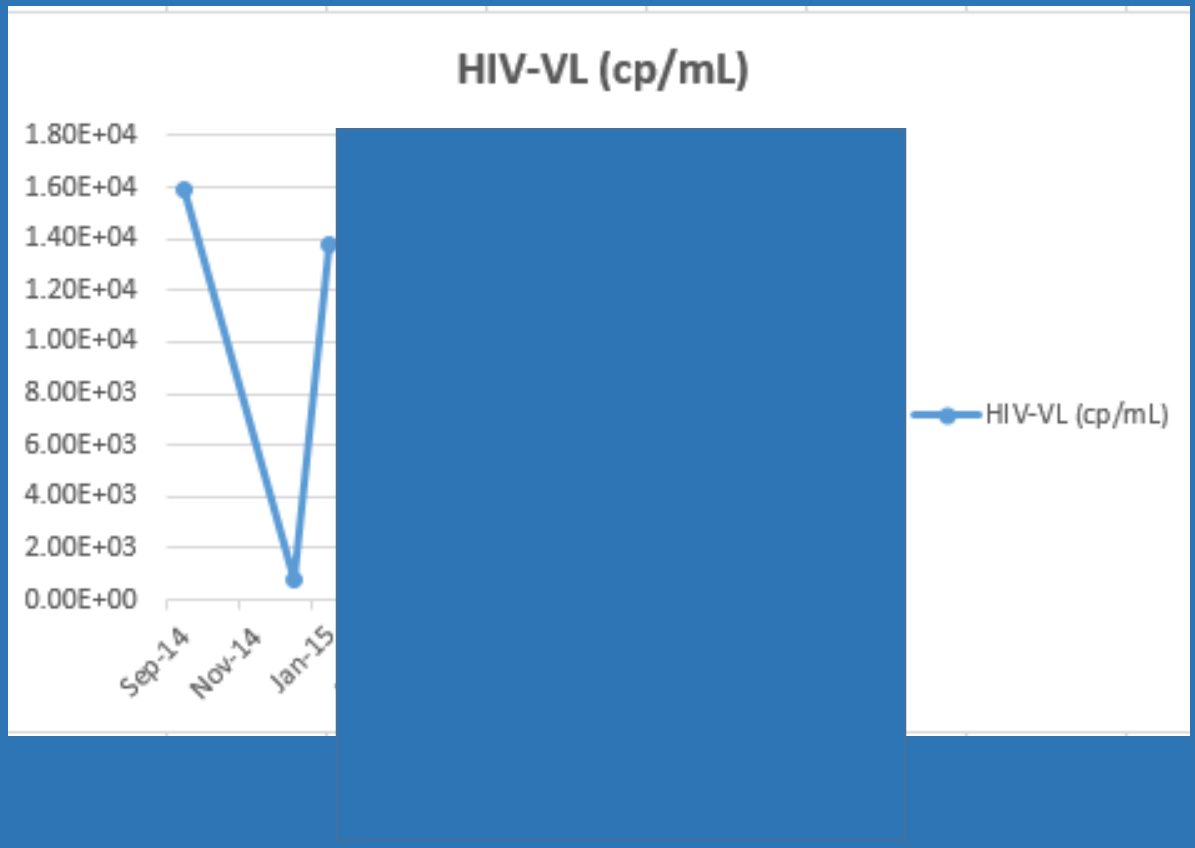
Case #3 – Mr LH

ART started in Nov 2014:

TDF/3TC/EFV



Case #3 - Mr LH


HIV-VL (cp/mL)
1.80E+04
1.60E+04
1.40E+04
1.20E+04
1.00E+04
8.00E+03
6.00E+03
4.00E+03
2.00E+03
0.00E+00
Sep-14
Nov-14
Jan-15
HIV-VL (cp/mL)

Case #3 - Mr LH

GRT February 2015

Test	Results		Unit	Reference interval
HIV Type 1 GRT				
HIV 1 GRT	Protease Drug Resistance Interpretation			
	Protease Inhibitor Major Resistance Mutations: None Protease Inhibitor Minor Resistance Mutations: None			
	Protease Inhibitors (PI)			
	atazanavir/r (ATV/r)	Susceptible		
	darunavir/r (DRV/r)	Susceptible		
	fosamprenavir/r (FPV/r)	Susceptible		
	indinavir/r (IDV/r)	Susceptible		
	lopinavir/r (LPV/r)	Susceptible		
	nelfinavir/r (NFV)	Susceptible		
	saquinavir/r (SQV/r)	Susceptible		
	tipranavir/r (TPV/r)	Susceptible		
	Reverse-transcriptase Drug Resistance Interpretation			
	Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: K65KR, M184IMV			
	Non-Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: V106I, V179DV, Y181CY, Y188L			
	~			
	~			
	Nucleoside Reverse Transcriptase Inhibitors (NRTI)			
	lamivudine (3TC)	High-level resistance		
	abacavir (ABC)	High-level resistance		
	zidovudine (AZT)	Susceptible		
	stavudine (D4T)	Intermediate resistance		
	didanosine (DDI)	High-level resistance		
	emtricitabine (FTC)	High-level resistance		
	tenofovir (TDF)	High-level resistance		
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	etravirine (ETR)	Intermediate resistance		
	nevirapine (NVP)	High-level resistance		
	rilpivirine (RPV)	High-level resistance		

Case #3 - Mr LH

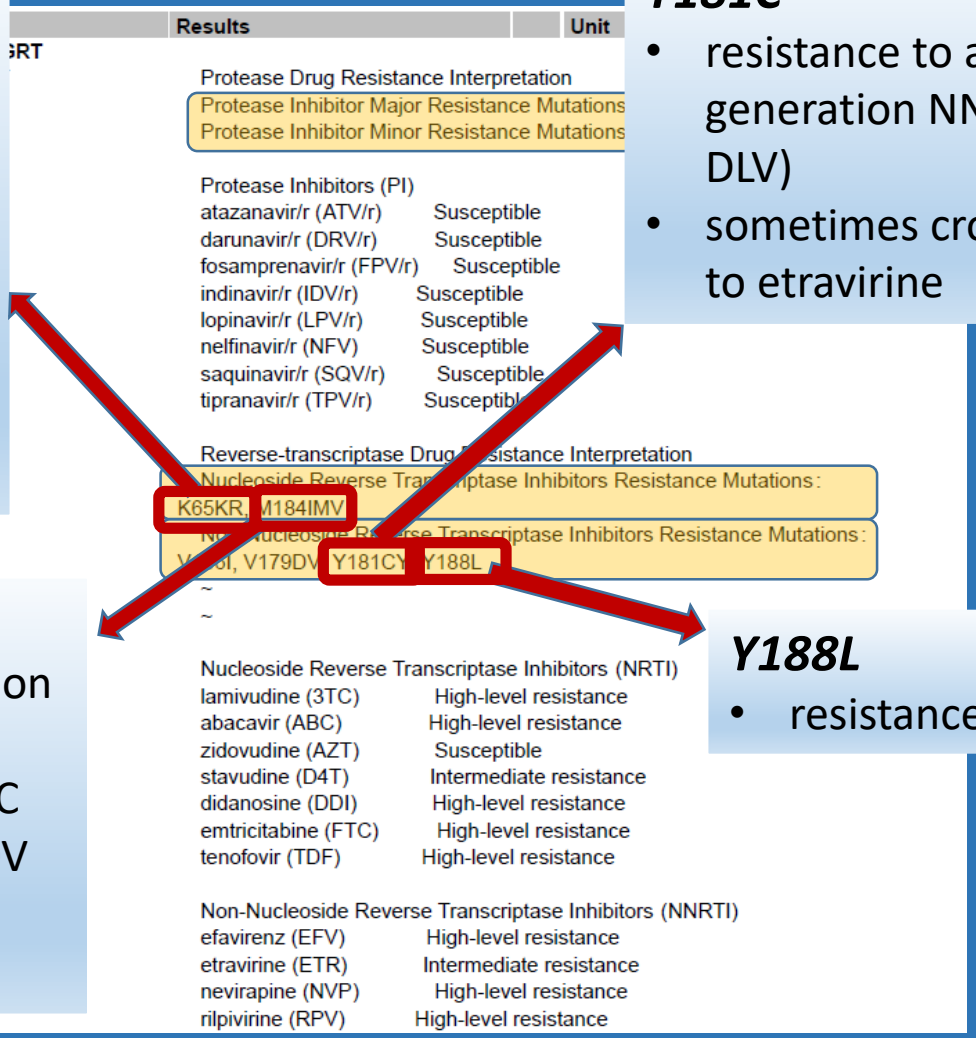
GRT February 2015

K65R

- most common mutation selected by TDF
- cross resistance to ABC, 3TC and FTC
- Hypersensitivity to ZDV
- less fit virus

Y181C

- resistance to all 1st generation NNRTIs (EFV, NVP, DLV)
- sometimes cross-resistance to etravirine



