How to Manage Drug-Drug Interactions – The Practice *(A Virologist's Perspective)*

Anna Maria Geretti

University of Liverpool, United Kingdom

Case History: Mr RS

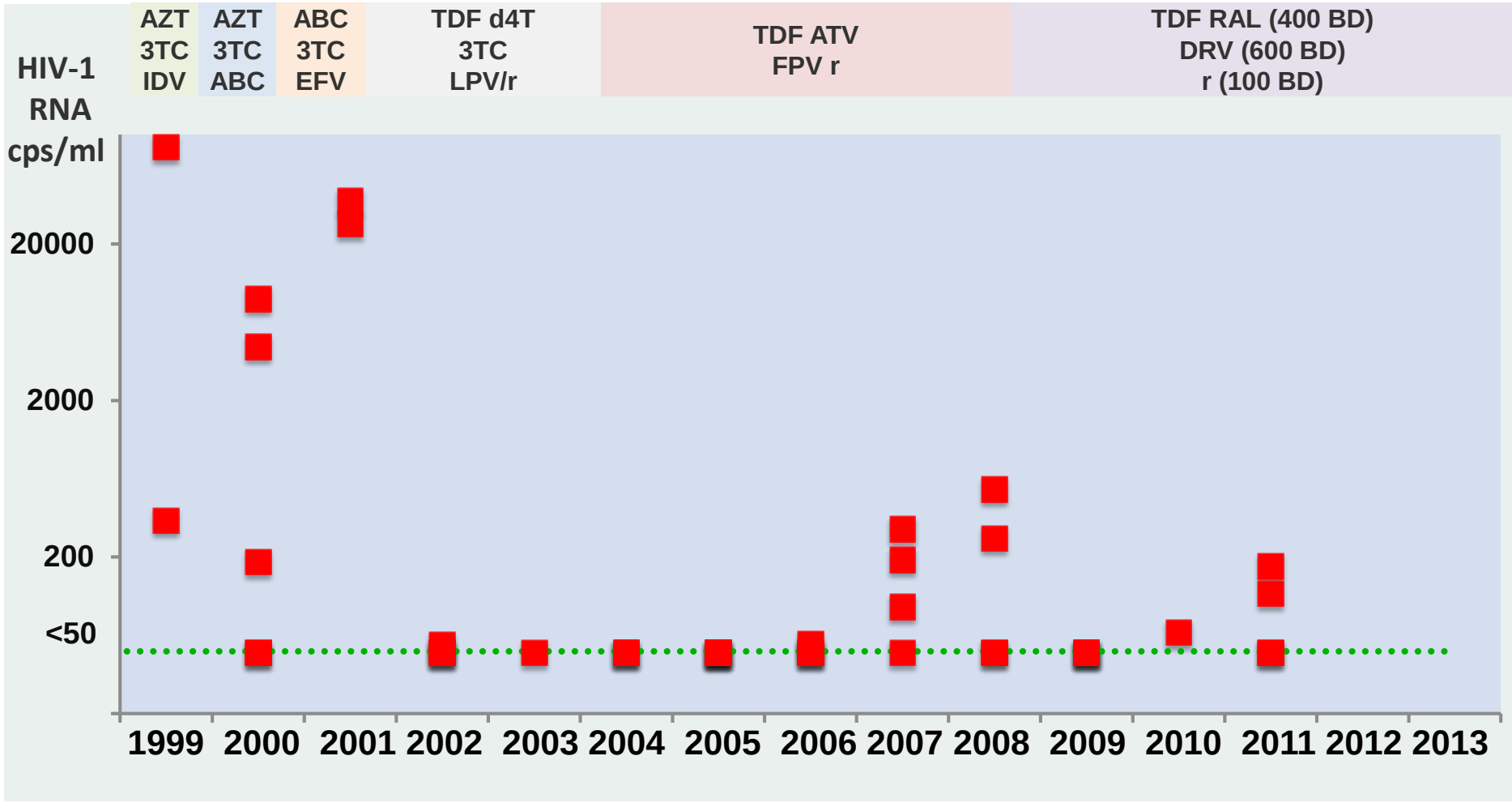
- 67-year-old male
- Diagnosed HIV positive in 1999
  - *Cryptococcus meningitis*
- Baseline CD4 count 46 cells
- Baseline viral load 83,000 cps
- Subtype C
- Past Hepatitis B infection
- Hepatitis C negative
- Oct 1999: AZT/3TC + IDV

Medical and ART history

Date started	Date stopped	ART	Problem	Viral load	CD4
Oct 1999	Jan 2000	AZT/3TC IDV	↑ Transaminases LLV_{50-400}	342	38
Jan 2000	Oct 2000	AZT/3TC ABC	AZT hepatotoxicity† Viraemia	8910	51
Oct 2000	Nov 2001	ABC/3TC EFV	Viraemia	37,600	117
Nov 2001	Jul 2004	TDF d4T 3TC LPV/r	Lipodystrophy	<50	256
Jul 2004	Jul 2008	TDF ATV FPV/r	LLV_{50-600}	542	349
Jul 2008	Nov 2011	TDF RAL DRV/r	LLV_{50-200} CKD-2 c/o poor memory	<50	447

†liver biopsy Jul 2000: Incomplete septal cirrhosis, active portal and interface hepatitis

