LIVERPOOL HEALTH PARTNERS

UNIVERSITY OF LIVERPOOL

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

INSTITUTE OF INFECTION AND GLOBAL HEALTH

A COMPARTMENTALIZATION STORY

Maria Tsakiroglou MD

Summary

1. Case patient
2. Drug penetration in compartments
3. Discussion

Hx 1995-1999

- 67 year-old African ♂
- Diagnosed with HIV in 1995 in South Africa
  - Presumed mode of transmission: Heterosexual
- Came to the UK in 1999
  - Presented with cryptococcal meningitis
  - CD4= 46/mm^3 and VL>75,000 copies/ml
  - HBsAg (-), HCV (-), Syphilis (-)
- Started on ART with AZT/3TC/IDV

AZT= Zidovudine, 3TC= Lamivudine, IDV= Indinavir

2000

Time point	ART composition	VL (copies/mL)	CD4 (per mm^3)	Events
Jan 2000	AZT/3TC/IDV	**186**	**29**	↑Transaminases
Mar 2000	AZT/3TC/ABC	<50	43	**↑↑↑ transaminases**
Aug 2000	AZT/3TC/ABC	**6,650**	54	Liver biopsy: "**Inflamation & fibrosis Drug induced, probably due to AZT**"

AZT= Zidovudine, 3TC= Lamivudine, IDV= Indinavir, ABC= Abacavir

Resistance test

- PI major: None & PI minor: T74S
- NNRTI: None
- NRTI: **D67N**, K70R, **M184V**, **T215Y**, K219R

	Resistance*
Zidovudine (AZT)	High-level
Didanosine (DDI)	Intermediate
Stavudine (D4T)	High-level
Lamivudine (3TC)	High-level
Abacavir (ABC)	High-level
Emtricitabine (FTC)	High-level
Tenofovir (TDF)	Intermediate

Subtype C

** Stanford Database*

ART switch

Replaced zidovudine with efavirenz

3TC/ABC/EFV suboptimal regimen

Efavirenz

- Low genetic barrier to resistance
- K103N emerges in 2 weeks of EFV monotherapy

Resistance Test- Added mutations

NNRTIs: L100I, **K103**

NNRTI: L74V, D67N, K70R, **M184V, T215Y**, K219R

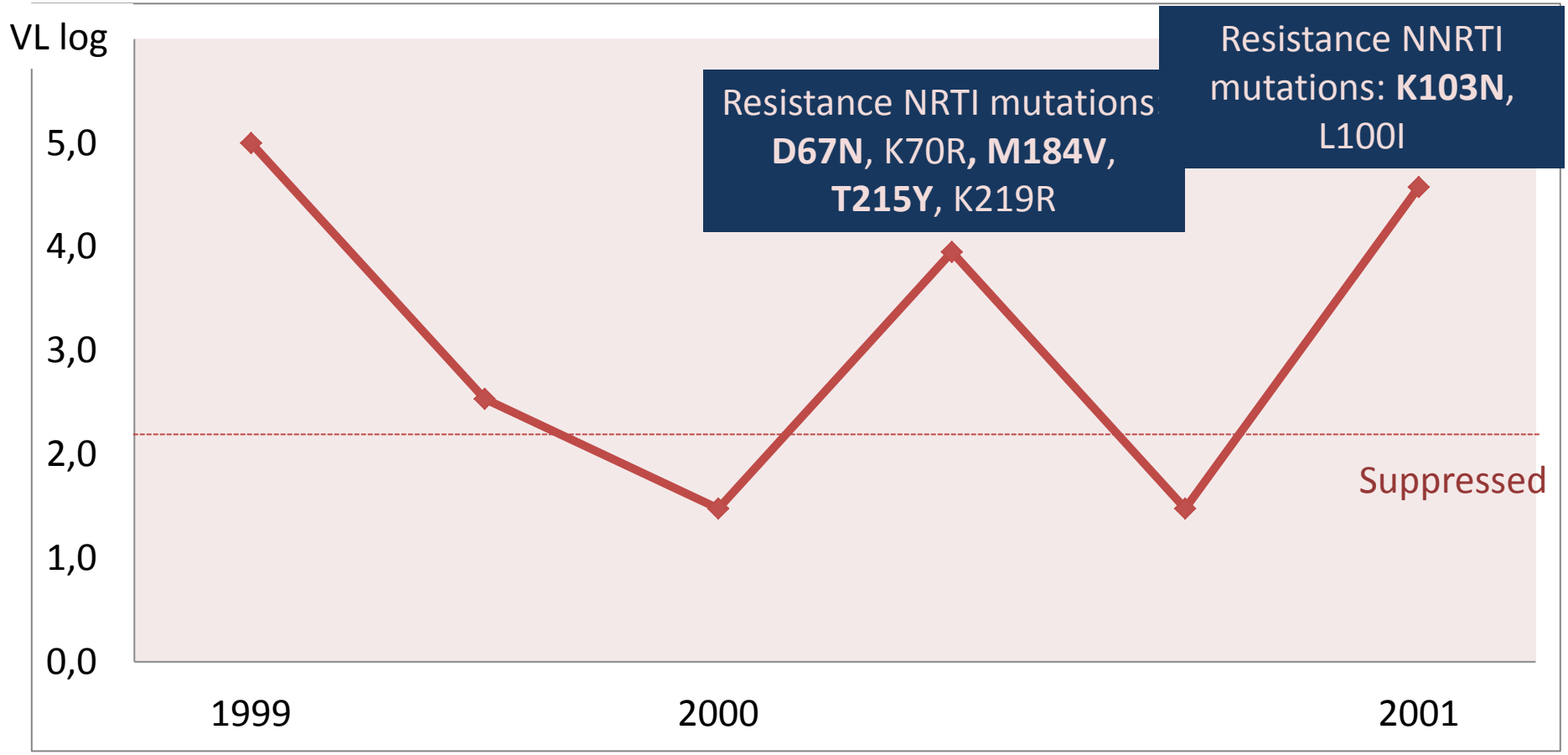
	Resistance*
Efavirenz (EFV)	High- level
Nevirapine (NVP)	High- level
Etravirine (ETR)	Intermediate
Rilpivirine (RLP)	High- level