	Results	Unit
GRT		
Protease Drug Resistance Interpretation		
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lopinavir/r (LPV/r)	Susceptible	
nelfinavir/r (NFV)	Susceptible	
saquinavir/r (SQV/r)	Susceptible	
tipranavir/r (TPV/r)	Susceptibl	
Reverse-transcriptase Drug [illegible]sistance Interpretation		
Nucleoside Reverse Tra[illegible]ptase Inhibitors Resistance Mutations:		
K65KR, M184IMV		
[illegible]ucleoside R[illegible]erse Transcriptase Inhibitors Resistance Mutations:		
[illegible]I, V179DV, Y181CY, Y188L		
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~		
Nucleoside Reverse Transcriptase Inhibitors (NRTI)		
lamivudine (3TC)	High-level resistance	
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didanosine (DDI)	High-level resistance	
emtricitabine (FTC)	High-level resistance	
tenofovir (TDF)	High-level resistance	
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)		
efavirenz (EFV)	High-level resistance	
etravirine (ETR)	Intermediate resistance	
nevirapine (NVP)	High-level resistance	
rilpivirine (RPV)	High-level resistance	

M184V

- most common mutation selected by 3TC
- cross resistance to FTC
- hypersensitivity to ZDV and TDF
- less fit virus

Y188L

- resistance EFV, NVP, DVD

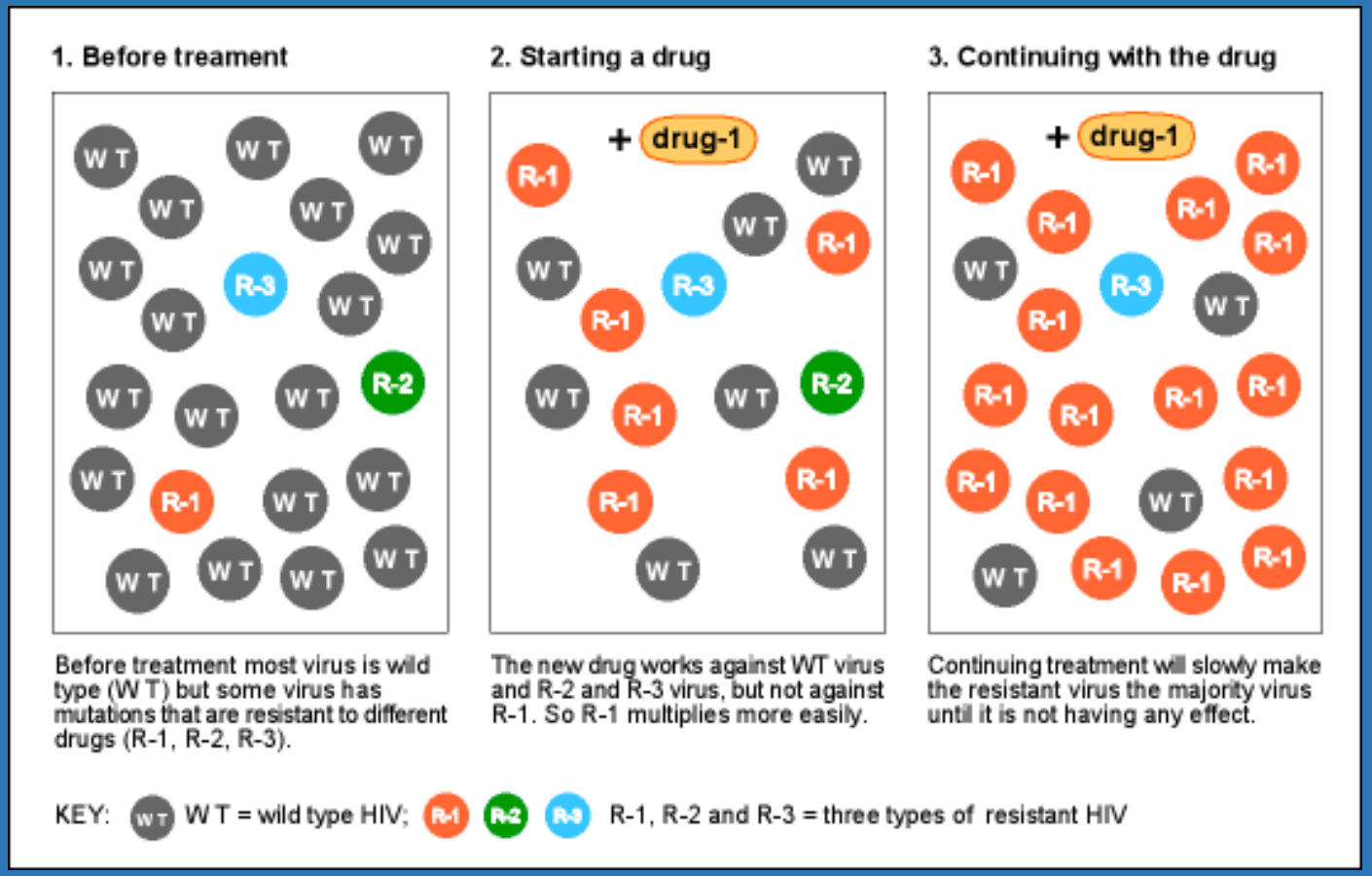
Archived Resistant Mutations

- No adherence/interaction issues
- Mr LH was infected with a pool of virus containing wild type virus and virus with resistant mutations
- When the first GRT was performed in Sep 2014, he was not on ART, hence there was no pressure to select the strain with mutations
- Once ART was started (TDF/3TC/EFV) it controlled wild type virus which became undetectable, but could not control resistant strain because that strain had mutations resistant to TDF, 3TC and EFV.

Archived Resistant Mutations

- these mutations develop under selective pressure of the ART
- when selective drug pressure is removed, the strain with the mutation becomes overgrown by the wild type virus

Wild Type vs Resistant Strains



Source: www.i-base.info

Wild Type vs Resistant Strains

- virus strains which developed mutations are generally less fit
- the fittest strains of the virus will prevail and form the main strain:
  - WT virus (when not on treatment)
  - mutated virus (when selective pressure of ART controls the WT virus, but select the strains with drug resistant mutations)

Wild Type vs Resistant Strains

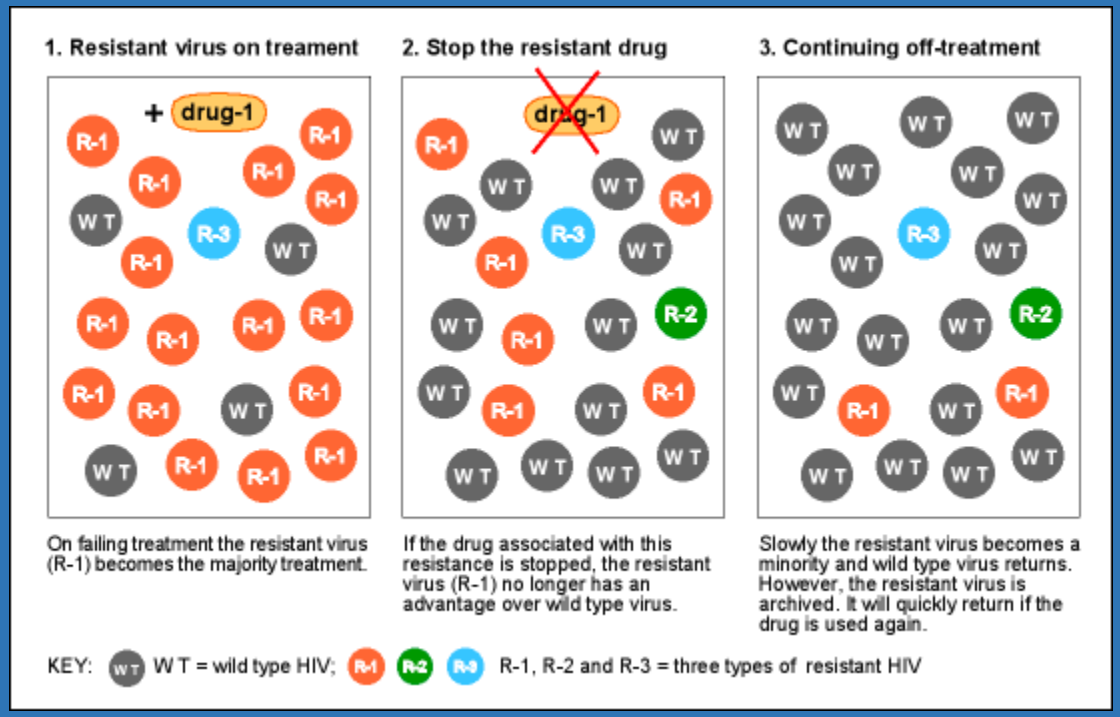
Drug resistance mutations are less fit, but because continuing current ART exerts this selective pressure on the virus populations, WT remains suppressed and the resistant strain multiplies more efficiently

Transmitted Resistance

- Individual infected with a resistant virus (eg from somebody with resistant virus who is failing treatment) will initially have resistant virus circulating as main strain – if diagnosed within weeks of infection, GRT will detect these mutations
- After 4-6 weeks the mutations will become archived and the WT will start dominate as there is no selective pressure from ART; GRT will show WT virus and will not detect archived mutations