LLV= Low-level viraemia; CKD = Chronic Kydney Disease; c/o= complains of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ABC 3TC EFV
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TDF ATV FPV r
TDF RAL (400 BD) DRV (600 BD) r (100 BD)
HIV-1 RNA cps/ml
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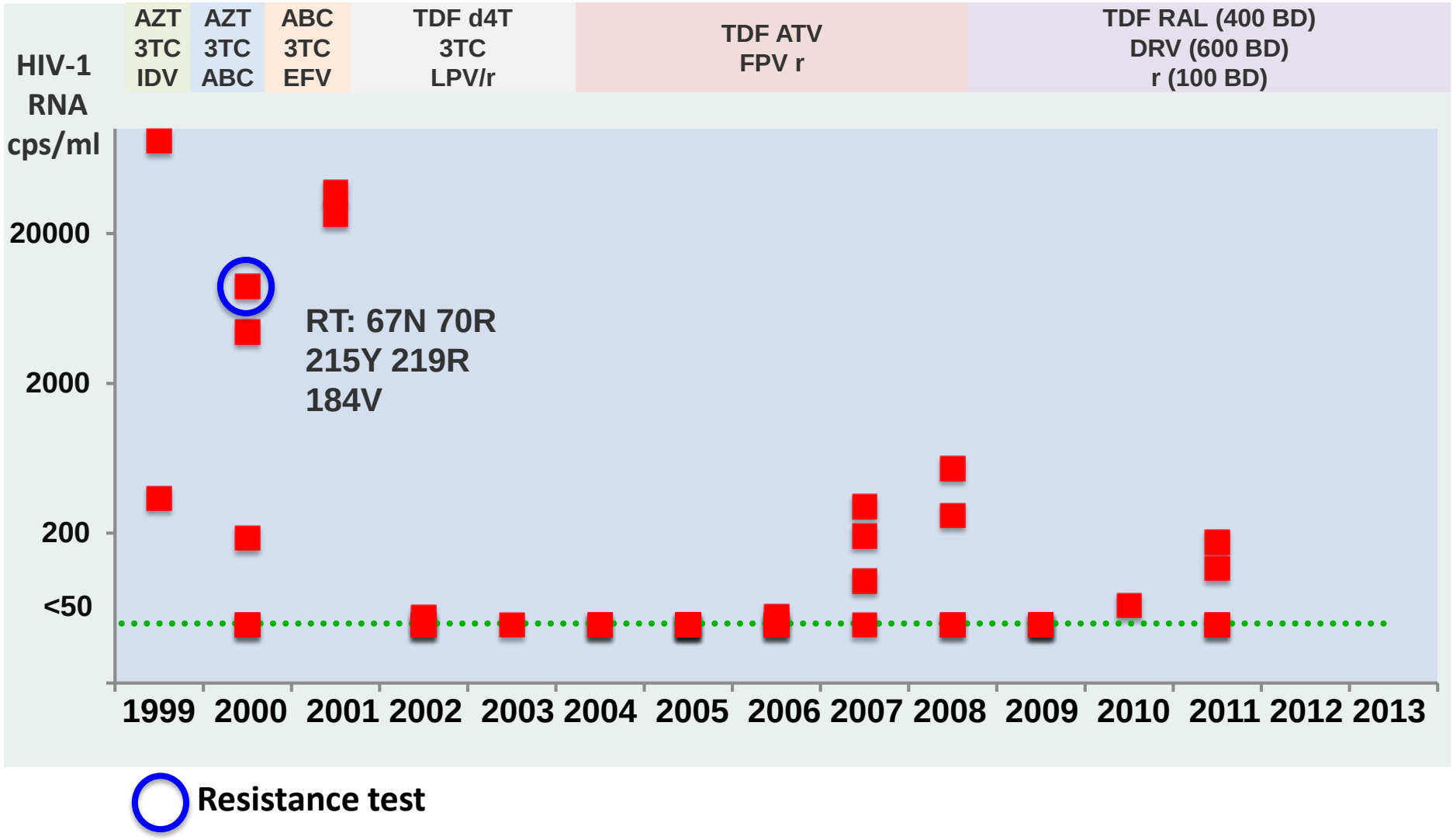
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TDF ATV FPV r
TDF RAL (400 BD) DRV (600 BD) r (100 BD)
HIV-1 RNA cps/ml
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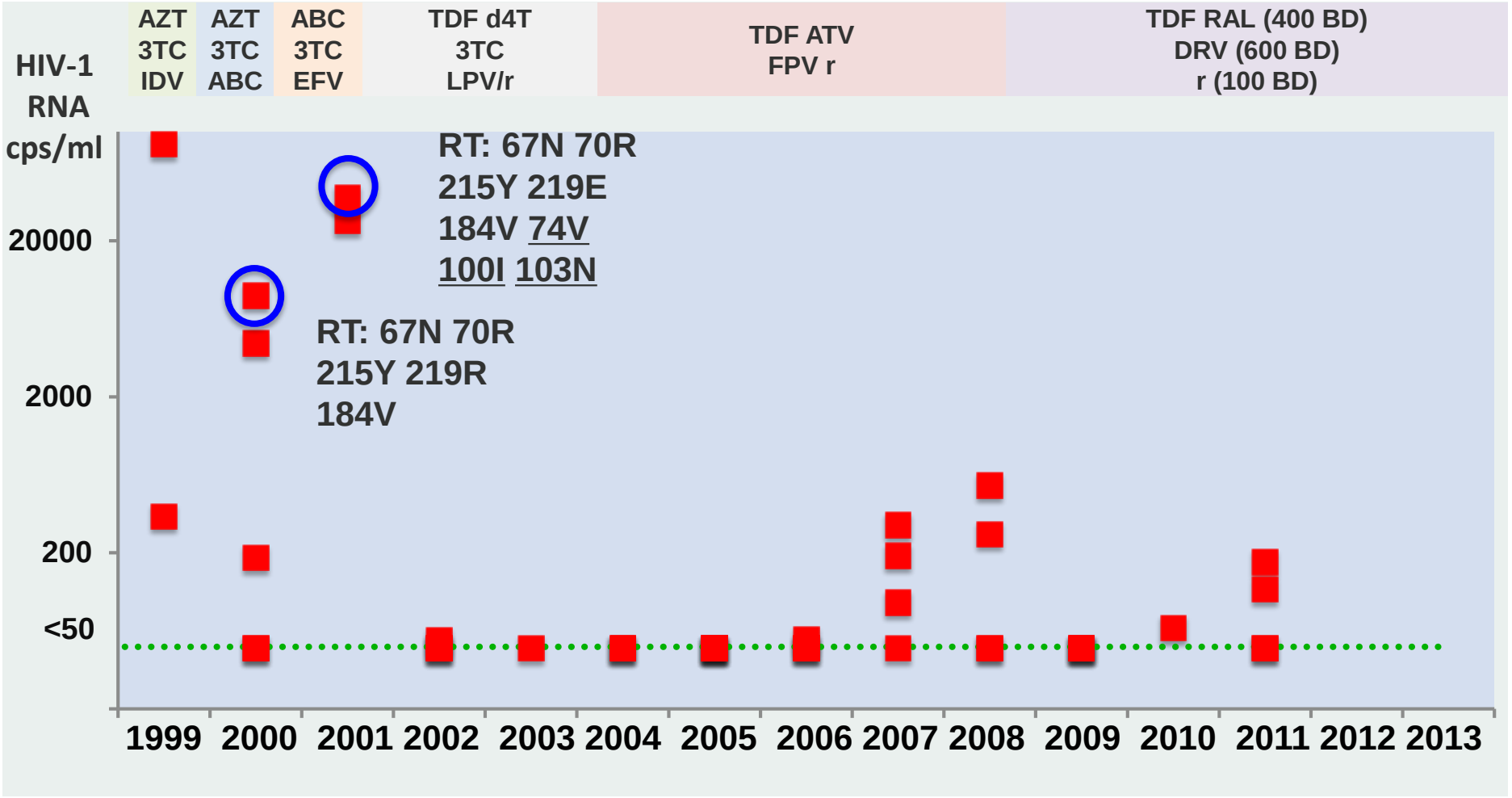
RT: 67N 70R
215Y 219R
184V
1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013
Resistance test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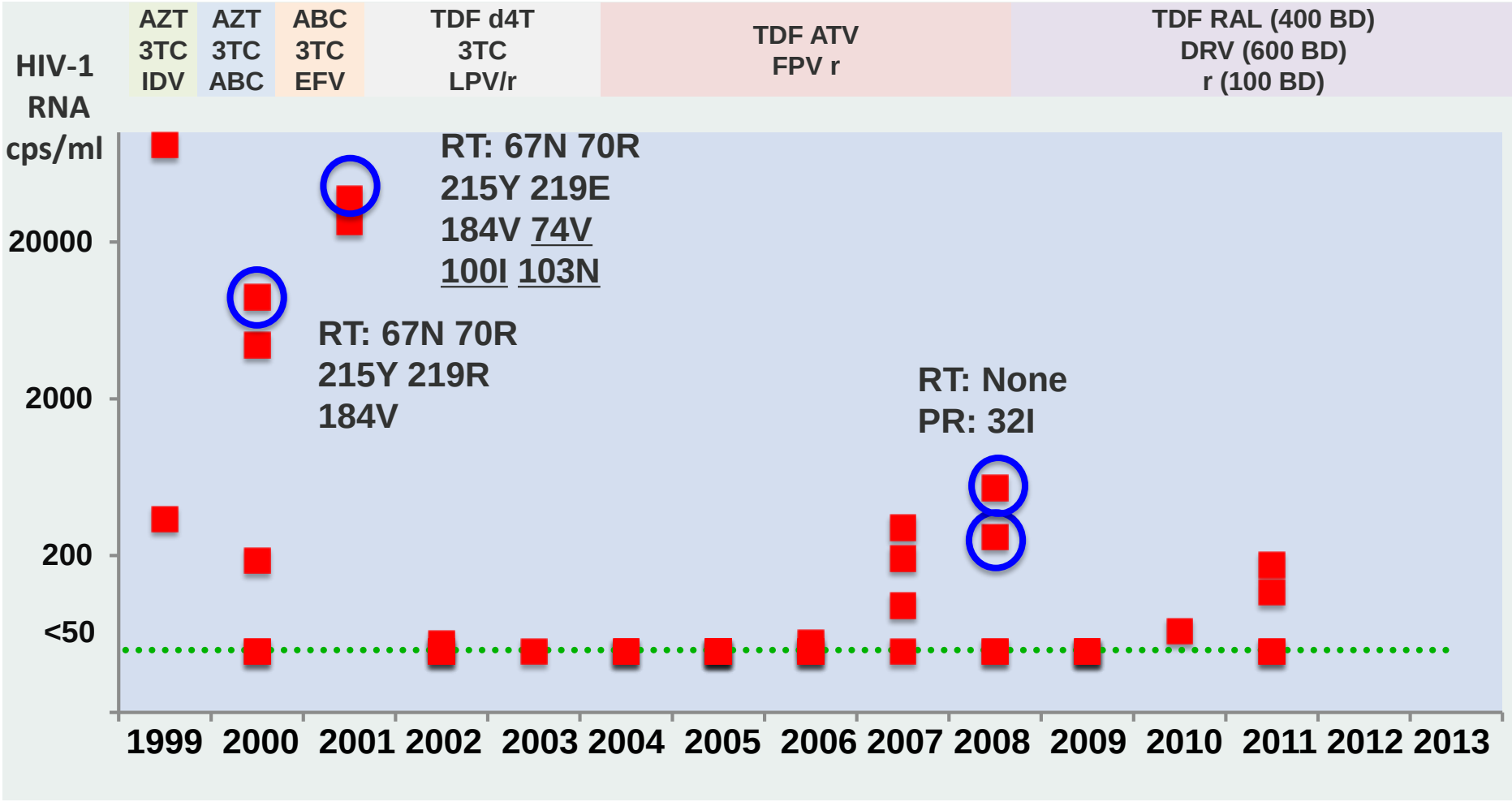
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RT: 67N 70R 215Y 219R 184V
RT: None PR: 32I
1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

Mr RS
Management options

1. **Address psycho-social issues & adherence and continue to monitor - *the viral load is still <200 cps***
2. **Request more investigations**
3. **Change or intensify the ART regimen**
4. **Address technical issues related to sample or test**

Mr RS
Management options: Your Yes or No vote

1. **Address psycho-social issues & adherence and**

   continue to monitor - *the viral load is still <200 cps*

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Management options: Your Yes or No vote

