THPE0136

British Columbia Centre *for* Excellence *in* HIV/AIDS

Combination of TMC114/ritonavir and TMC125 in patients with multidrug resistant HIV

Julio Montaner[1], Marianne Harris[1], Thomas Kakuda[2], Gerene Larsen[1], Brian Woodfall[3], Diego Miralles[3], P. Richard Harrigan[1]

[1]BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Vancouver Canada; [2]Tibotec Inc., Yardley, Pennsylvania, USA; [3]Tibotec, Mechelen, Belgium

Background

TMC114 and TMC125 are investigational antiretroviral drugs with activity against HIV that is resistant to available PIs and NNRTIs, respectively. Patients with multidrug-resistant HIV may benefit from the use of these agents in combination.

Methods

Patients

- HIV+ adults
- extensive treatment experience with NRTIs/NtRTIs, NNRTIs, and PIs
- evidence of drug resistance on genotypic testing

Medication regimens

TMC114 600 mg with ritonavir 100 mg twice daily
TMC125 200 mg twice daily
+/- NRTIs/NtRTIs
+/- enfuvirtide (T20)

Clinical and Laboratory Assessments

Plasma viral load (VL), CD4 cell count, and safety parameters (hematology, chemistry)

- at baseline
- weekly until week 4
- every 2 weeks until week 12
- every 4 weeks until week 24

Genotypic resistance

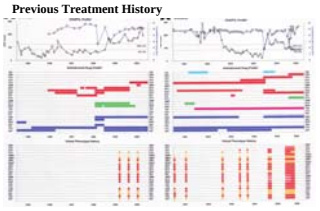
- vircoTYPE HIV-1 Virtual Phenotype was assessed at baseline from archived samples and on the most recent sample with VL>200 copies/mL
- Virtual Phenotype was repeated on samples where VL >200 copies/mL on therapy

Pharmacokinetic (PK) methods

- 12-hour PK assessments were conducted between weeks 4 and 8
- Plasma concentrations of TMC114, TMC125, and ritonavir were determined using a validated liquid chromatographic-tandem mass spectrometric (LC0-MS/MS) method
- PK analyses were performed using WinNonlin professional ™ (version 5.1;Pharsight Corporation, Mountain View, California, USA)
- A non-compartmental model with extravascular input was used
- The primary PK parameters were maximum and minimum plasma concentration (Cmax and Cmin, respectively), time to Cmax (Tmax), and area under the plasma concentration-time curve from 0 to 12 hours (AUC12) as calculated using the linear-up/log-down trapezoidal rule

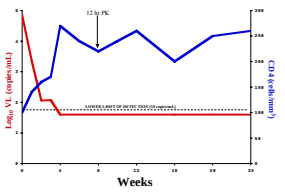
Results

PATIENT 1
Previous Treatment History

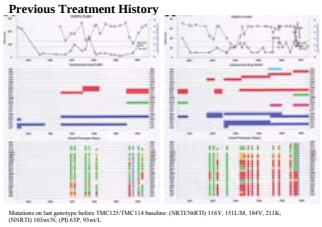


Mutations on last genotype before TMC125/TMC114 baseline: (NRTI/NtRTI) 41L, 44D, 67N, 70R, 74I, 118I, 184V, 203K, 208Y, 210W, 211K, 215Y, 219R, 221Y, 228H; (NNRTI) 103S, 108I, 135T, 221Y; (PI) 10V, 13V, 20R/V, 33V, 36I, 47V, 48M, 53vsL, 54A/V, 58E, 63P, 66vsI/V, 71T, 73S, 82T, 89V, 90M

PATIENT 1
Regimen: TMC125/TMC114/RTV/TDF/ABC/3TC

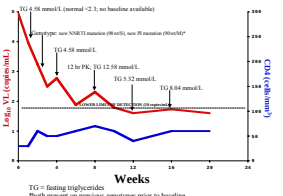


PATIENT 2
Previous Treatment History



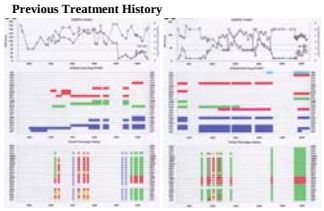
Mutations on last genotype before TMC125/TMC114 baseline: (NRTI/NtRTI) 116Y, 151I/M, 184V, 211K; (NNRTI) 103vsN; (PI) 63P, 93vsL