Testing for HIV Drug Resistance

Resistance-associated mutations become archived 4-6 weeks after removing selective pressure of ART and the wild type virus dominates again

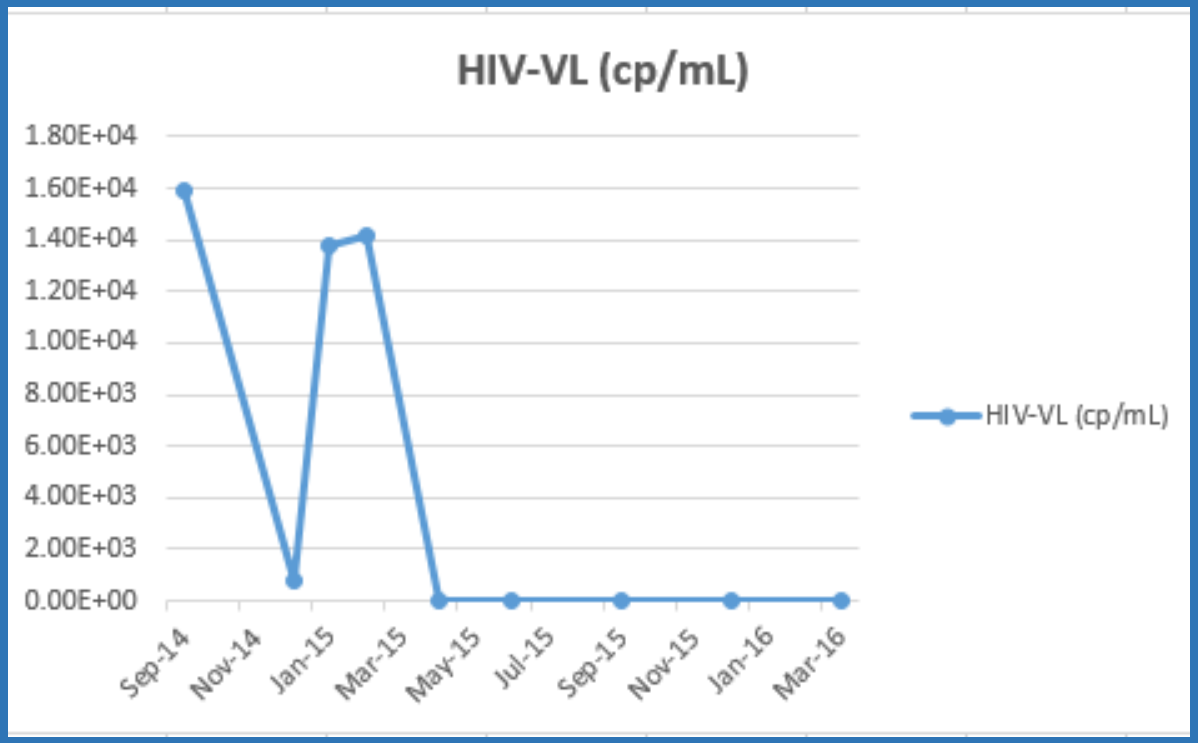


Source: www.i-base.info

Case #3 – Mr LH

ART switch in Feb 2015:

3TC/RAL/DRV(r)



Learning points from this case

- Standard baseline GRT (IDR 5,300,000) did not make any difference for this patient
- Regular HIV-VL monitoring was essential in detecting treatment failure
- Treatment failure is not always due to lack of adherence of interactions with new medications / jamu

Case #4

Approach to treatment failure

in Indonesia / Angsamerah…

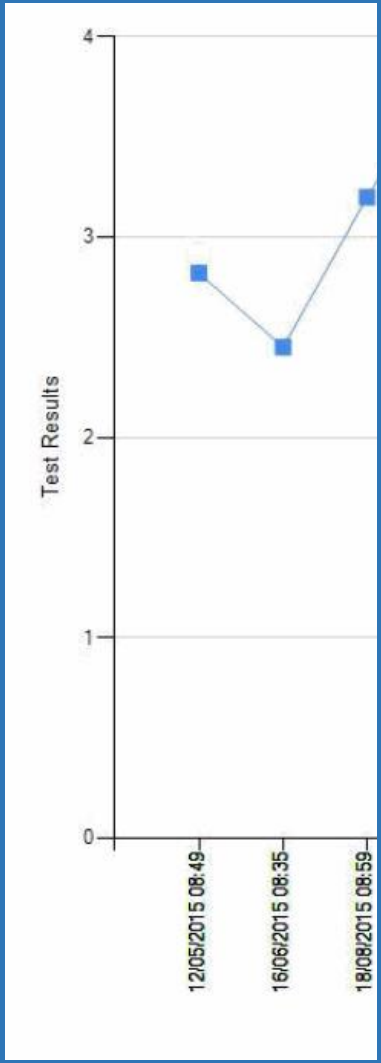
Case #4 - Mr TH

- heterosexual man diagnosed in 2015 with CMV encephalitis
- CD4 nadir: 71 cells/microL
- baseline HIV-VL: 3.12E+06 copies/mL
- baseline GRT: WT virus (no primary resistance)

ART initiated in May 2015:

TDF/3TC/DRV(r)

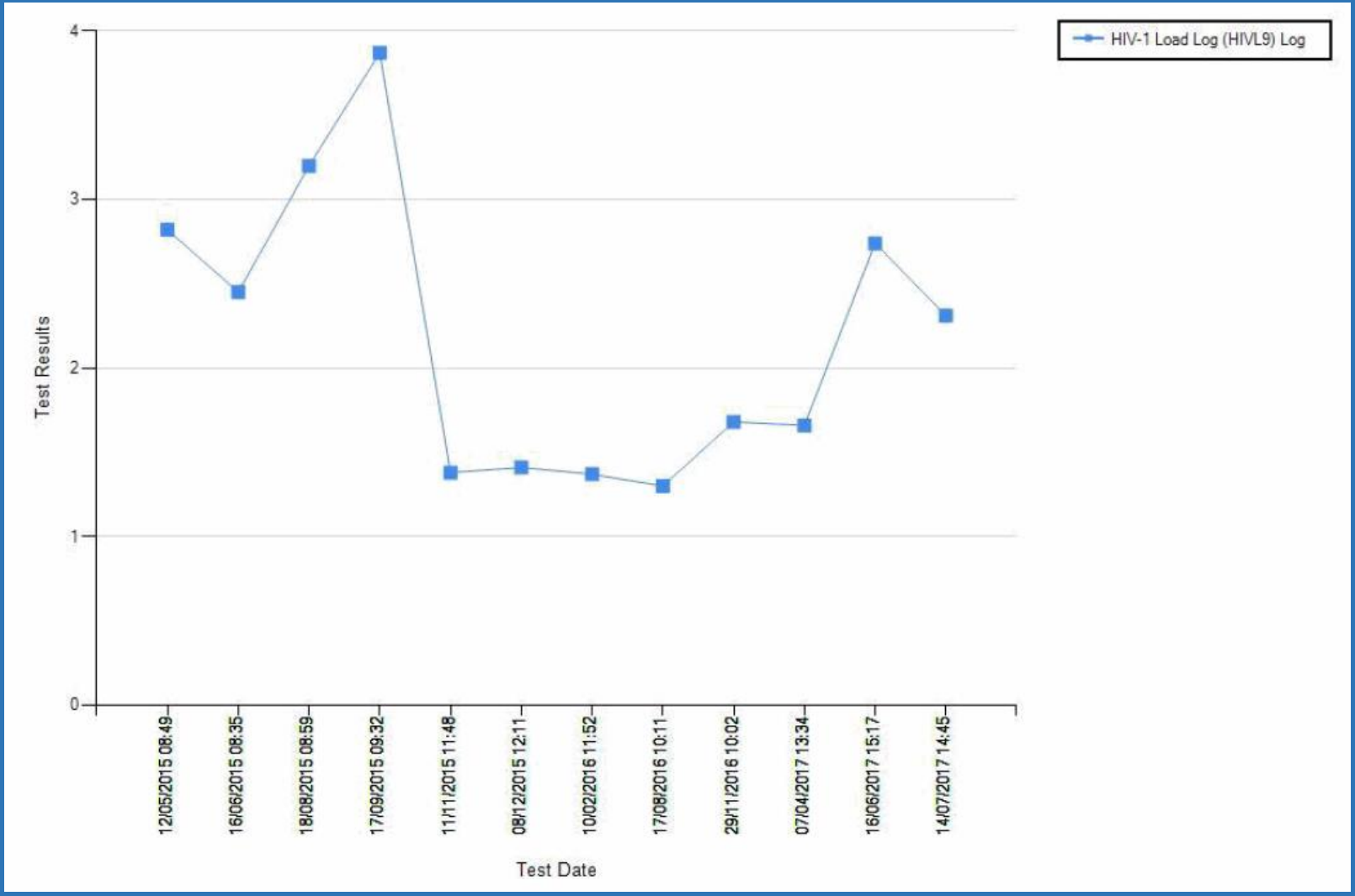
Case #4 - Mr TH


Test Results
4
3
2
1
0
12/05/2015 08:49
16/06/2015 08:35
18/08/2015 08:59

What do you do?