	Resistance*
Zidovudine (AZT)	High-level
Didanosine (DDI)	**High-level**
Stavudine (D4T)	High-level
Lamivudine (3TC)	High-level
Abacavir (ABC)	High-level
Emtricitabine (FTC)	High-level
Tenofovir (TDF)	Intermediate

No PI resistance

** Stanford Database*

Sum up



	Δ		↑ transaminases				Drug induced hepatitis	
ART	AZT/3TC/IDV		AZT/3TC/ABC				3TC/ABC/EFV	
CD4	46	38	29	43	56	51	96	117

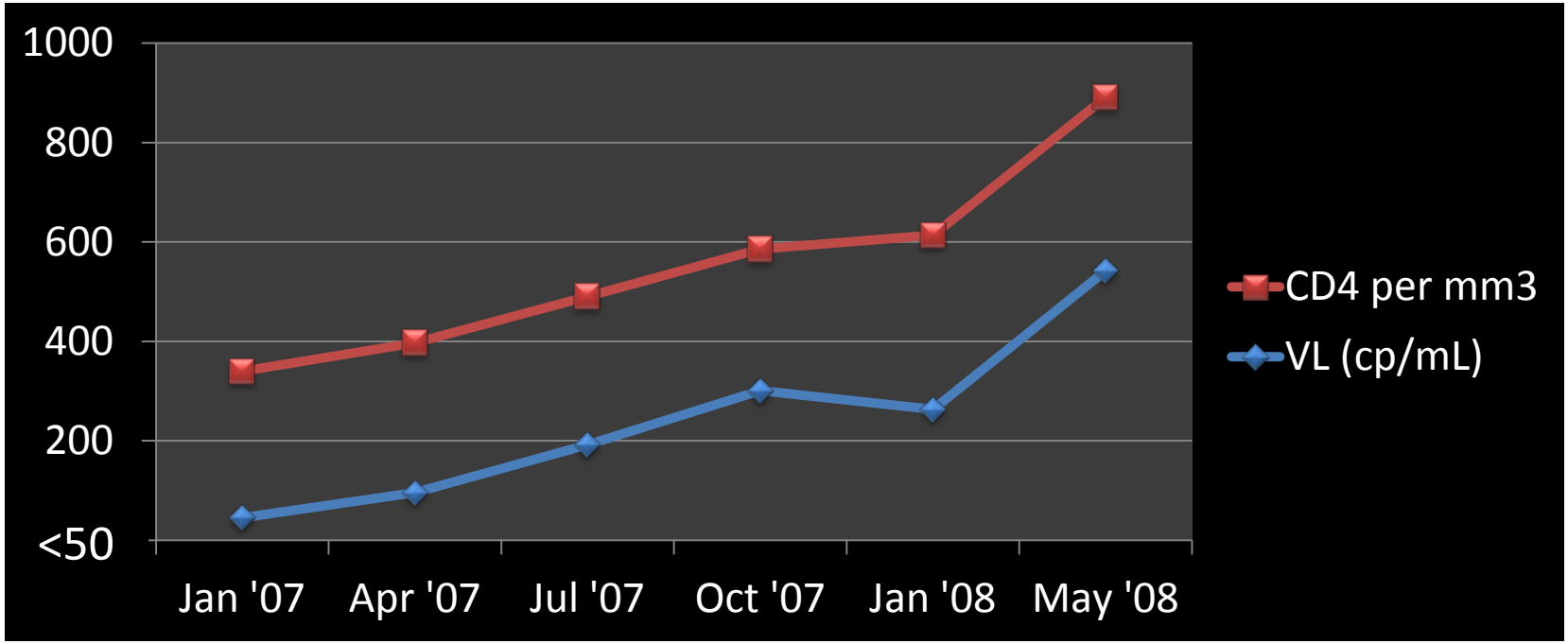
2001- 2007: “Undetectable”

- **LPV/r/TDF/D4T/3TC**
  - 2001-2004 suppressed VL (<50 copies/mL)
- Treatment switch
  - **ATV/r/TDF/FPV**
  - Reason: lipodystrophy
  - 2004-2007 suppressed VL

LPV/r = Lopinavir/ritonavir, FPV = Fosamprenavir

Low level viraemia starts in 2007

- Patient claims full adherence
- Therapeutic drug monitoring satisfactory
- New partner HIV (+)



Resistance test (X2 in 2008)

ATV/r/TDF/FPV

- NO NRTI &
- NO NNRTI resistance mutations detected

- PI major: **V32I**
- PI minor: G73GS, T74S

	Resistance*
ATV, DRV, IDV, NFV, SQV, FPV	Low-level resistance
LPV, TPV	Potential low-level resistance