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3. **Change or intensify the ART regimen**

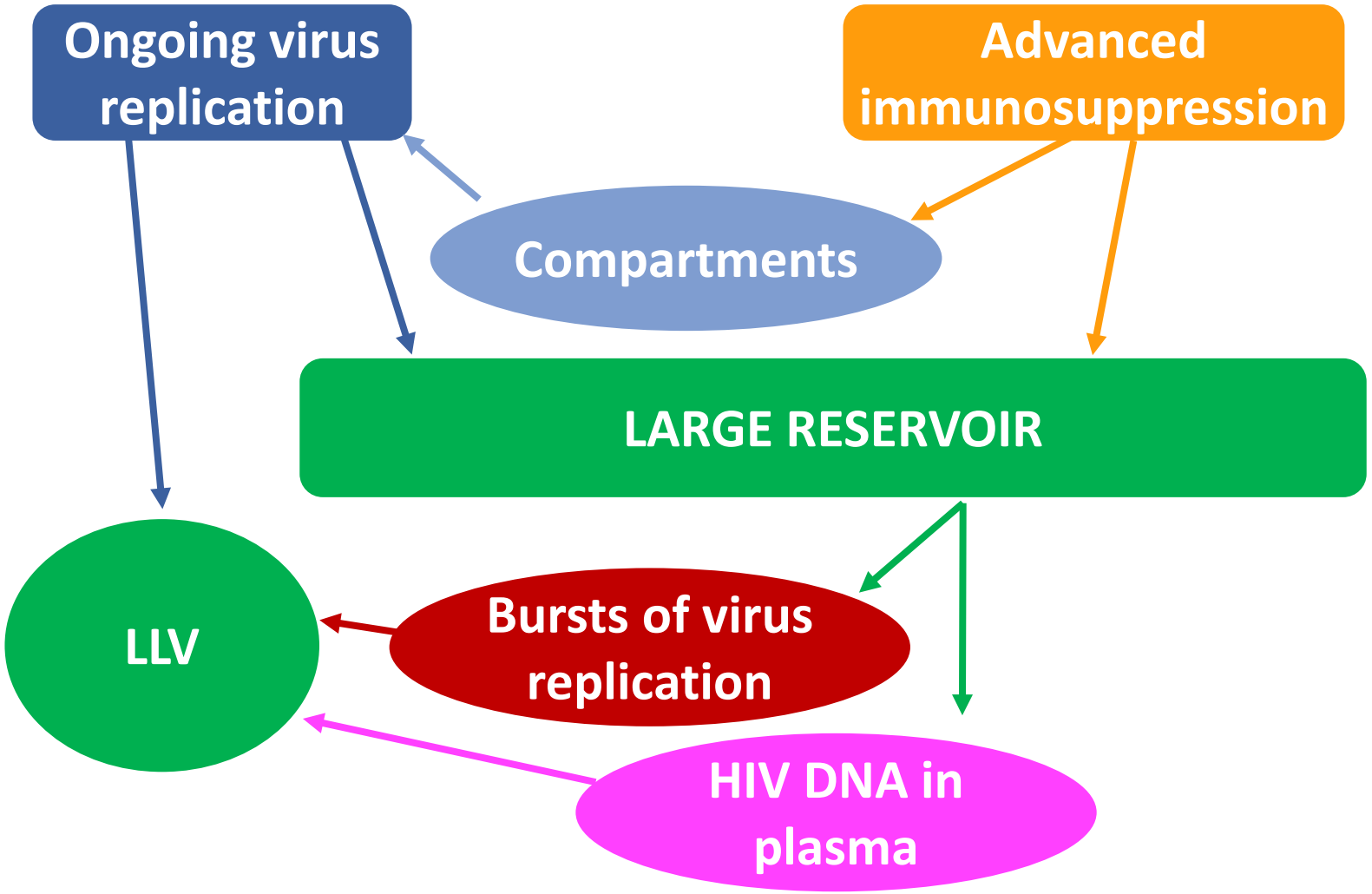
Management strategies: What to review -1

- Adherence, tolerability, psycho-social issues
- Technical issues of sampling and viral load testing
- Expected potency of the regimen
- Drug-drug interactions (DDIs) and food requirements

Management strategies: What to review -2

- **Reasonable to perform a drug resistance test**
- **Reasonable to check drug levels**
- **CD4 cell count nadir and pre-ART viral load inform**
  - ***Size of HIV DNA reservoir which may impact on occurrence or detection of LLV***
  - ***Likelihood of compartmentalised virus replication***

Relationship between HIV DNA burden and LLV

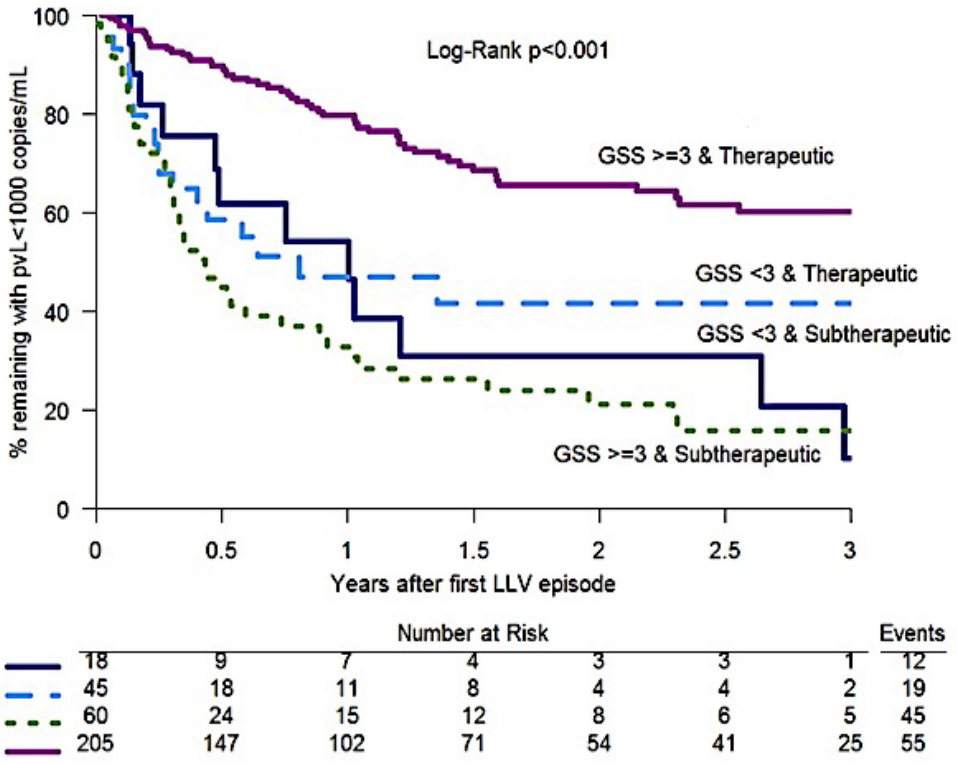


Untimed drug levels & resistance test at LLV predict viral load rebound >1000 cps

- First LLV plasma sample: PI/NNRTI concentration and resistance test (n=328)
- Concentrations classed as ‘therapeutic' or ‘suboptimal' based on target C_{trough}
- Genotypic sensitivity score (GSS) of regimen by Stanford algorithm