local approach…

Case #4 - Mr TH


HIV-1 Load Log (HIVL9) Log
Test Results
0
1
2
3
4
12/05/2015 08:49
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17/09/2015 09:32
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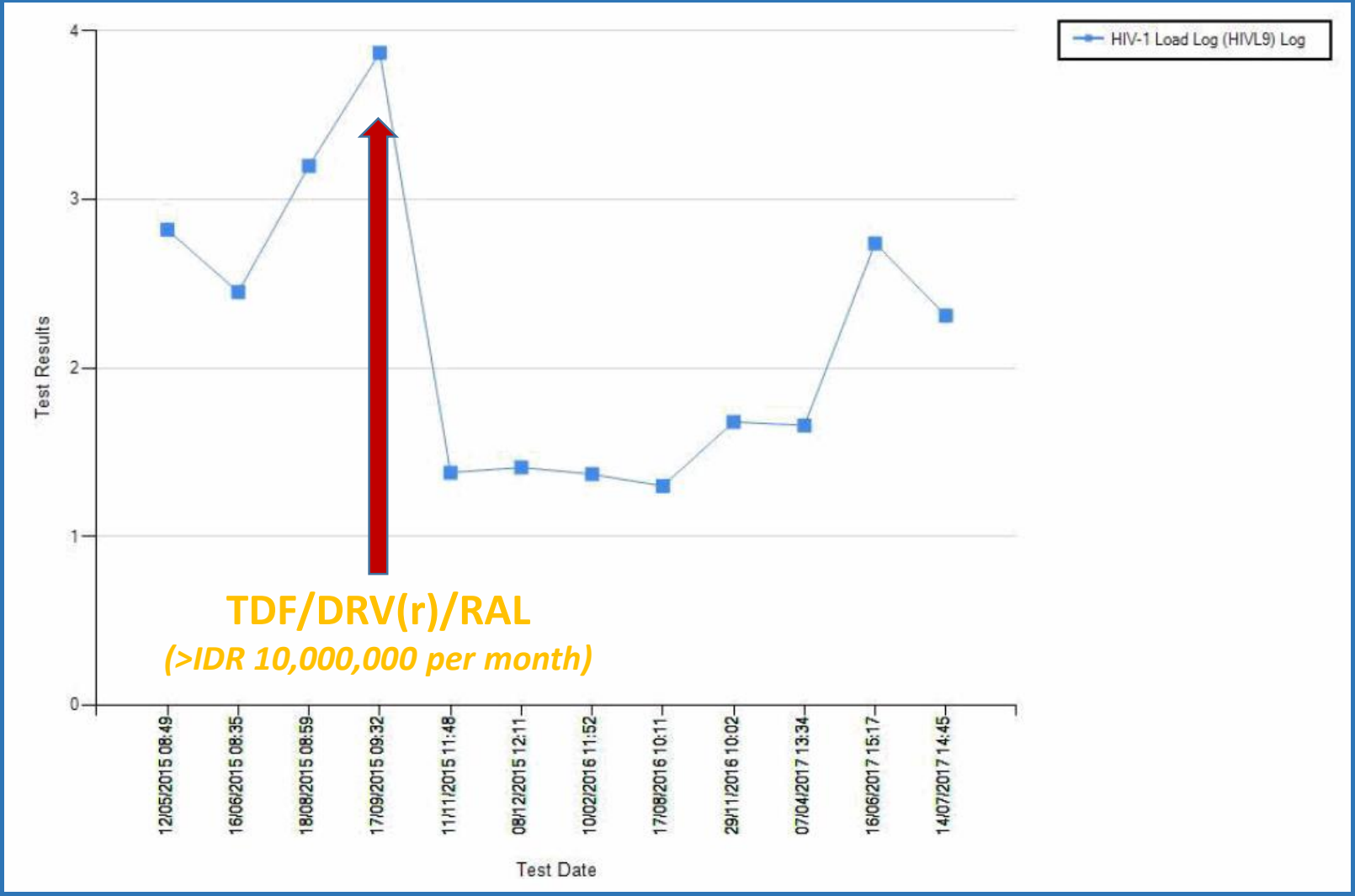
08/12/2015 12:11
10/02/2016 11:52
17/08/2016 10:11
29/11/2016 10:02
07/04/2017 13:34
16/06/2017 15:17
14/07/2017 14:45
Test Date

Case #4 - Mr TH

GRT – Mar 2015

Test	Results		Unit	Reference interval
HIV Type 1 GRT				
HIV 1 GRT	Protease Drug Resistance Interpretation Protease Inhibitor Major Resistance Mutations: None Protease Inhibitor Minor Resistance Mutations: K20I			
	Protease Inhibitors (PI)			
	atazanavir/r (ATV/r)	Susceptible		
	darunavir/r (DRV/r)	Susceptible		
	fosamprenavir/r (FPV/r)	Susceptible		
	indinavir/r (IDV/r)	Susceptible		
	lopinavir/r (LPV/r)	Susceptible		
	nelfinavir/r (NFV)	Potential low-level resistance		
	saquinavir/r (SQV/r)	Susceptible		
	tipranavir/r (TPV/r)	Susceptible		
	Reverse-transcriptase Drug Resistance Interpretation Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: M184I, T215AT Non-Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: None			
	Nucleoside Reverse Transcriptase Inhibitors (NRTI)			
	lamivudine (3TC)	High-level resistance		
	abacavir (ABC)	Low-level resistance		
	zidovudine (AZT)	Potential low-level resistance		
	stavudine (D4T)	Potential low-level resistance		
	didanosine (DDI)	Low-level resistance		
	emtricitabine (FTC)	High-level resistance		
	tenofovir (TDF)	Susceptible		
	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)			
	efavirenz (EFV)	Susceptible		
	etravirine (ETR)	Susceptible		
	nevirapine (NVP)	Susceptible		
	rilpivirine (RPV)	Susceptible		

Case #4 - Mr TH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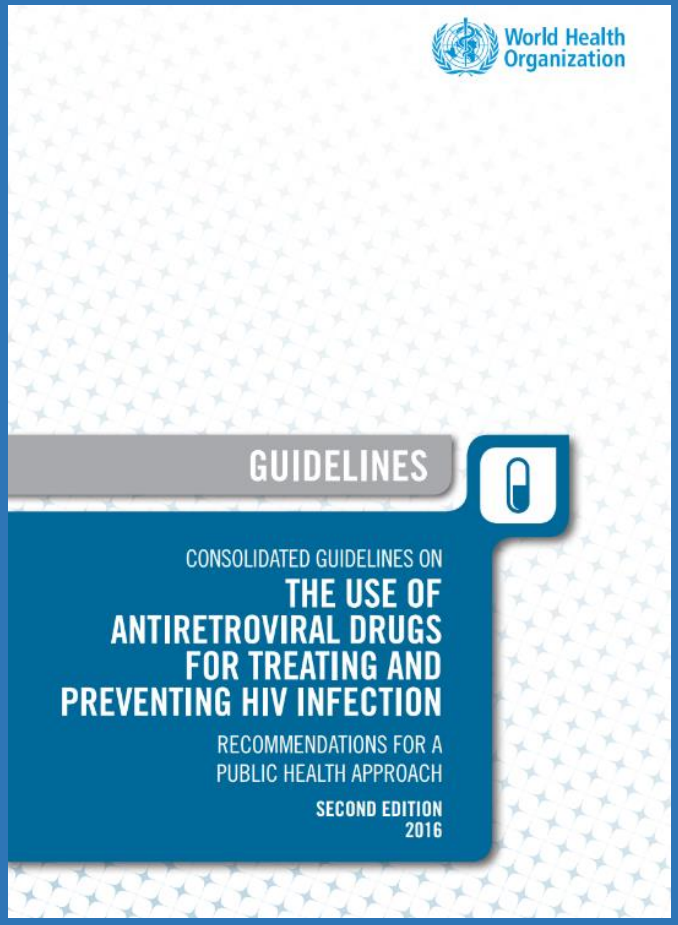
17/08/2016 10:11
29/11/2016 10:02
07/04/2017 13:34
16/06/2017 15:17
14/07/2017 14:45
Test Date
TDF/DRV(r)/RAL
(>IDR 10,000,000 per month)

Learning points from this case

- nonadherence usually most important cause of developing new resistance
- treatment failure and resistance mean *higher costs*
- approach to treatment failure need be individualized (avoiding 3TC in this case)

Approach to treatment failure in resource-limited setting



World Health Organization

WHO definition of viral failure

- two consecutive viral loads exceeding 1000 cp/mL after at least 6 months of starting a new ART regimen
  - within 3 month interval with adherence support between measurements
- plasma viral load is preferred
  - dried blood spot specimens can also be used (conditional recommendation)

World Health Organization

Routine vs targeted VL monitoring

- What is targeted VL monitoring?
  - HIV-VL performed to confirm virologic failure suspected based on clinical or immunologic criteria
- Advantages of targeted VL monitoring
  - less costly
- Risks of targeted VL monitoring
  - potential to delay switching to second line ART
  - increased risk of disease progression
  - selection of ARV drug resistance
  - HIV transmission

World Health Organization

Table 4.11. WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)[a] after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with the exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART For … clinical stage 3 c… sev… ind…
Immunological failure	**…dolescents** …cells/mm³ *Older than 5 y…* Persistent CD4 levels b… 100 cells/mm³	With… infection to c… …the CD4 cell count …O clinical and …cal criteria have low …nd positive predictive …entifying individuals …gical failure. There is …o proposed alternative …f treatment failure and …d alternative definition of …gical failure
Virologic failure	Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed

…ions associated with advanced or severe HIV disease associated with immunodeficiency in Annex 10.