PATIENT 2
Regimen: TMC125/TMC114/RTV/TDF/d4T/3TC



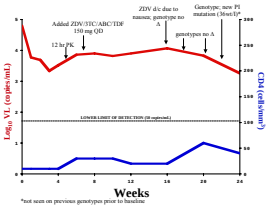
TG = fasting triglycerides
*both present on previous genotypes prior to baseline

PATIENT 3
Previous Treatment History



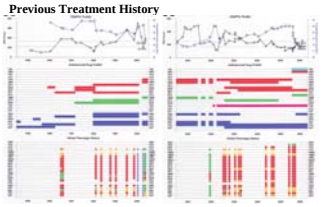
Mutations on last genotype before TMC125/TMC114 baseline: (NRTI/NtRTI) 211K; (NNRTI) 103N; (PI) 63P, 77I, 93L

PATIENT 3
Regimen: TMC125/TMC114/RTV/T20



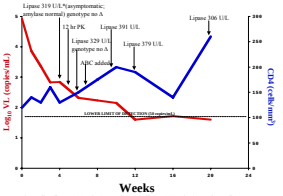
*not seen on previous genotypes prior to baseline

PATIENT 4
Previous Treatment History



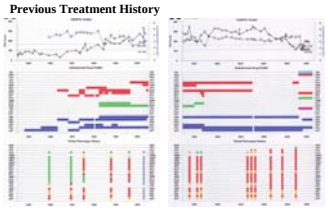
Mutations on last genotype before TMC125/TMC114 baseline: (NRTI/NtRTI) 20R, 41L, 43Q, 44D, 67N, 70M, 181C, 184V, 203vsD, 208Y, 210W, 211K, 215Y; (NNRTI) 98G, 103N, 135T, 179I, 181C; (PI) 10I, 13V, 24I, 33F, 35D, 36L, 46vsL, 48V, 54T, 63P/S, 71V, 74S, 77I, 82A, 93L

PATIENT 4
Regimen: TMC125/TMC114/RTV/T20/TDF/ZDV/3TC



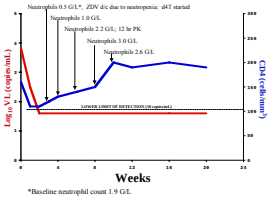
*Baseline lipase 259 U/L (normal <265); lipase 322 U/L 4 months earlier

PATIENT 5
Previous Treatment History



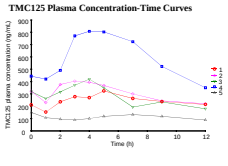
Mutations on last genotype before TMC125/TMC114 baseline: (NRTI/NtRTI) 41L, 43E, 44A, 67N, 69N, 70R, 74I, 118I, 181C; 184V, 210W, 211K, 215Y, 219E, 228H; (NNRTI)106I, 179I, 181C; (PI)10F, 11I, 13V, 20I, 36I, 54V, 63P, 71V, 73vsS, 79A, 84V, 90M

PATIENT 5
Regimen: TMC125/TMC114/RTV/T20/TDF/ZDV/3TC

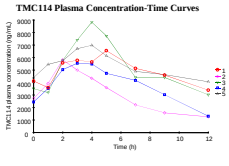


*Baseline neutrophil count 1.9 G/L

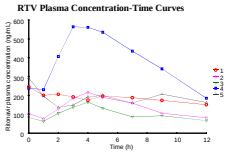
TMC125 Plasma Concentration-Time Curves



TMC114 Plasma Concentration-Time Curves



RTV Plasma Concentration-Time Curves



Mean (SD) PK Parameters for TMC125, TMC114, and ritonavir (RTV)

	C_{max} (ng/mL)	T_{max} (h)	AUC_{12} (ng•h/mL)	C_{min} (ng/mL)
TMC125	401 (241)	3.2	3675 (2142)	210 (94)
	361 / 569 (125) / (381)	ND / ND	3116 / 4921 (1126) / (2982)	166 / 291 (66) / (188)
TMC114	6744 (1299)	3.6	53304 (12155)	2508 (1264)
	8312 / 9109 (2921) / (2482)	ND / ND	71856 / 72321 (34810) / (21687)	3561 / 3309 (2497) / (1486)
RTV	296 (157)	2.2	2384 (1337)	129 (52)
	ND / ND	ND / ND	ND / ND	ND / ND

PK parameters derived from this cohort (n=5)
PK parameters derived from Chelsea & Westminister cohort on Day 7 / Day 28 (n=10; Boffito et al., CROI 2006, abstract 575c)