** Stanford Database*

5th ART switch

DRV/r (600/100mg bid)+ RAL + TDF

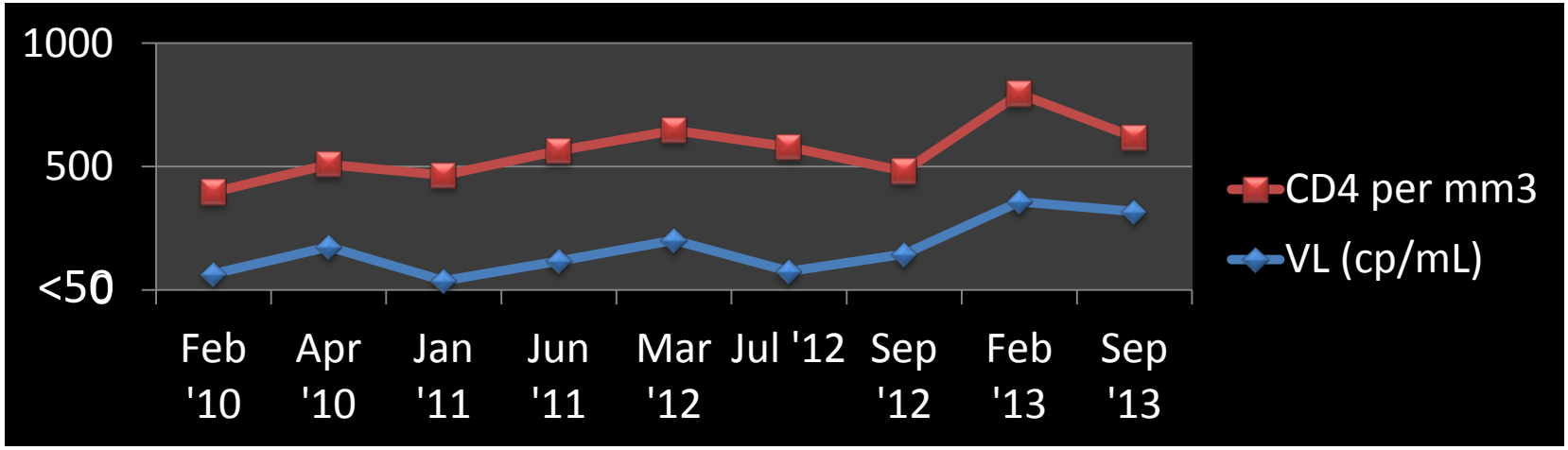
VL<50 copies/mL

between Aug ‘08 & Oct ‘09

DRV/r = Darunavir/ritonavir, RAL= Raltegravir

Problem list 2010-2013

1. Valciferal malaria Jul ’09 → Responded to quinine
2. Patient complaints for memory deterioration
3. Renal impairment (CKD I→III)
   - Biopsy inconclusive
4. Low level viraemia