[a] Previous guidelines d…d immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation. The option of CD4 cell count at or below 250 cells/mm³ following clinical failure is based on an analysis of data from Uganda and Zimbabwe *(379)*.

clinical failure

immunologic failure

virologic failure

Table 4.11. WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)[a] after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with the exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure[a]
Immunological failure	**Adults and adolescents** CD4 count at or below 250 cells/mm³ following clinical failure[b] or Persistent CD4 levels below 100 cells/mm³ **Children** *Younger than 5 years* Persistent CD4 levels below 200 cells/mm³ *Older than 5 years* Persistent CD4 levels below 100 cells/mm³	Without concomitant or recent infection to cause a transient decline in the CD4 cell count Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
Virological failure	Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed

[a] See the list of clinical conditions associated with advanced or severe HIV disease associated with immunodeficiency in Annex 10.

[b] Previous guidelines defined immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation. The option of CD4 cell count at or below 250 cells/mm³ following clinical failure is based on an analysis of data from Uganda and Zimbabwe *(379)*.

Role of Resistance Testing

Testing for HIV Drug Resistance

Genotypic Resistance Testing

- identifying mutations in patient's HIV virus which are associated with resistance to certain agents
  - reverse transcriptase: NRTIs and NNRTIs
  - protease: PIs
  - Integrase: NSTIs

- can only be performed if HIV-VL > 1,000 cp/mL

DHHS: Recommendations for Resistance Testing

- Results used to inform design of new ART regimens for pts experiencing VF

Question	Recommendation
Who should receive resistance testing?	▪ Pts with VF and HIV-1 RNA levels > 1000 copies/mL ▪ May be considered for pts with 500-1000 copies/mL
When should testing be conducted?	▪ While on failing ART regimen or < 4 wks from treatment end ▪ May still be considered after 4 wks
What types of testing should be conducted?	▪ First-/second-line failure: genotypic testing ▪ **Suspected MDR: genotypic plus phenotypic testing** ▪ **When considering CCR5 antagonist: tropism assay** ▪ If prior failure on INSTI-containing regimen, test for INSTI resistance
Other considerations	▪ Prior treatment history should be obtained

DHHS Guidelines.

Slide credit: clinicaloptions.com

Should be performed within 4 weeks of stopping a failing regimen

GRT is widely used in high income settings before starting ART and to guide clinician while choosing second and third line treatment during ART failures.

Data on suitability of using GRT in such situations is rather old and scarce.

GRT is expensive (IDR 5,300,000) and not available in many limited-resource settings

Resistance Consequences of First-Line Antiretroviral Regimen Failure

DHHS "Preferred" and/or IAS-USA "Recommended" Regimens	HIV-1 RNA < 50 copies/mL at Week 48, %	Detectable Resistance at Virologic Failure† — Likely (> 30%) / Less likely (10% to 30%) / Rare (< 10%) or none			
		NRTI		NNRTI	PI‡
		M184V/I	Other		
NNRTI-based regimens					
EFV, ABC/3TC* (QD arm)	**66** (n = 384)[1]	M184V/I	K65R, L74V, Y115F	K103N	NA
	70 (n = 324)[2]	M184V/I		K103N, G190S, P225H	NA
EFV, TDF, FTC	**80** (n = 244)[3]	M184V/I		K101E, K103N/E, V108I/M, V179D, Y188H, G190A/S/E, P225H, M230L	NA
EFV, TDF, 3TC	**76.3** (n = 299)[4]	M184V/I	K65R	K103N, V106M, Y188C/L, G190A/S/E/Q	NA
Meta-analysis of NNRTI-based regimens	**67-80** (n = 4212)[5]	M184V/I	K65R, TAMs	L100, K103, V106, V108, Y181, Y188, G190, P225	NA
PI-based regimens					
ATV/RTV, TDF/FTC*	**78** (n = 440)[6]	M184V/I	K65R, K70E, TAMs	NA	V32I, M46I, N88S, L90M
DRV/RTV, TDF/FTC*	**84** (n = 340)[7]	M184V/I		NA	
FPV/RTV, ABC/3TC*	**66** (n = 434)[8]	M184V/I		NA	I54L
LPV/RTV,* ABC/3TC*	**65** (n = 444)[8]	M184V/I	TAMs	NA	
	68 (n = 343)[9]	M184V/I	K70R	NA	
LPV/RTV,* TDF/FTC*	**76** (n = 443)[6]	M184V/I	TAMs	NA	
	78 (n = 346)[7]	M184V/I		NA	
	67 (n = 345)[9]	M184V/I		NA	
	63.5 (n = 170)[10]	M184V/I		NA	
	77 (n = 664)[11]	M184V/I		NA	
SQV/RTV, TDF/FTC*	**64.7** (n = 167)[10]	M184V/I		NA	G48V, I54V, V82A, I84V§
Meta-analysis of RTV-boosted PI-based regimens	**65-67** (n = 3063)[5]	M184V/I	TAMs	NA	D30, L33, M46, G48, I50, I54, V82, I84, L90

WHO recommendation for second line ART

Table 4.16. Summary of preferred second-line ART regimens for adults and adolescents

Target population	Preferred second-line regimen[a]	
Adults and adolescents	If d4T or AZT was used in first-line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r [b,c]
	If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r [b,c]
Pregnant or breastfeeding women	Same regimens as recommended for adults and adolescents	
HIV and TB coinfection	If rifabutin is available	Standard PI-containing regimens as recommended for adults and adolescents
	If rifabutin is not available	Same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800 mg/200 mg twice daily)[d]
HIV and HBV coinfection	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)[b]	

[a] ABC and didanosine (ddI) can be … without clinical advantages.

[b] DRV/r can be used as an alternat…

[c] RAL + LPV/r can be used as an a… …, low-quality evidence).

"NRTI recycling"

World Health Organization

Original Article

Assessment of Second-Line Antiretroviral Regimens for HIV Therapy in Africa

Nicholas I. Paton, M.D., Cissy Kityo, M.Sc., Anne Hoppe, Ph.D., Andrew Reid, M.R.C.P., Andrew Kambugu, M.Med., Abbas Lugemwa, M.D., Joep J. van Oosterhout, Ph.D., Mary Kiconco, M.P.H., Abraham Siika, M.Med., Raymond Mwebaze, M.Med., Mary Abwola, M.Med., George Abongomera, M.Sc., Aggrey Mweemba, M.Med., Hillary Alima, M.P.H., Dickens Atwongyeire, M.B., Ch.B., Rose Nyirenda, M.Sc., Justine Boles, M.Sc., Jennifer Thompson, M.Sc., Dinah Tumukunde, M.P.H., Ennie Chidziva, Dipl.G.N., Ivan Mambule, M.B., Ch.B., Jose R. Arribas, M.D., Philippa J. Easterbrook, M.D., James Hakim, F.R.C.P., A. Sarah Walker, Ph.D., Peter Mugyenyi, F.R.C.P., for the EARNEST Trial Team