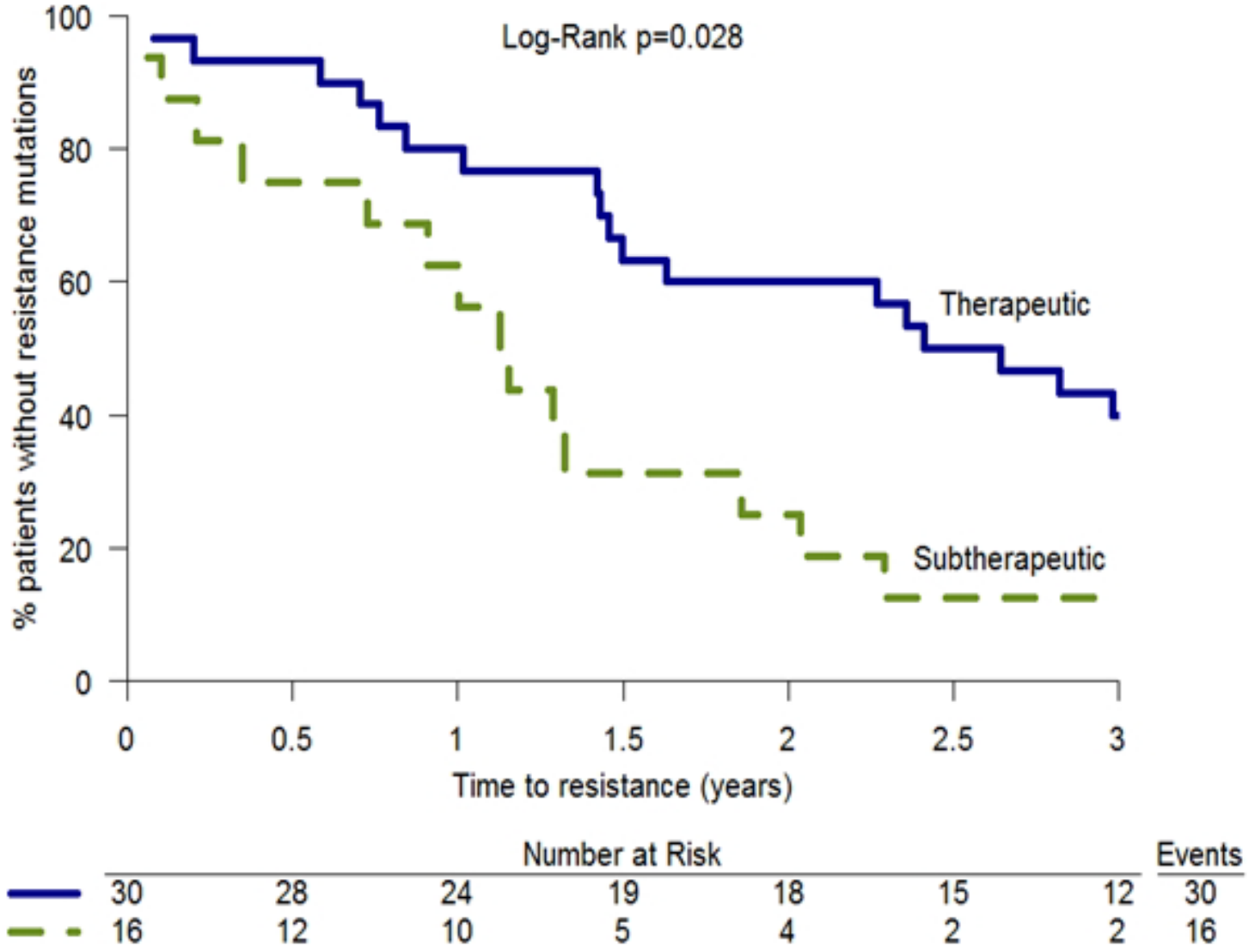
Independent predictors of VL rebound >1000 cps (adjusted OR)

- **Suboptimal drug levels = 2.53 (95% CI 1.72-3.72; p<0.001)**
- **GSS <3 = 1.55 (1.02-2.34; p=0.04)**
- **LLV (cps):**
  - **250-499 = 2.48 (0.99-6.22)**
  - **500-749 = 2.36 (0.91-6.11)**
  - **750-999 = 3.65 (1.42-9.39)**
  - **(p<0.001)**



Gonzalez-Serna et al. CROI 2015

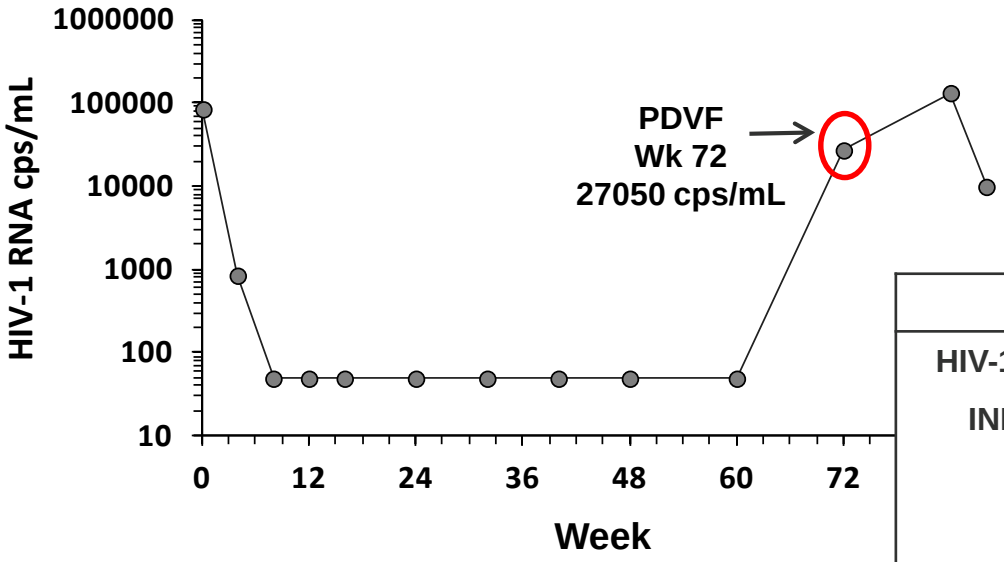
Low drug levels predict faster resistance



Gonzalez-Serna et al. CROI 2015

SAILING Study: Case History 2

- Clade C
- ART-experienced, INI-naive
- Regimen (PSS): TDF (1) + DRV/r (1) + DTG 50 mg OD



	Day 1	PDVF
HIV-1 RNA cps/ml	84313	27050
INI mutations	-	I60L, T97A, N155H
DTG FC	0.66	2.4
RAL FC	0.52	113
IN RC	NA	NA
No emergent resistance to TDF and DRV, loss of RT M184V and PR L10F, M36I, M46I, I54V, V82A		

PSS = Phenotypic susceptibility score

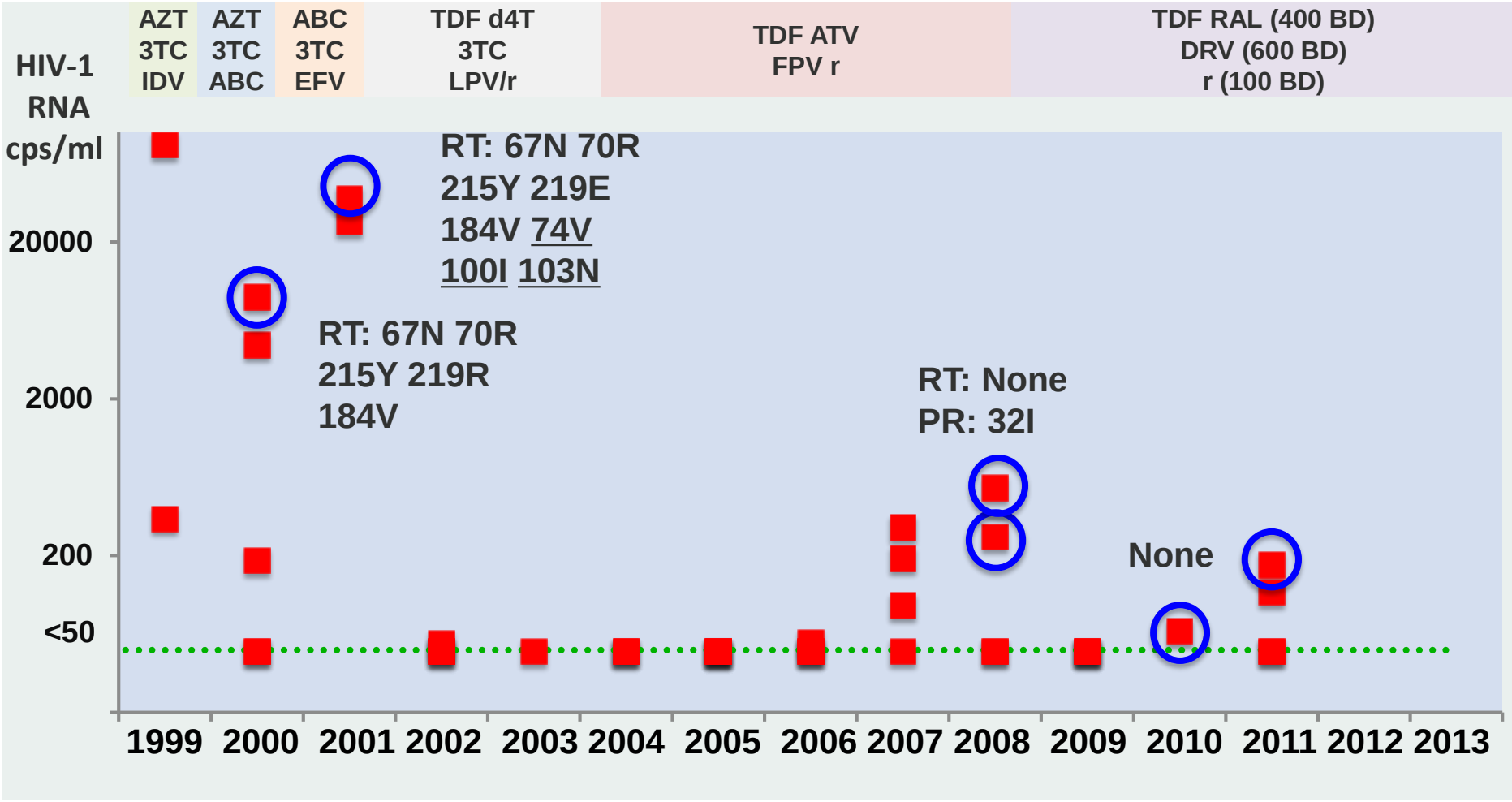
PDVF = Protocol-defined virological failure