CV= Cardiovascular

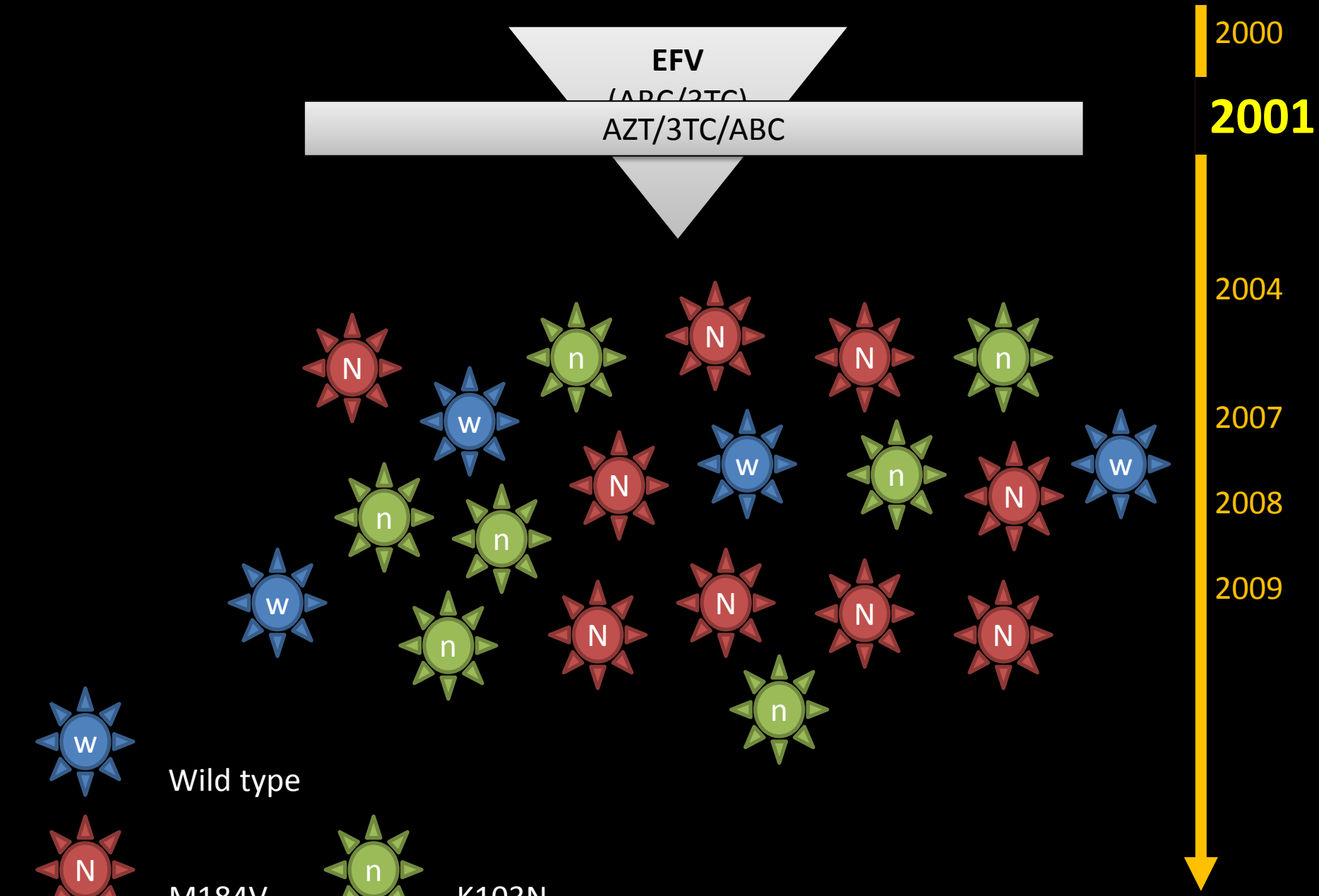
Genotype tests

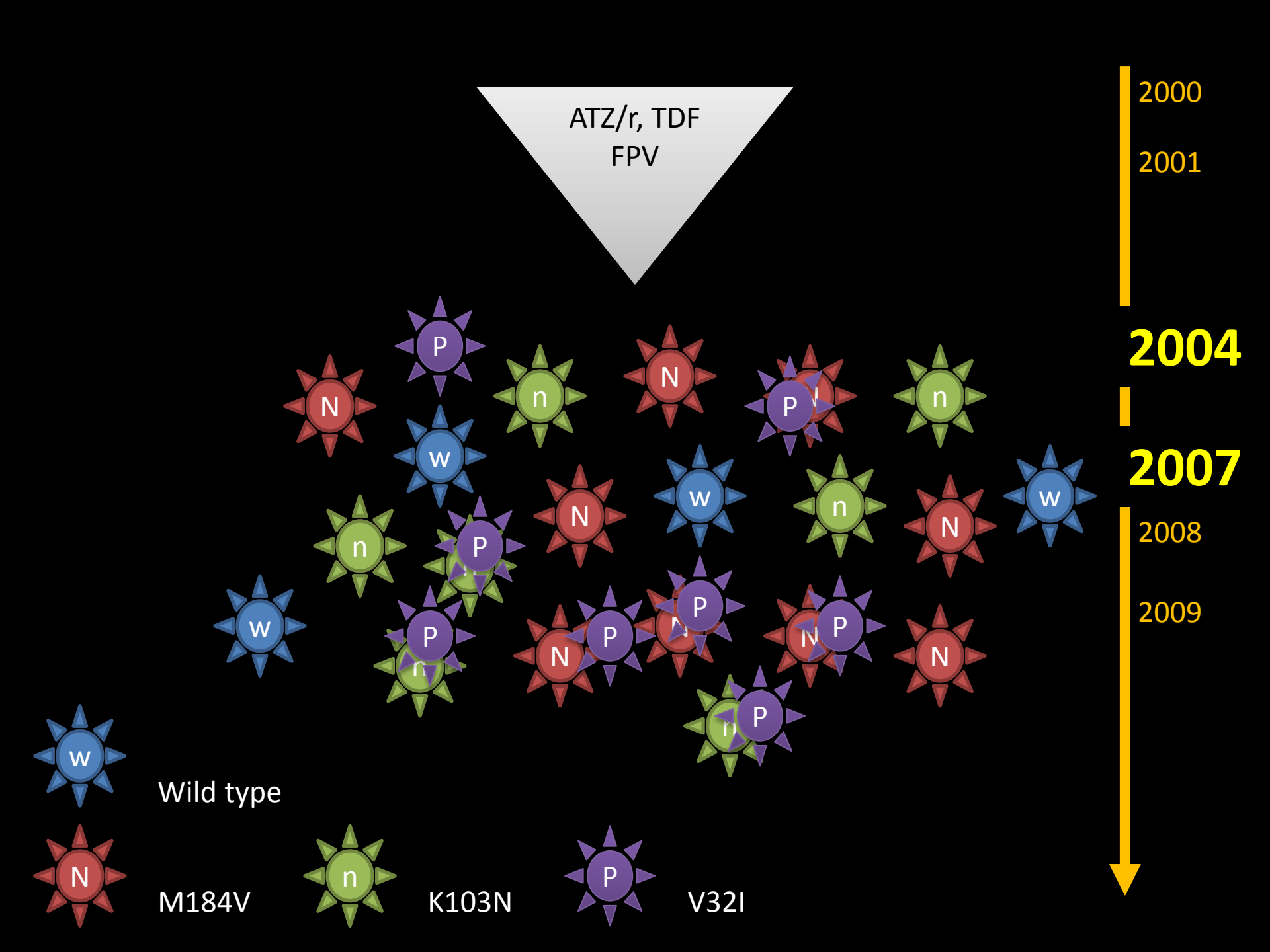
2010 Resistance mutations

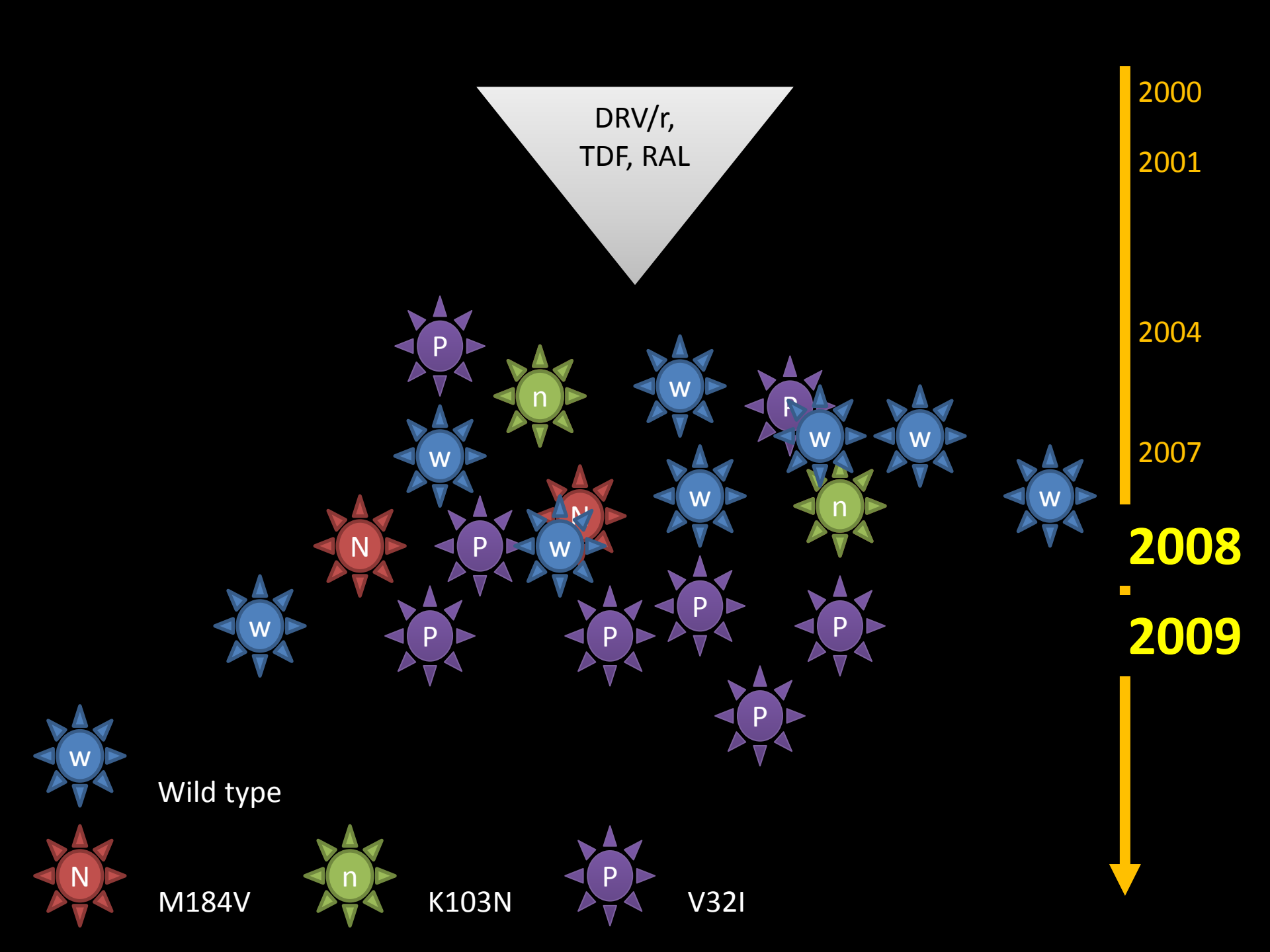
- None NNRTI