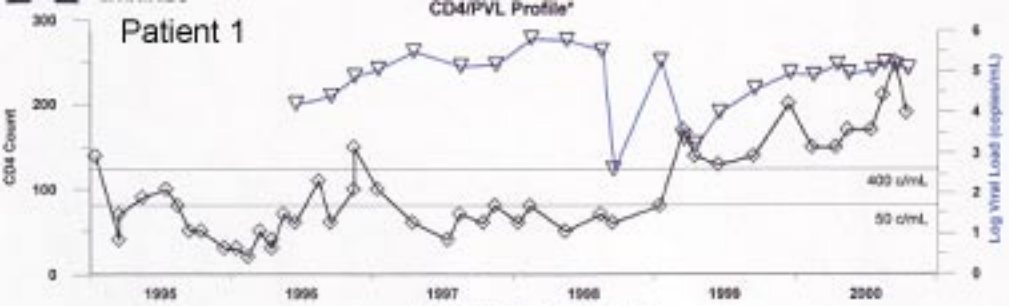
Conclusions

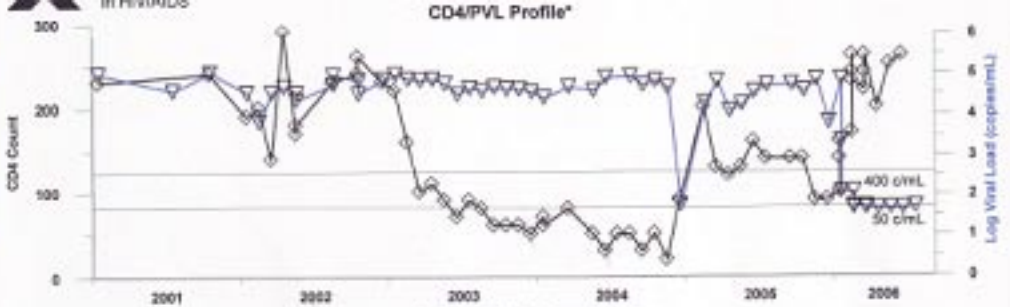
- **Combination therapy including TMC114/ritonavir and TMC125 resulted in substantial viral load declines and CD4 cell count increases over 20-24 weeks in these 5 treatment-experienced patients with drug-resistant HIV.**
- **4/5 achieved undetectable viral load (<50 copies/mL).**
- **No major safety concerns were identified.**
- **TMC114 and TMC125 plasma levels were generally comparable with data previously presented for HIV+ patients (given the substantial variability of levels for both drugs), and not obviously related to virologic response (NB patient #3).**
- **This combination may present a viable treatment option for patients with multidrug-resistant HIV.**

For additional information, please contact:
Marianne Harris, MD
BC Centre for Excellence in HIV/AIDS
St. Paul's Hospital
5th Floor, 1081 Burrard Street, Vancouver, British Columbia, Canada. V6Z 1Y6
Tel. 604-806-8771 / Fax 604-806-8412 / E-mail: mharris@cfenet.ubc.ca