FC = Fold-change

IN = Integrase

RC = Replication capacity

Underwood et al. European HIV & Hepatitis Workshop 2015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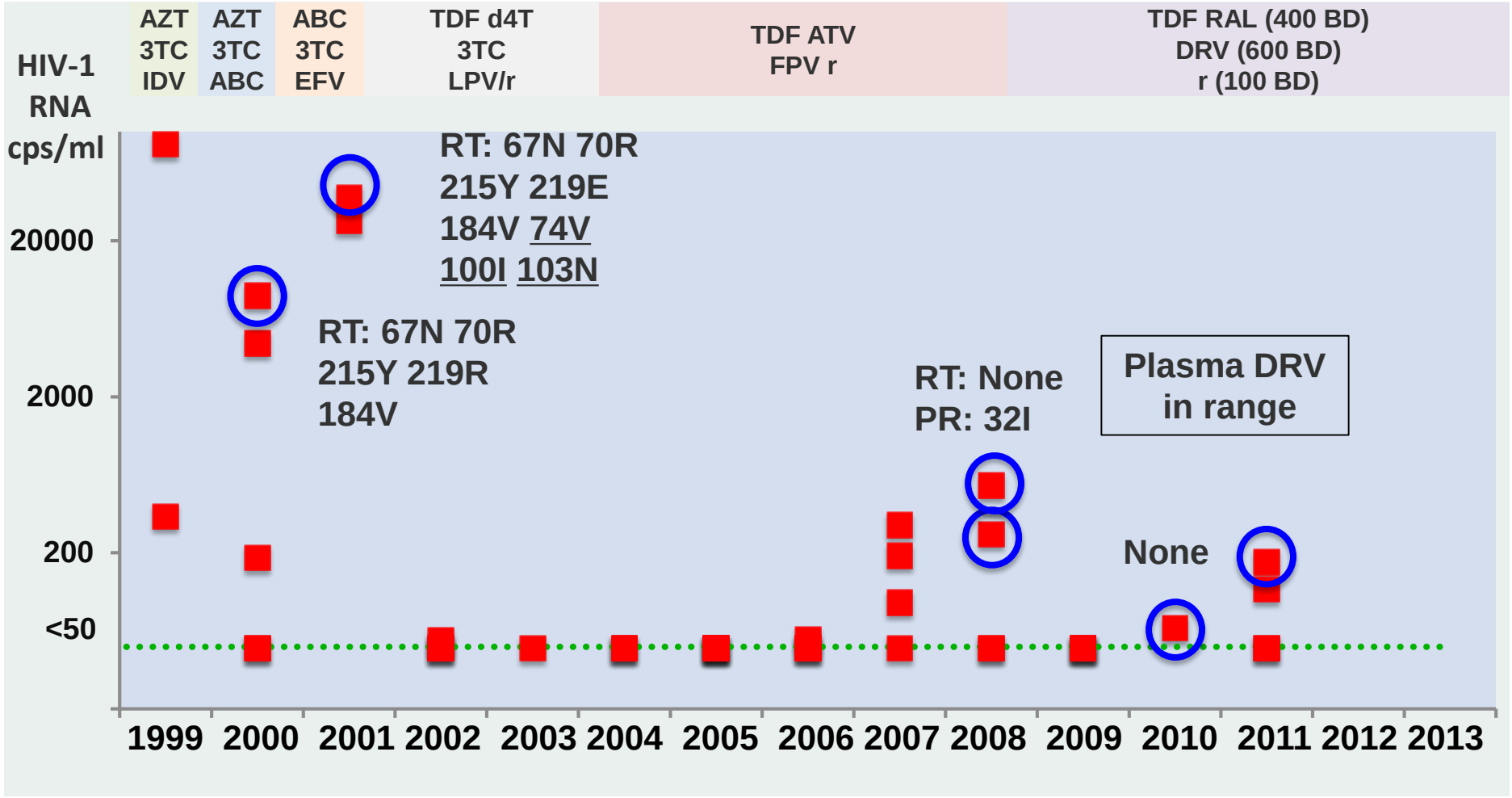
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20000
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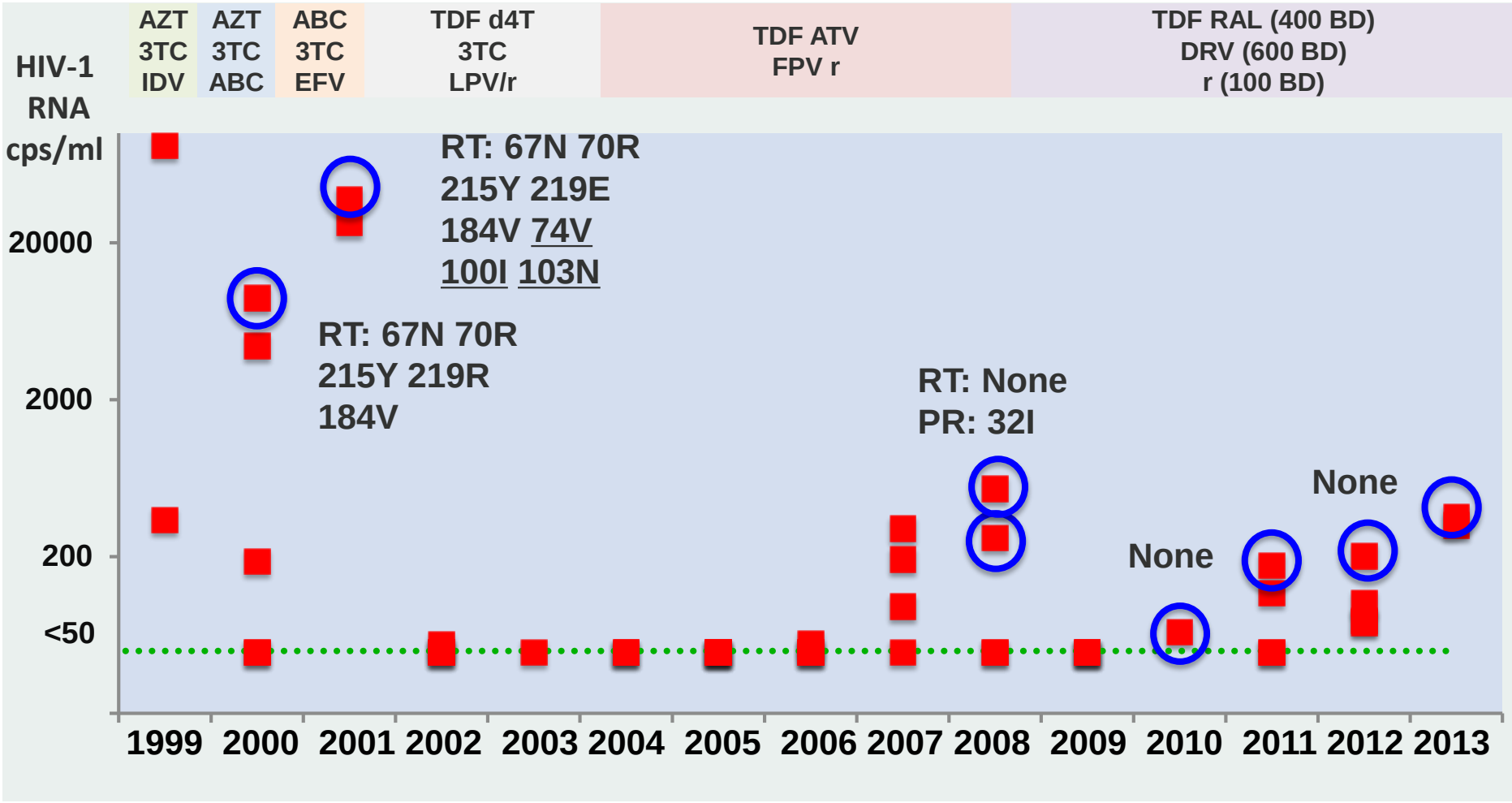
RT: 67N 70R 215Y 219E 184V 74V 100I 103N
RT: 67N 70R 215Y 219R 184V
RT: None PR: 32I
Plasma DRV in range
None
1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013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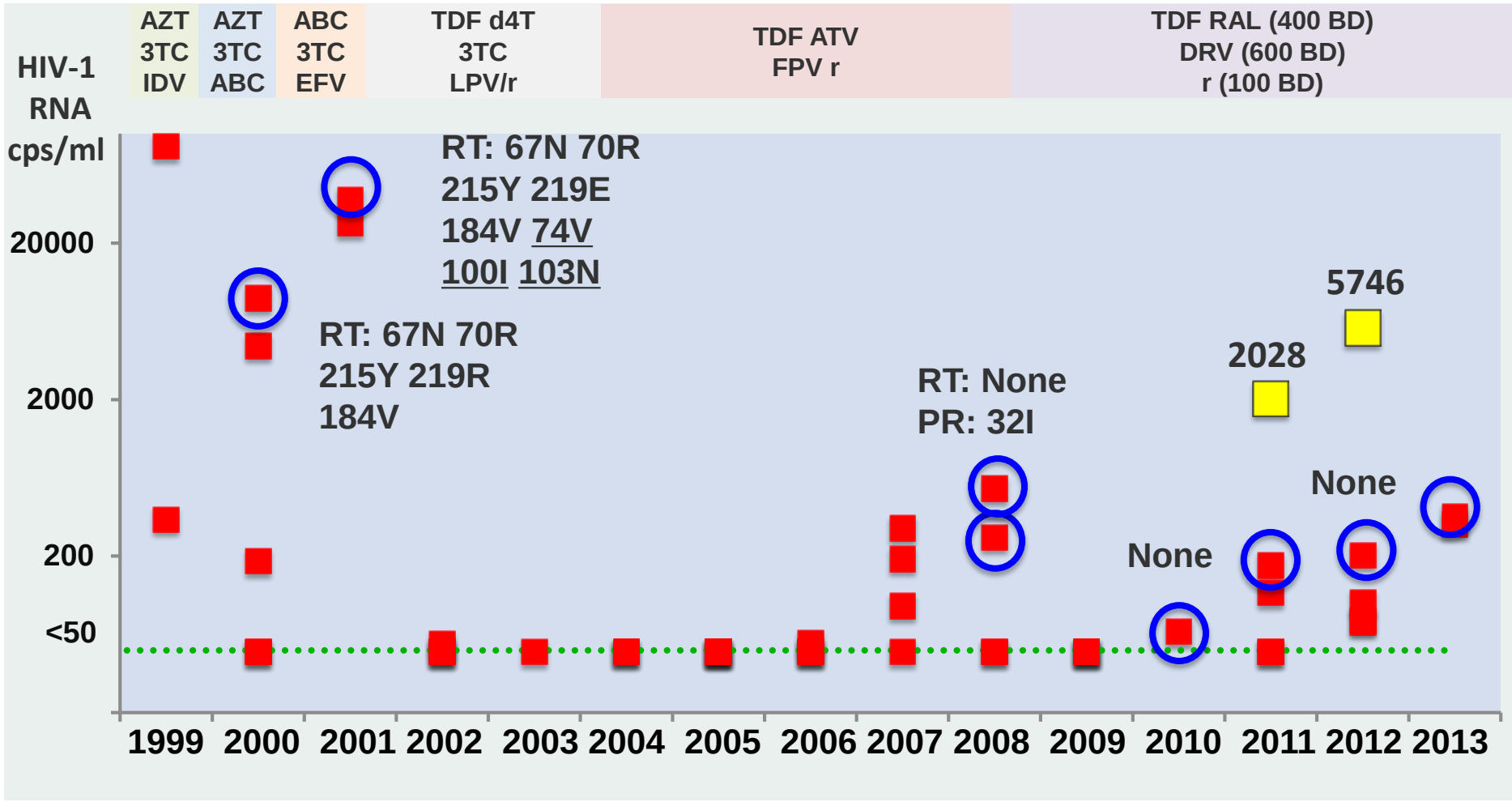
Mr RS
Management options