- None NRTI
- None PI major
- PI minor: T74S

2013 resistance mutations

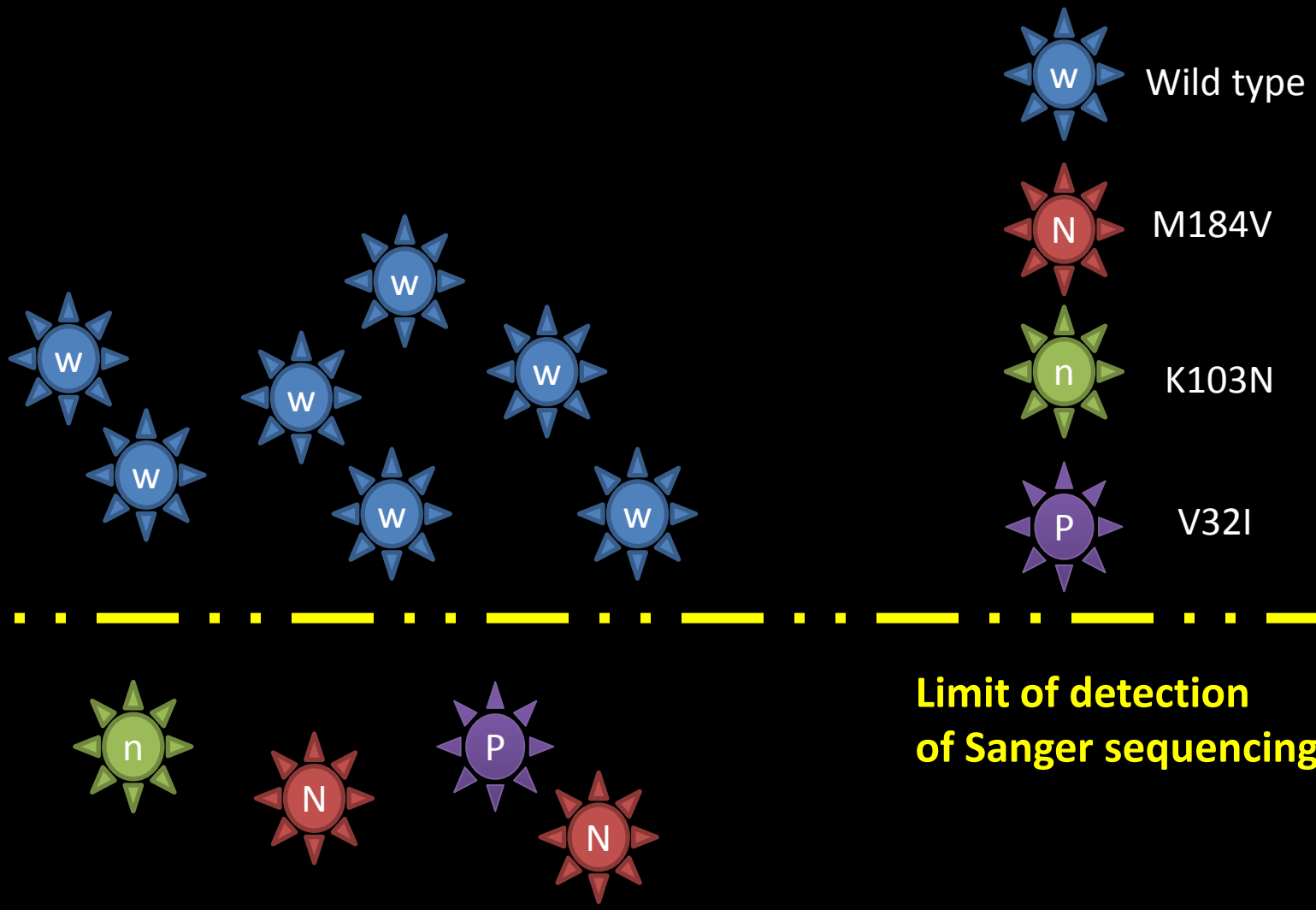
- None NNRTI
- None NRTI
- None PI major
- None PI minor
- Unable to amplify integrase region.