N Engl J Med
Volume 371(3):234-247
July 17, 2014

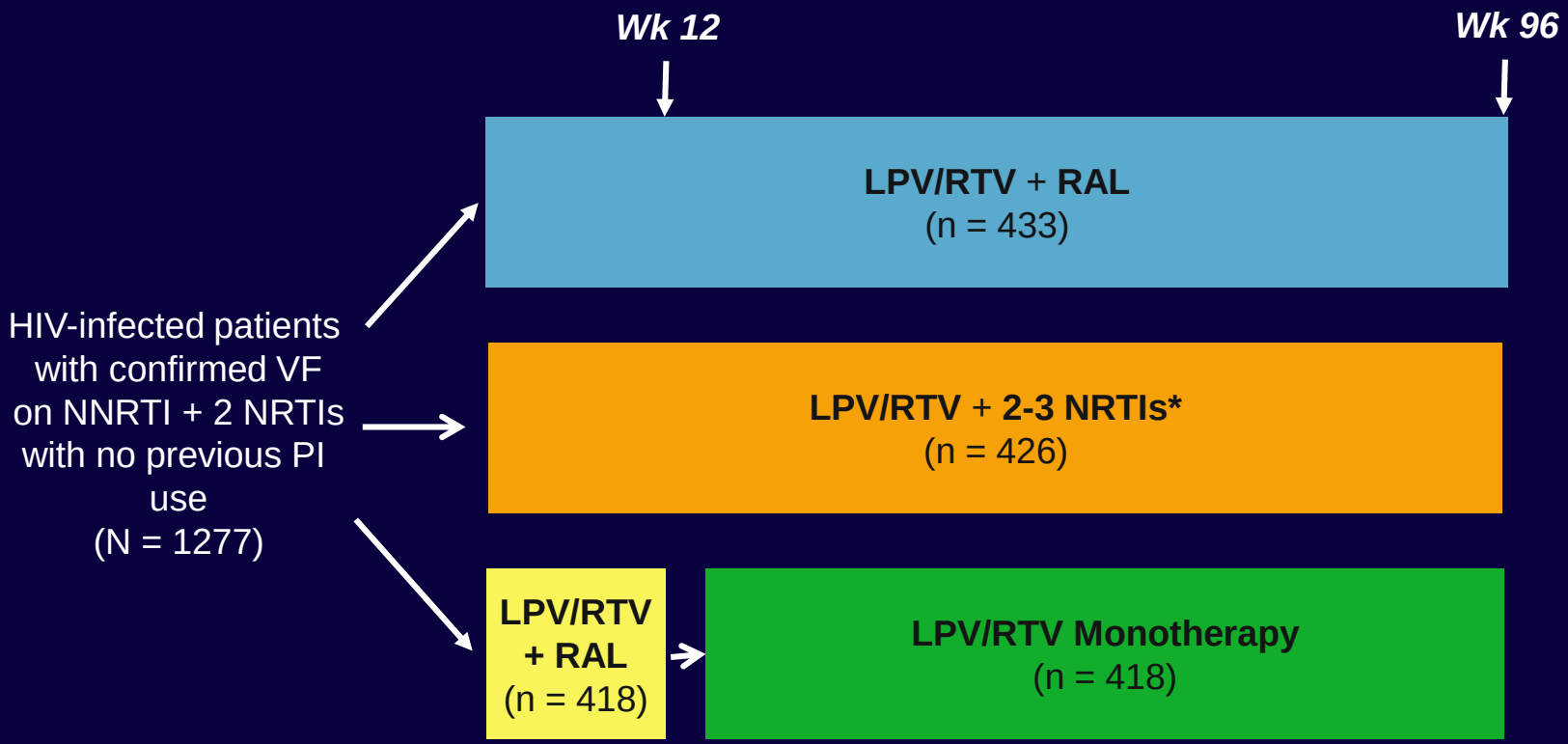
Assessment of Second-Line Antiretroviral Regimens for HIV Therapy in Africa

- What is an appropriate second-line therapy in a resource-limited setting where GRT is not available?

The NEW ENGLAND JOURNAL of MEDICINE

EARNEST: Study Design

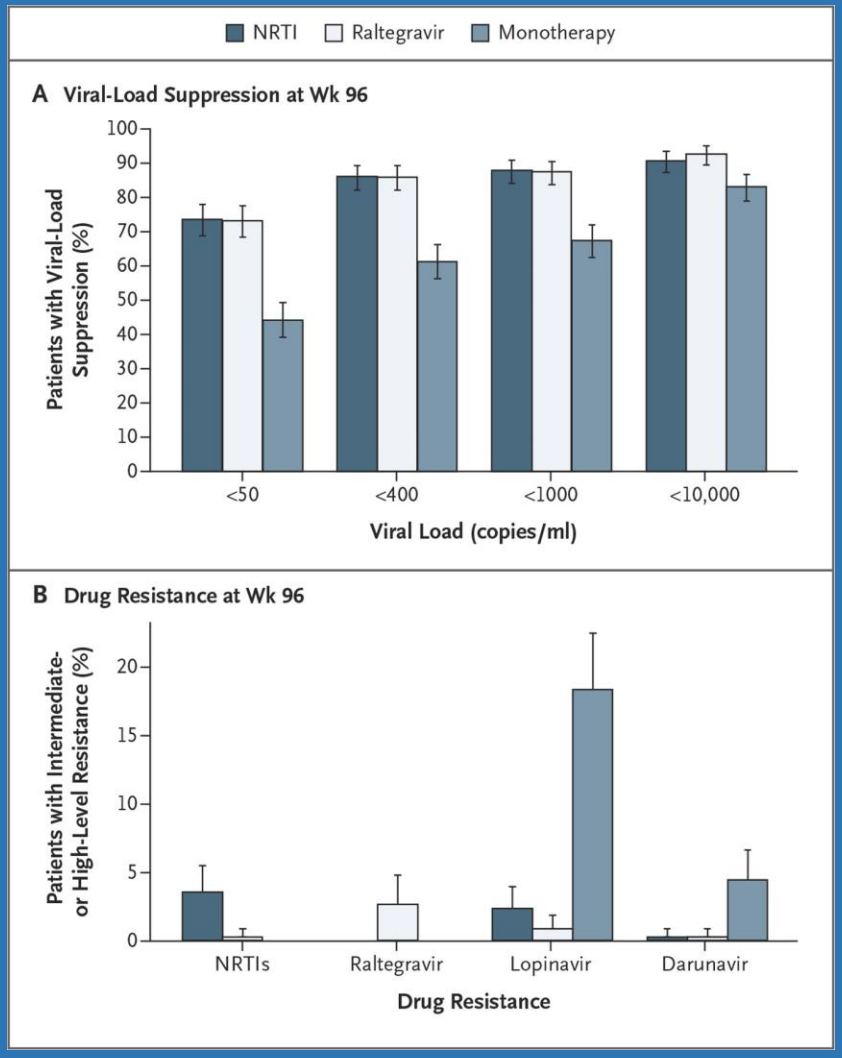
- Randomized, open-label, multicenter trial



*NRTIs selected by clinician.

Paton NI, et al. N Engl J Med. 2014; 371:234-247.

Viral-Load Suppression and Drug Resistance at Week 96.



Paton NI et al. N Engl J Med 2014;371:234-247

The NEW ENGLAND JOURNAL of MEDICINE

Conclusions

- When given with a protease inhibitor in second-line therapy, NRTIs retained substantial virologic activity without evidence of increased toxicity, and there was no advantage to replacing them with raltegravir.

- Virologic control was inferior with protease-inhibitor monotherapy.

The NEW ENGLAND JOURNAL of MEDICINE

Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study

SECOND-LINE Study Group*

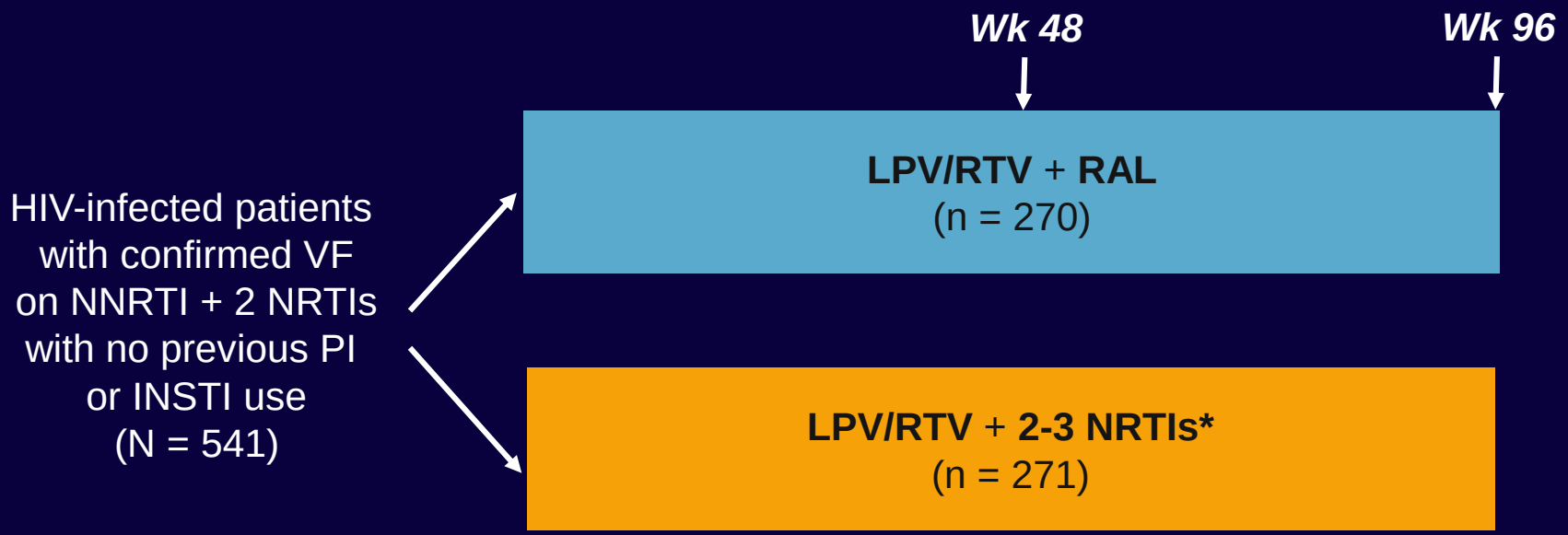
Compared WHO-recommended second line regimen to a regimen containing two new classes of drug

- 15 high income and middle income countries
- Primary endpoint: percentage of participants with plasma VL < 200 cp/mL at week 24

Lancet 2013

SECOND-LINE: Study Design

- Randomized, open-label, multicenter trial



*NRTIs selected by genotypic resistance test or by algorithm.

Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study

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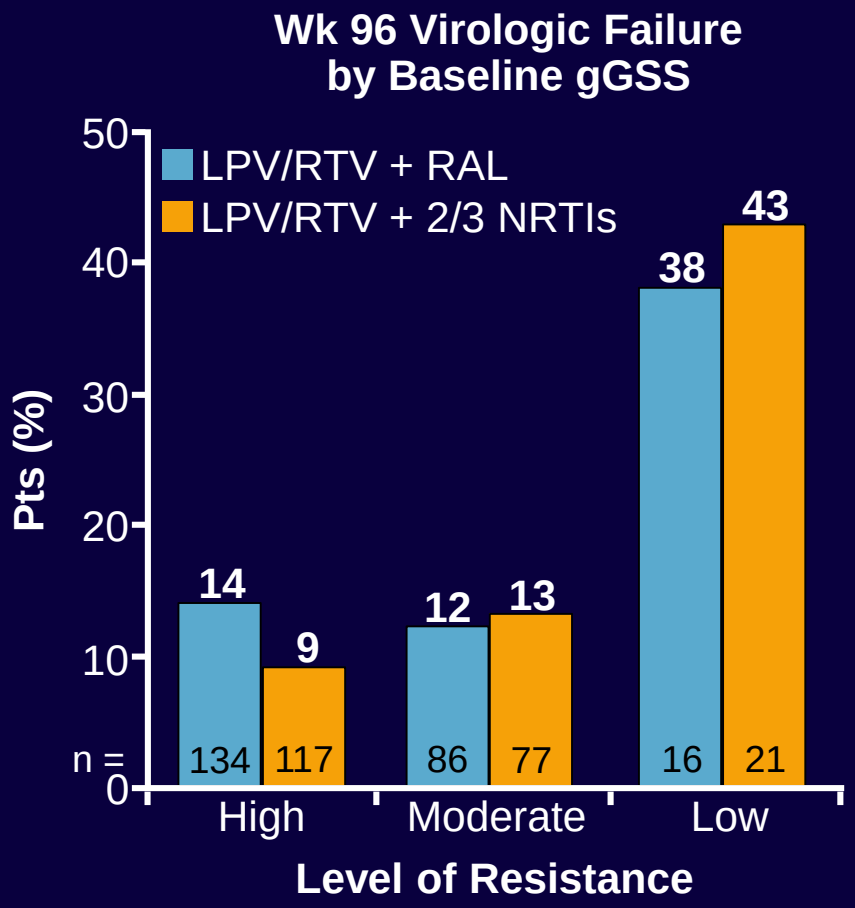
Compared WHO-recommended second line regimen to a regimen containing two new classes of drug

- 15 high income and middle income countries
- Primary endpoint: percentage of participants with plasma VL < 200 cp/mL at week 24

82% participants reached primary endpoint in both groups at week 48

Lancet 2013

SECOND-LINE Resistance Substudy: Predictors of Virologic Failure



Predictors of Virologic Failure at Wk 96

Variable	Multivariate OR (95% CI)	*P* Value
Black race (ref: Asian)	3.49 (1.68-7.28)	.007
BL VL > 100,000 c/mL (ref: ≤ 100,000)	3.43 (1.70-6.94)	< .001
Adherence (Wk 4)*	2.18 (1.07-4.47)	.032
Adherence (Wk 48)*	3.43 (1.09-5.69)	.03
Low resistance by gGSS (ref: high resistance)	4.73 (1.04-11.46)	.002

*< All ART taken in last 7 days (ref: all ART taken).

Boyd M, et al. AIDS 2014. Abstract TUAB0105LB.

Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study

*SECOND-LINE Study Group**

Study supports WHO guidelines for choosing second line regimen

Noninferiority of LPV(r)/RAL regimen

Both regimens well tolerated

Lancet 2013

DHHS Guidelines: Management of First-line ARV Failure

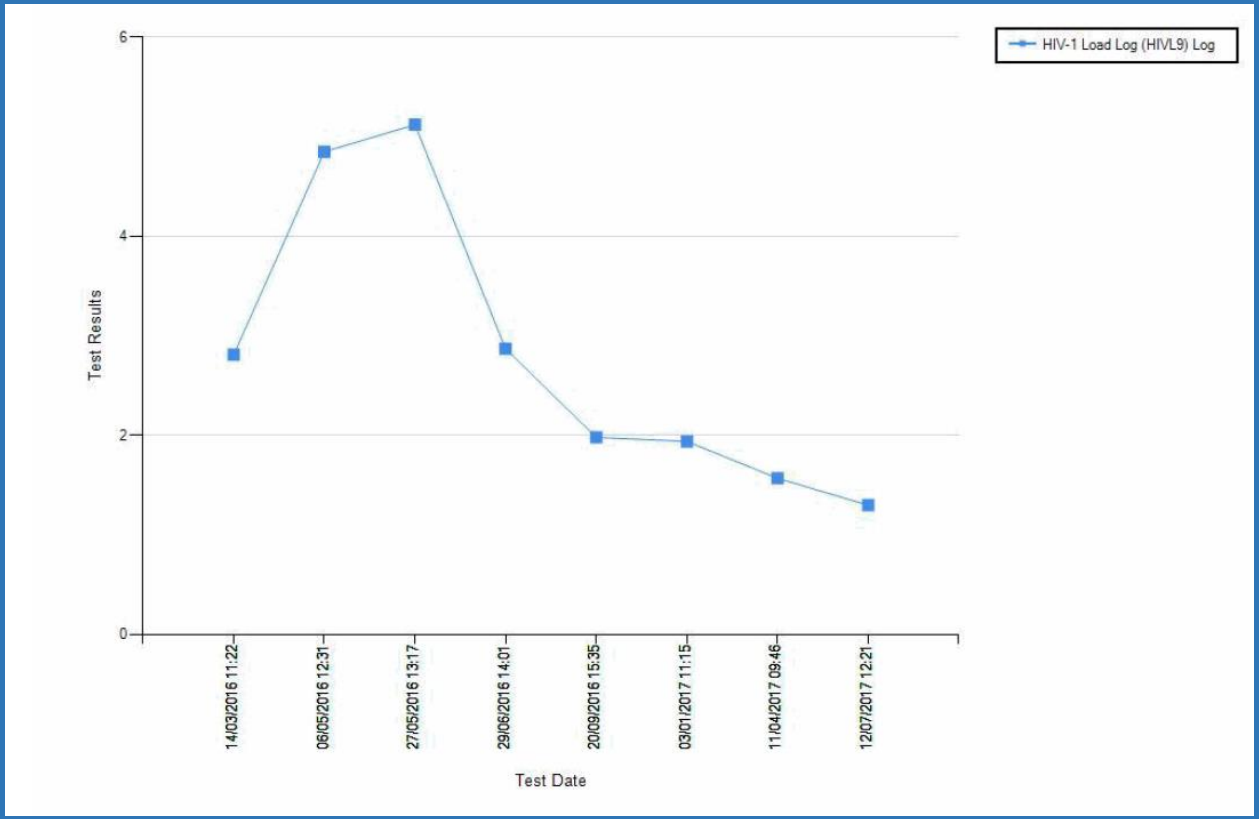
Failing Regimen	Comments
NNRTI + NRTI	Even pts with NRTI resistance can often be treated with a boosted PI + NRTIs or RAL
Boosted PI + NRTI	A systematic review of multiple randomized studies of first-line boosted PI therapy showed that maintaining the same regimen, presumably with efforts to enhance adherence is as effective as changing to new regimens
INSTI + NRTI	▪ Pts should respond to a boosted PI + NRTIs ▪ A boosted PI + INSTI may also be a viable option if there is no INSTI resistance ▪ If RAL or EVG resistance detected, DTG + a boosted PI “can be used”

DHHS Guidelines. May 2015.