1. **Request more investigations**
2. **Intensify or change the ART regimen**

Mr RS
Management options: Your Yes or No vote

1. **Request more investigations**


CSF
AZT 3TC IDV
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TDF d4T 3TC LPV/r
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TDF RAL (400 BD) DRV (600 BD) r (100 BD)
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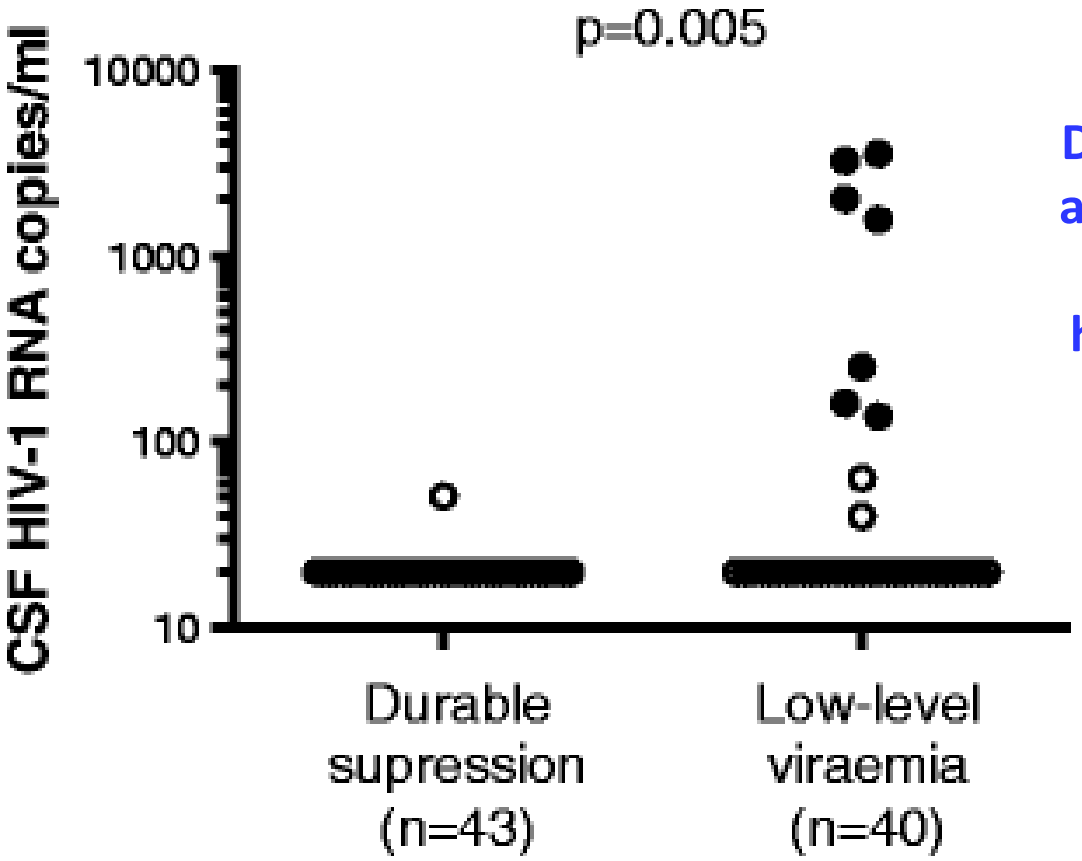
RT: 67N 70R 215Y 219R 184V
RT: None PR: 32I
None
2028
5746
None
1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

HIV-1 RNA Detection in CSF according to LLV

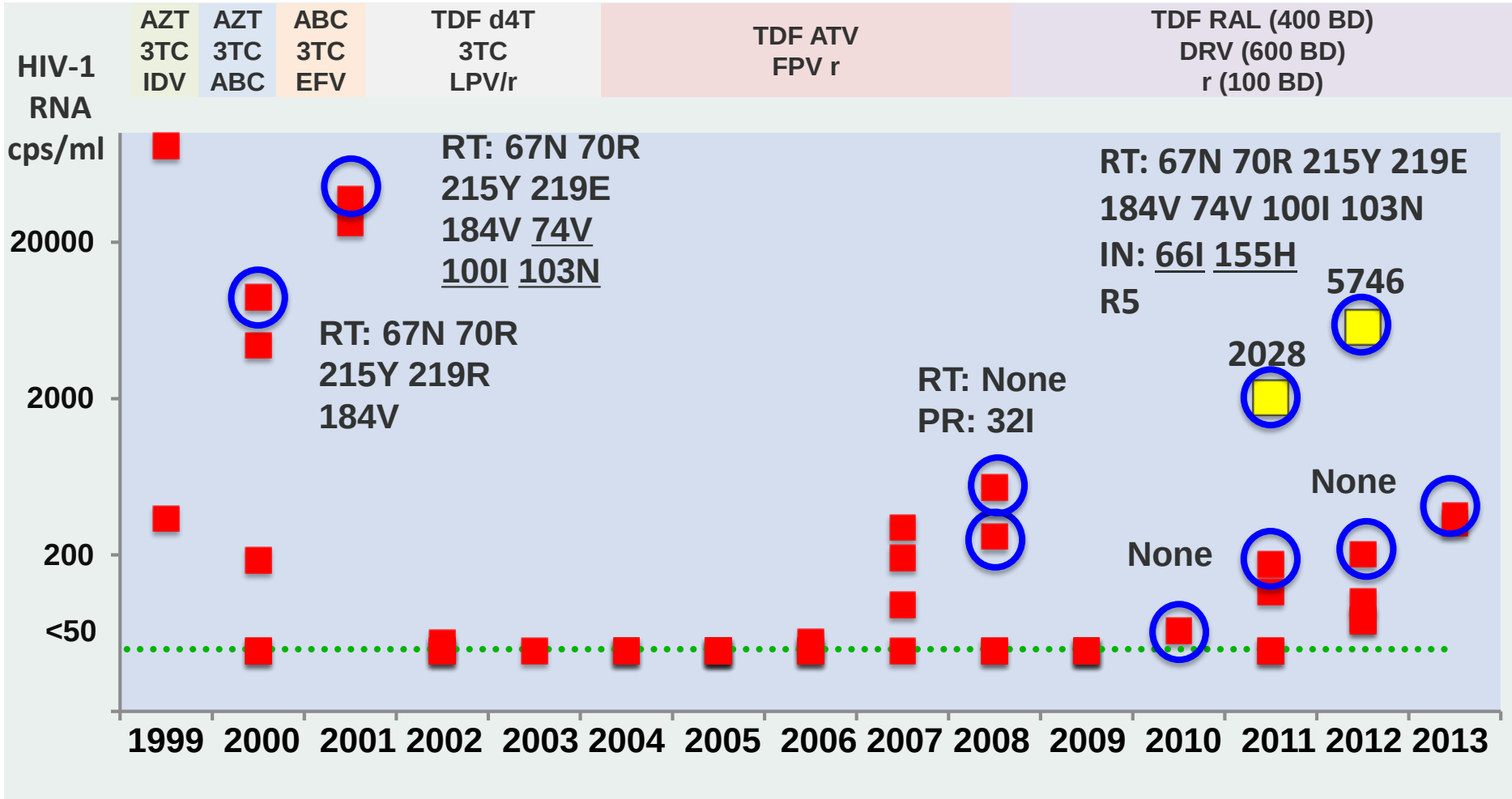
- HIV-1 RNA measured in paired plasma and CSF of 43 subjects with plasma VL <50 cps over ≥12 months of ART and in 40 subjects with a history of LLV
- HIV-1 RNA detected in CSF in 0/43 vs. 9/40 (22%) respectively