EFV
(ABC/3TC)
AZT/3TC/ABC
2000
2001
2004
2007
2008
2009
Wild type
M184V
K103N


ATZ/r, TDF
FPV
2000
2001
2004
2007
2008
2009
Wild type
M184V
K103N
V32I


DRV/r,
TDF, RAL
2000
2001
2004
2007
2008
2009
Wild type
M184V
K103N
V32I

Deep sequencing would offer a better indication of the full extent of resistance, however the viral load is too low



In Summary

According to the resistance test the low level viraemia consists of non-resistant strains that are susceptible to the current regimen.

Neurocognitive dysfunction

- Cryptococcal meningitis in 1999 left him with mild cognitive impairment
- Worsening NCD since 2008
  - Coinciding with the emergence of low level viraemia
- No clinical neurological findings
- Enrollment in PARTITION study, LP performed in 2011 and CSF analysis:
  - **VL = 2,028 copies/mL (Plasma VL=48 copies/mL)**
  - WBC = 4, RBC<1, Protein = 0.83↑, Glu = 3

CSF Resistance Test 2011

NNRTIs: L100I, **K103N**

	Resistance*
Efavirenz (EFV)	High- level
Nevirapine (NVP)	High- level
Etravirine (ETR)	Low-level
Rilpivirine (RLP)	Low- level

InIn: Y143C

	Resistance*
Raltegravir (RAL)	High- level
Elvitegravir (EVG)	Low- level
Dolutegravir (DTG)	Susceptible

NRTIs: **D67N**, K70R, L74V, **M184V**, **T215Y**, K219R

	Resistance*
Zidovudine (AZT)	High-level
Didanosine (DDI)	High-level
Stavudine (D4T)	High-level
Lamivudine (3TC)	High-level
Abacavir (ABC)	High-level
Emtricitabine (FTC)	High-level
Tenofovir (TDF)	Low-level

No PI resistance mutations

** Stanford Database*

Plasma Resistance Test 2001

NNRTIs: L100I , **K103N**

NRTI: **D67N**, K70R, L74V
M184V, **T215Y**, K219R

	Resistance*
Efavirenz (EFV)	High- level
Nevirapine (NVP)	High- level
Etravirine (ETR)	Intermediate
Rilpivirine (RLP)	High- level

	Resistance*
Zidovudine (AZT)	High-level
Didanosine (DDI)	**High-level**
Stavudine (D4T)	High-level
Lamivudine (3TC)	High-level
Abacavir (ABC)	High-level
Emtricitabine (FTC)	High-level
Tenofovir (TDF)	Intermediate

No PI resistance

** Stanford Database*

The CNS virus in 2011 is the same with the plasma virus in 2001 with an additional mutation in the integrase gene. Since 2001 this multi-resistant virus has never been detected again in plasma in 3 subsequent tests.

CSF Resistance Test 2013

CSF VL = 5,746cp/mL

NNRTIs: L100I, **K103N**

	Resistance*
Efavirenz (EFV)	High- level
Nevirapine (NVP)	High- level
Etravirine (ETR)	Intermediate
Rilpivirine (RLP)	High- level

InIn: Y143C

	Resistance*
Raltegravir (RAL)	High- level
Elvitegravir (EVG)	Low- level
Dolutegravir (DTG)	Susceptible