Case #5 - Mr HE

- 46 man has been on TDF/3TC/EFV for 5 years
- lost to follow up, but continued taking his ART until 5 months ago.
- a few weeks ago developed symptoms of cough and shortness of breath and decided to restart his ART on his own
- admitted for PCP, initially did not admit to his positive status and secretly kept taking ART on the ward

Case #5 - Mr HE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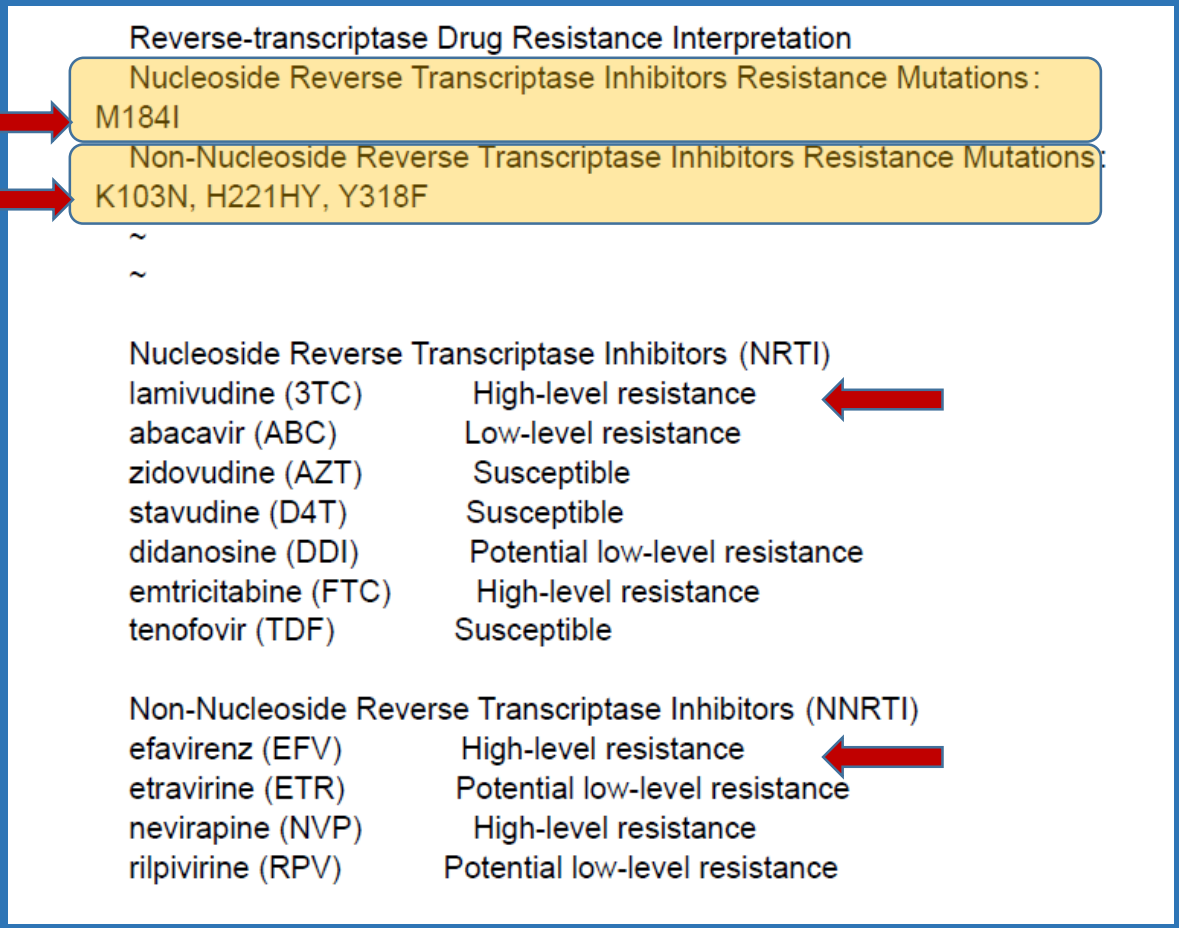

Reverse-transcriptase Drug Resistance Interpretation

Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: M184I

Non-Nucleoside Reverse Transcriptase Inhibitors Resistance Mutations: K103N, H221HY, Y318F

~

~

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

lamivudine (3TC)	High-level resistance
abacavir (ABC)	Low-level resistance
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
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emtricitabine (FTC)	High-level resistance
tenofovir (TDF)	Susceptible

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

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nevirapine (NVP)	High-level resistance
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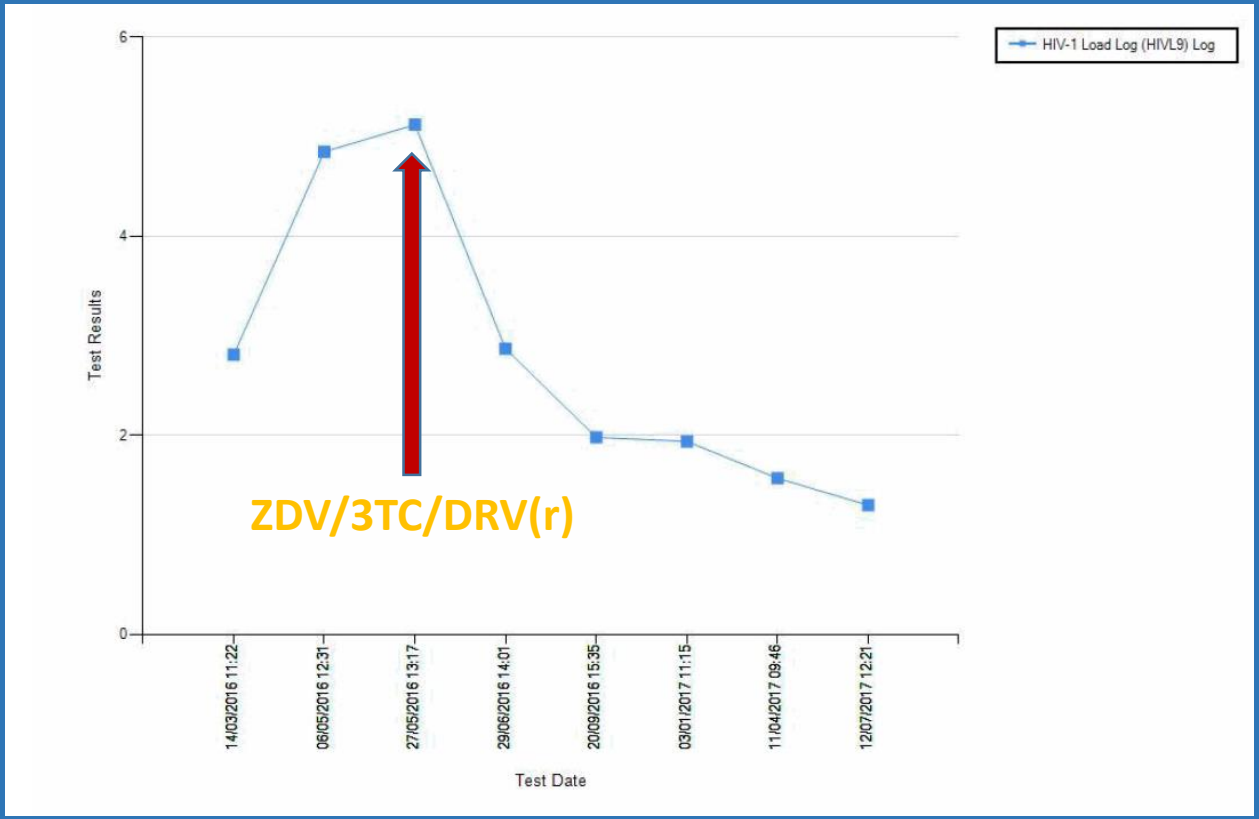
Case #5 - Mr HE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		M184V/I	Other		
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DRV/RTV, TDF/FTC*	**84** (n = 340)[7]	M184V/I		NA	
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SQV/RTV, TDF/FTC*	**64.7** (n = 167)[10]	M184V/I		NA	G48V, I54V, V82A, I84V§
Meta-analysis of RTV-boosted PI-based regimens	**65-67** (n = 3063)[5]	M184V/I	TAMs	NA	D30, L33, M46, G48, I50, I54, V82, I84, L90

Case #5 - Mr HE

- So this shows that we basically did what WHO and EARNEST recommend

Closing remarks

Management of treatment failure

Learning points(I)

- Not every detectable viral load means treatment failure (viral blips)
- Not all treatment failures are due to poor adherence
- Transmitted resistance may not be detected on initial GRT if patient is diagnosed after acute infection
- M184V mutation is selected by 3TC, leads to less viral fitness and hypersensitivity to ZDV and TDF

Management of treatment failure
Learning points (II)

- goal of second/third line regimen should be full virologic suppression
- aim to have at least two, preferably three active agents (not necessarily based on GRT)
- do not add a single new active agent to a failing regimen
- for some highly ART-experienced patients, virologic suppression is not possible, instead new regimen should:
  - minimize toxicity
  - preserve CD4 cell counts
  - delay clinical progression

Management of treatment failure
Learning points (III)

- Boosted PI is the cornerstone of second line ART in both resource rich and limited setting
- WHO recommends "NRTI recycling" + boosted PI for second-line ART
- Even with documented resistant mutations, NRTIs retain substantial activity
- Failure of first line ART with a boosted PI is usually due to nonadherence rather than resistance