Detection of HIV-1 RNA in CSF associated with low nadir CD4 count (p=0.030) and black heterosexual exposure group (p=0.007) - not with drug concentration or CPE score

CPE= Antiretroviral CNS Penetration-Effectiveness

Nightingale et al. J NeuroVirol 2016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5746
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None
None
1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

Mr RS
Management options

1. **DRV/b + DTG + ETR**
2. **DRV/b + DTG + MVC**
3. **DRV/b + DTG + MVC + ETR**

Add TDF or TAF to one of the above +/- FTC?

Which dose of DTG?

What other considerations?

Impact of ARVs on DTG exposure

ARV	DTG C_{trough} or C_{24} *Geometric mean change*	Recommendation for DTG dose
Protease inhibitors		
DRV/r 600/100 mg BID	↓38%	No adjustment required
ATV 400 mg OD	↑180%	No adjustment required
ATV/r 300/100 mg OD	↑121%	No adjustment required
NNRTIs		
RPV 25 mg OD	↑22%	No adjustment required
EFV 600 mg OD	↓75%	50 mg BID‡
ETR 200 mg BD	↓88%	Not to be given without ATV/r, DRV/r, or LPV/r
NRTIs		
TDF 300 mg OD	↓8%	No adjustment required

‡INI-naive patients; alternative combinations should be considered where possible for INI-experienced patients

1.Tivicay SmPC January 2014

www.hiv-druginteractions.org

LATEST ARTICLES

Drug Interactions - Dolutegravir and methadone

Drug Interactions - Elvitegravir/cobicistat and methadone.

Drug Interactions - Dolutegravir and prednisone.

Case Report - Atazanavir/ritonavir and charcoal.

Review - ART and cardiovascular disease.

Drug Interactions - Tenofovir and diclofenac.

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SITE UPDATES

Interactions with Dolutegravir Dolutegravir (Tivicay®), an integrase inhibitor, was licensed in America a few months ago and i...

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A new presentation on Drug-Drug Interactions with Stribild has been adde...

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New cytotoxics added as comedications
Ten new cytotoxic drugs have been added to the interaction charts - dasatinib, erlotinib, evero...

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DRUG INTERACTION CHARTS

To view low bandwidth version click here

INTERACTIONS ON MOBILE DEVICES

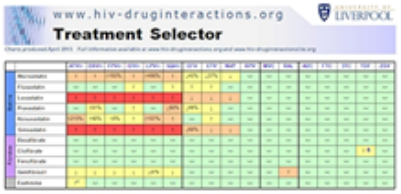
HIV iCharts - we want your opinions

Recent changes to the Apple operating system have caused issues with the update feature of the HIV iCharts app. We are taking this opportunity to investigate alternative options for accessing our drug interaction information on mobile devices and would be grateful if you could take a few minutes to answer a few short questions and to give us any comments.

Click here to take the survey

TREATMENT SELECTOR TABLES

Treatment Selector Tables - now with dolutegravir



We have produced a series of printable tables showing interactions between key antiretrovirals and drugs used to treat a range of common comorbidities.
The tables can be accessed from the Printable Chart & Treatment Selector sub menu on the Interaction Charts menu.

INTERACTION CHARTS FOR YOUR SMART PHONE AND TABLET

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www.hep-druginteractions.org

A reliable guide to drug-drug interactions in the treatment of hepatitis.

www.hiv-druginteractions.org

UNIVERSITY OF LIVERPOOL

Interaction Report

Report ID: RS
Date Produced: 16 July 2016

Antiretroviral Treatment	Co-medications
Dolutegravir	Ritonavir
Emtricitabine/TAF	
Etravirine	

Potential interaction - may require close monitoring, alteration of drug dose or timing of administration (AMBER)

ETR MVC = MVC ↓ (600 / 150 mg bd without / with PI/b)
RTV MVC = MVC ↑ (150mg bd)
RTV DTG = potentially DTG ↓
ETR DTG = DTG ↓

Pharmacology of integrase inhibitors

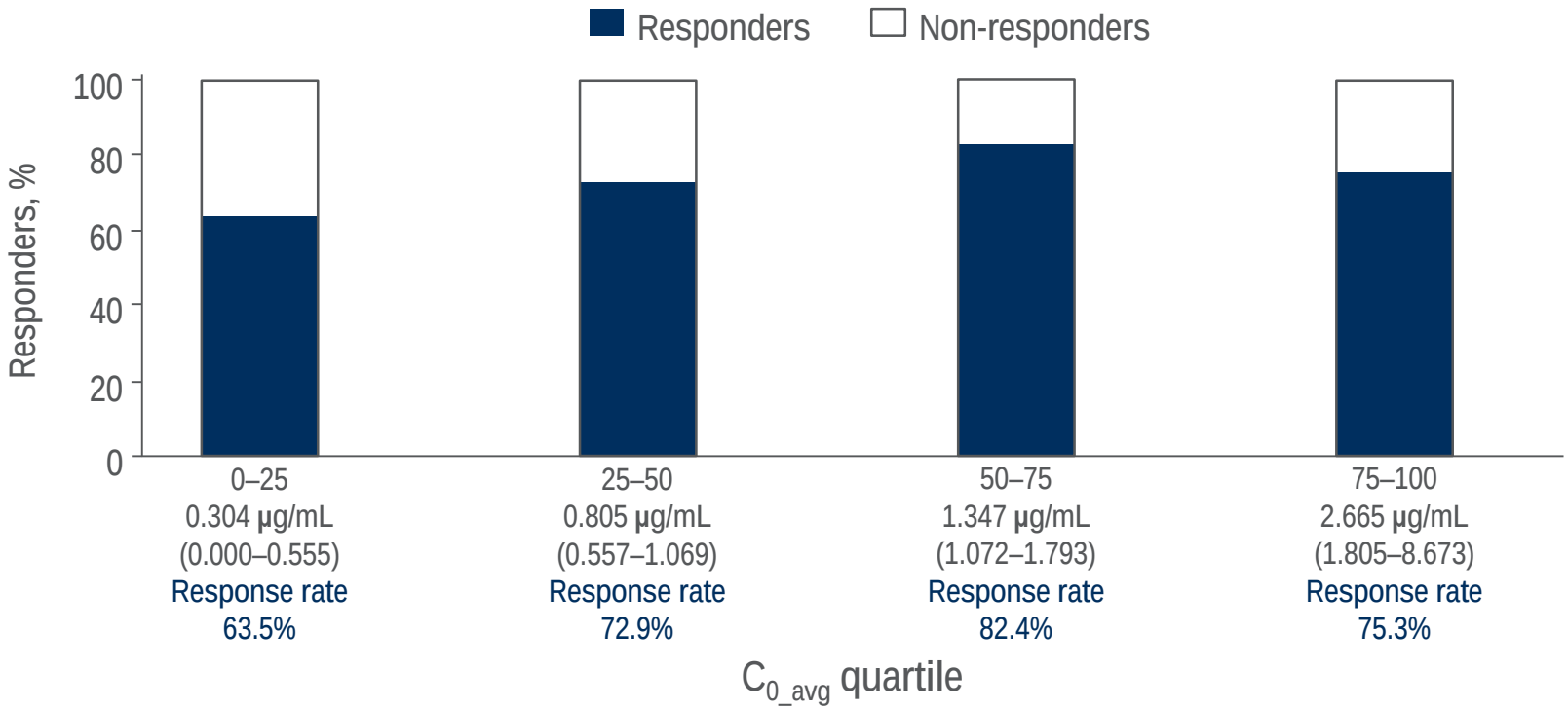
	DTG	EVG	RAL
Dose	50mg od to 100mg bd	150mg od (+ cobicistat)	400mg bd
Dose-exposure	Proportional	Less than proportional	Nearly proportional
Half-life	11-12h	9h	9h
Protein binding	>99%	99%	76-83%
Metabolism	UGT1A1 (CYP3A 10-15%)	CYP3A / UGT1A1/3	UGT1A1
Take with food?	Yes if increased exposure desirable AUC increases with low (↑33%), moderate (↑41%), and high (↑33%) fat meals	Yes AUC increases with low (↑36%), and high (↑91%) fat meals	Not requirted High fat meals double AUC, food increases PK variability