NRTIs: **D67N**, K70R, L74V, **M184V**, **T215Y**, K219R

	Resistance*
Zidovudine (AZT)	High-level
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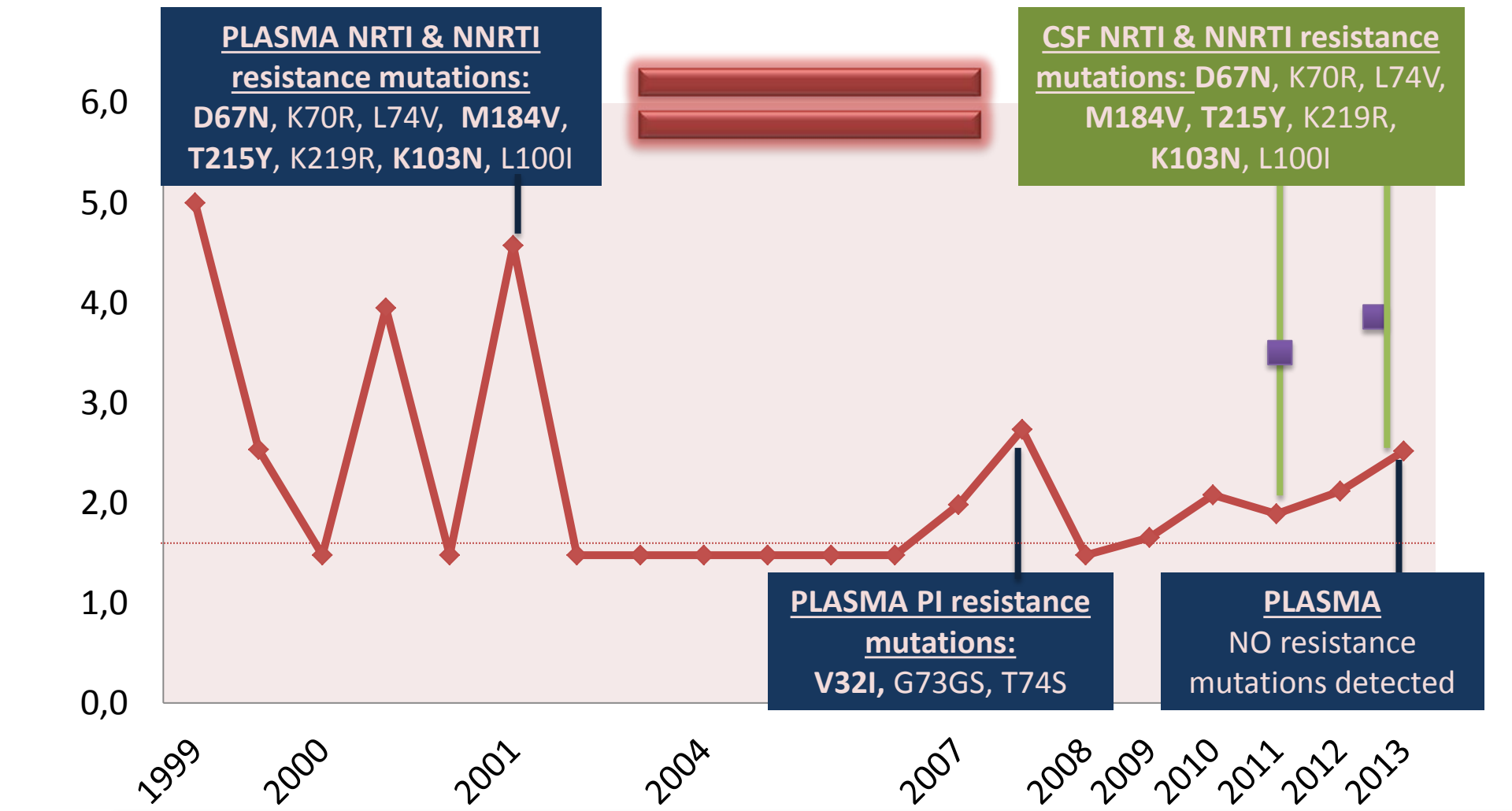
Tenofovir (TDF)	Low-level

No PI resistance mutations

** Stanford Database*



Δ	Drug-induced hepatitis		Lipodystrophy		Renal impairment	
AZT 3TC IDV	AZT 3TC ABC	3TC ABC EFV	LPV/r TDF D4T 3TC	ATZ/r TDF FPV	DRV/r TDF RAL	DRV/r ETR T20

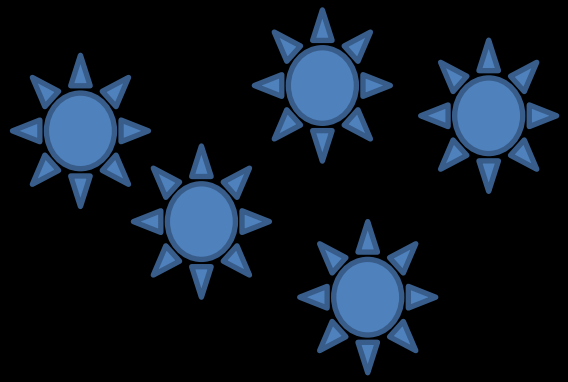
Scenario 1

- During the 2001 virological failure the multi-resistant virus went to the CNS
- Remained as latent CNS reservoirs 2001-2007
- In 2008 started an independent ongoing replication spreading viruses in peripheral blood and causing the LLV in plasma