- Protein binding-adjusted IC_{90}/IC_{95} values in the low ng/ml range
- High inhibitory quotient: DTG > EVG > RAL
- PK variability RAL > EVG > DTG (low to moderate for DTG)
- Hepatic metabolism: RAL and DTG minimal CYP450 involvement; EVG primarily through CYP3A4; EVG/c greater DDI potential

Podany et al. 2016

SAILING Study: Responses by DTG concentration

SAILING: Phase III study in ART-experienced, INI-naïve subjects



The average plasma concentration of DTG was a significant predictor of virological response: subjects in the lowest quartile had a lower response

Song et al. ICAAC 2013

Special groups

	DTG	EVG	RAL
Swallowing	Granule being developed (↑ bioavailability)	Cannot be chewed or crushed	Chewable tablets, granules (↑bioavailability)
Children	12 years	12 years	4 weeks
Pregnancy	No data FDA Cat B	Limited data FDA Cat B	Some data FDA Cat C
Renal impairment	No adjustment – DTG exposure reduced in severe renal disease	FDC with TDF >70 FDC with TAF >30	No adjustment
Cirrhosis CP-A	No adjustment	No adjustment	No adjustment
CP C	Caution	Not recommended	Caution

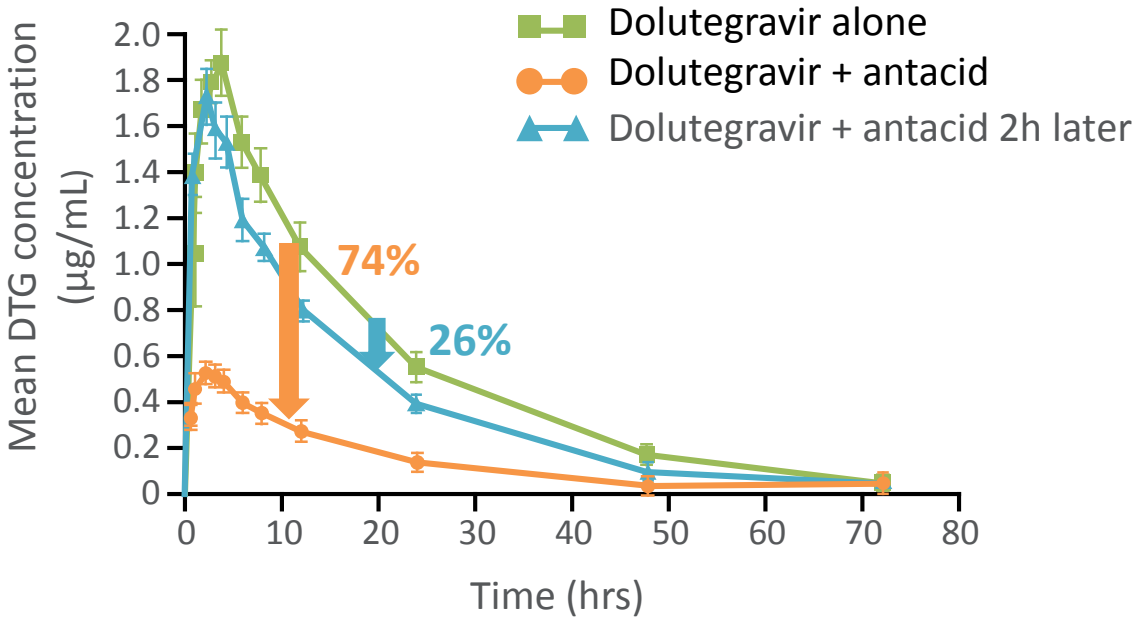
Pharmacology of integrase inhibitors

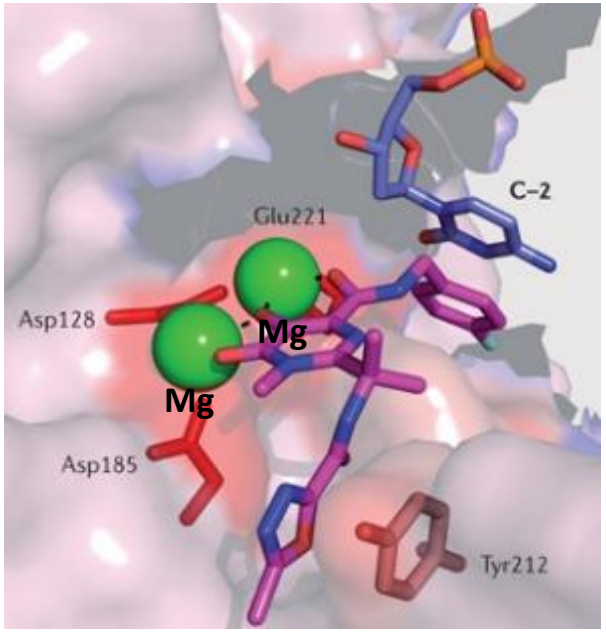
	DTG	EVG	RAL
Cations	Al/Mg/Ca/Fe Multivitamins Separate -6h or +2h	Al/Mg ± 2h Multivitamins ± 4h	Al/Mg contraindicated Ca not clinically meaningful
Gastric pH	No significant interaction	No significant interaction	RAL absorption with OMP (↑39%) / FAM (↑45%) - No adjustment needed

- Absorption reduced by divalent/trivalent cations (e.g., multivitamins, antacids)

Podany et al. 2016

INI chelation with cations





Co-administered drug	DTG C_{trough} or C_{24} *geometric mean change*	Recommendation
Antacids and supplements		
Mg/Al containing antacid	AUC ↓74%	**Take a minimum of 2 hrs after or 6 hrs before DTG**
Ca supplements	↓39%	
Fe supplements	↓56%	
Multivitamins	↓32%	
Acid-lowering agents		
Omeprazole	↓5%	**No action required**

Patel et al. JAC 2011; Pommier et al. Nat Rev 2005; Tivicay SmPc Oct 1st 2015

Other DTG interactions

Commonly used medications	Interactions
Oral contraceptives	No dose adjustment necessary
H_2-receptor antagonists (e.g.,ranitidine, cimetidine)	No dose adjustment necessary
Prednisone, Methadone, Rifabutin	No dose adjustment necessary
Metformin	Limit Met to 1000 mg total daily dose. When stopping DTG, Met dose may require adjustment. Monitor blood glucose when initiating concomitant use and after withdrawal of DTG
Carbamazepine, rifampicin, EFV, NVP, TPV/r	DTG 50 mg BID. Avoid if INI resistance

Note: Co-administration of dofetilide and dolutegravir is contraindicated.[1,2]

1. *TIVICAY Summary of Product Characteristics. September 2015*
2. *TRIUMEQ Summary of Product Characteristics. September 2015*

Mr RS
Management options

1. **DRV/b + DTG + ETR**
2. **DRV/b + DTG + MVC**
3. **DRV/b + DTG + MVC + ETR**

Add TDF or TAF to one of the above +/- FTC?

Which dose of DTG?

What other considerations?

Mr RS
Management options: Your Yes or No vote

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Mr RS
Management options: Your Yes or No vote

1. DRV/b + DTG + ETR
2. **DRV/b + DTG + MVC**

Mr RS
Management options: Your Yes or No vote

1. DRV/b + DTG + ETR
2. DRV/b + DTG + MVC
3. **DRV/b + DTG + MVC + ETR**

Mr RS
Management decision

DRV/b + DTG 100mg bid + MVC 150 bid

Monitor and consider TAF/FTC

Take with food

Counsel about concomitant meds (by GP or over the counter)

Thanks to
Saye Khoo (UoL)
David Back (UoL)
Romina Quercia (ViiV)