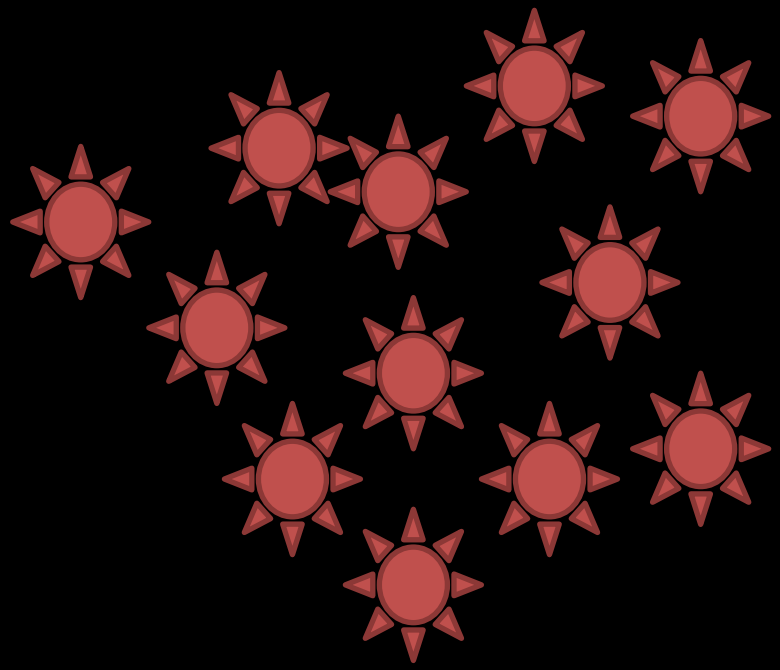
LLV = Low level viraemia

If the source of LLV is the CNS, the virus detected in the 2 compartments should be the same, but…

PLASMA



CNS



No resistance mutations

D67N, K103N, M184V, T215Y, Y143C

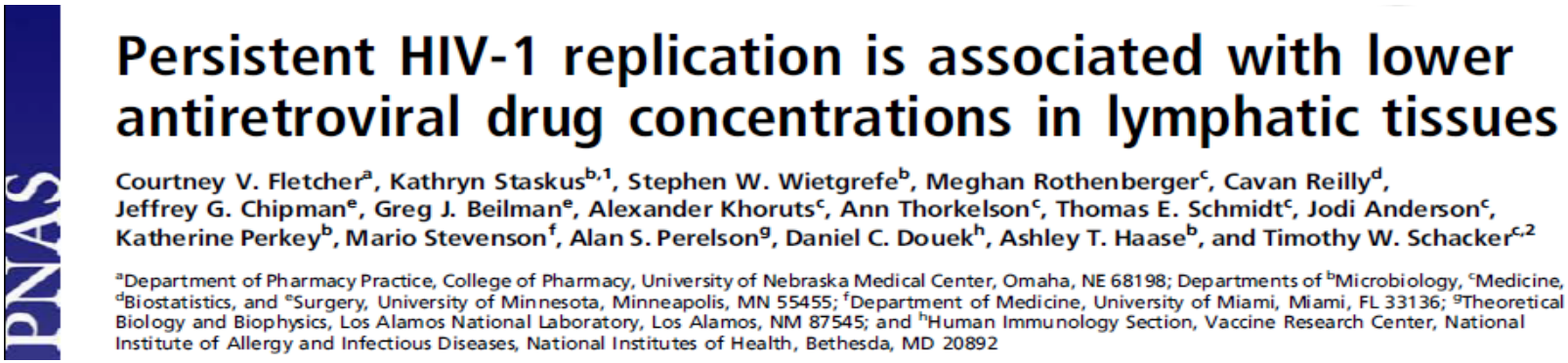
Scenario 2

- During the 2001 virological failure the NRTI/NNRTI resistant virus goes to the CNS and establishes itself.
- Boosted PI therapy finally causes resistance in the plasma but not in the CSF.
  - PI more effective in the CNS?
- RAL pressure results in the Y134C, because DRV/r fails to support it.
  - Indication of PI penetration in CNS cells is problematic

Manifestation of drug ineffectiveness in two different compartments with separate evolving of the same archived virus.

Compartmentalization, PK & PD

- DRV levels in CSF were adequate
- Intracellular kinetics



PNAS

Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues

Courtney V. Fletcher[a], Kathryn Staskus[b,1], Stephen W. Wietgrefe[b], Meghan Rothenberger[c], Cavan Reilly[d], Jeffrey G. Chipman[e], Greg J. Beilman[e], Alexander Khoruts[c], Ann Thorkelson[c], Thomas E. Schmidt[c], Jodi Anderson[c], Katherine Perkey[b], Mario Stevenson[f], Alan S. Perelson[g], Daniel C. Douek[h], Ashley T. Haase[b], and Timothy W. Schacker[c,2]

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- Protein binding (eg a1-acid glycoprotein) and drug efflux pump (eg P-glycoprotein)
- Inter-individual variability

PK= Pharmacokinetics, PD= Pharmacodynamics

CSF-Plasma discordance (1)

- UK PARTITION study (CROI 2014 poster)
  - Group A (n=105) had indications of neurological disease. Group B (n=40) experienced unexplained viraemia (≥50 copies/ml) within the previous 12 months, in the absence of neurological disease.
  - CSF/plasma discordance, was present in 13.1% of the study population.
  - Association between CSF/plasma discordance and nadir CD4 demonstrated (as previously shown).

CSF-Plasma discordance (2)

- Viral Escape in CSF during suppressive ART (Eden et al)
  - Asymptomatic with VL<50cp/mL (n=69)
  - 10% of subjects had CSF HIV-1 RNA >50 copies/mL
  - significantly longer exposure to ART and higher levels of intrathecal immune activation
  - CPE ranking was not correlated with either detectable CSF HIV-1 RNA or level of intrathecal immune activation

Take home messages - Discussion

1. Drug effectiveness against virus replication is not necessarily predicted by TDM.
2. Ongoing virus replication at “sanctuary” sites is not always the source of LLV in plasma.
3. How does LLV due to non-resistant virus detected in genotype tests persist?
4. Which patients should undergo a LP?