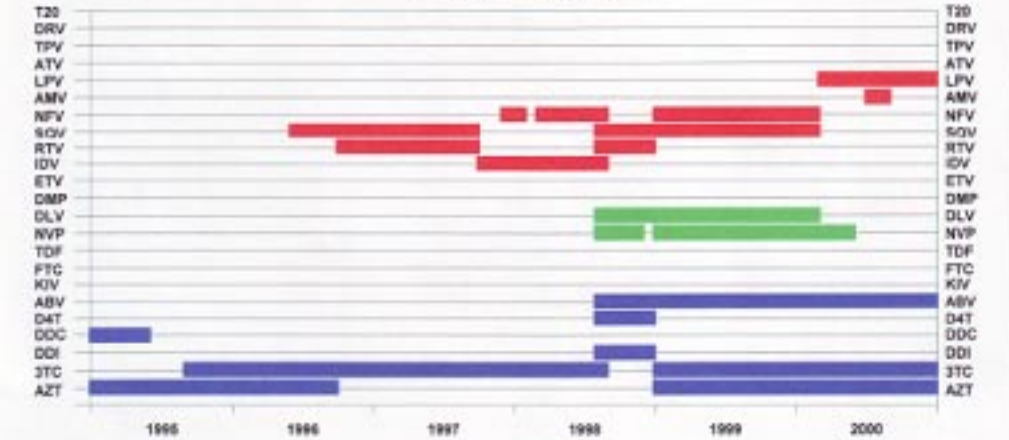
Patient 1

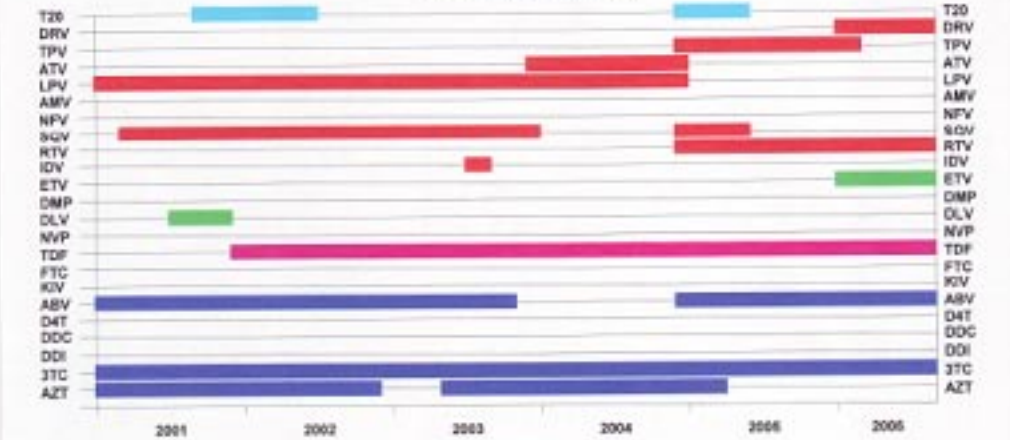
CD4/PVL Profile*



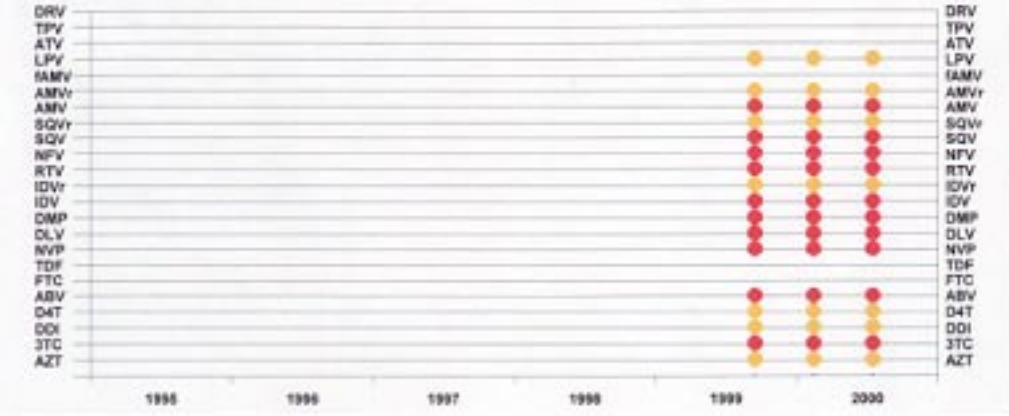


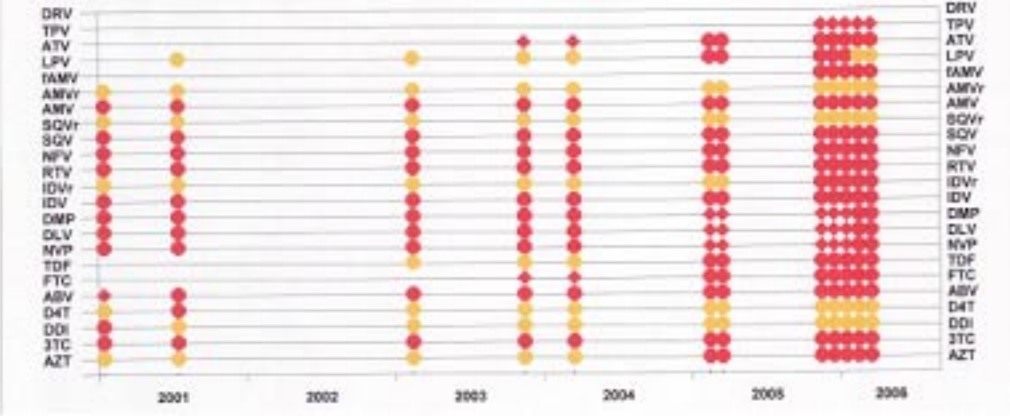
Antiretroviral Drug Profile*

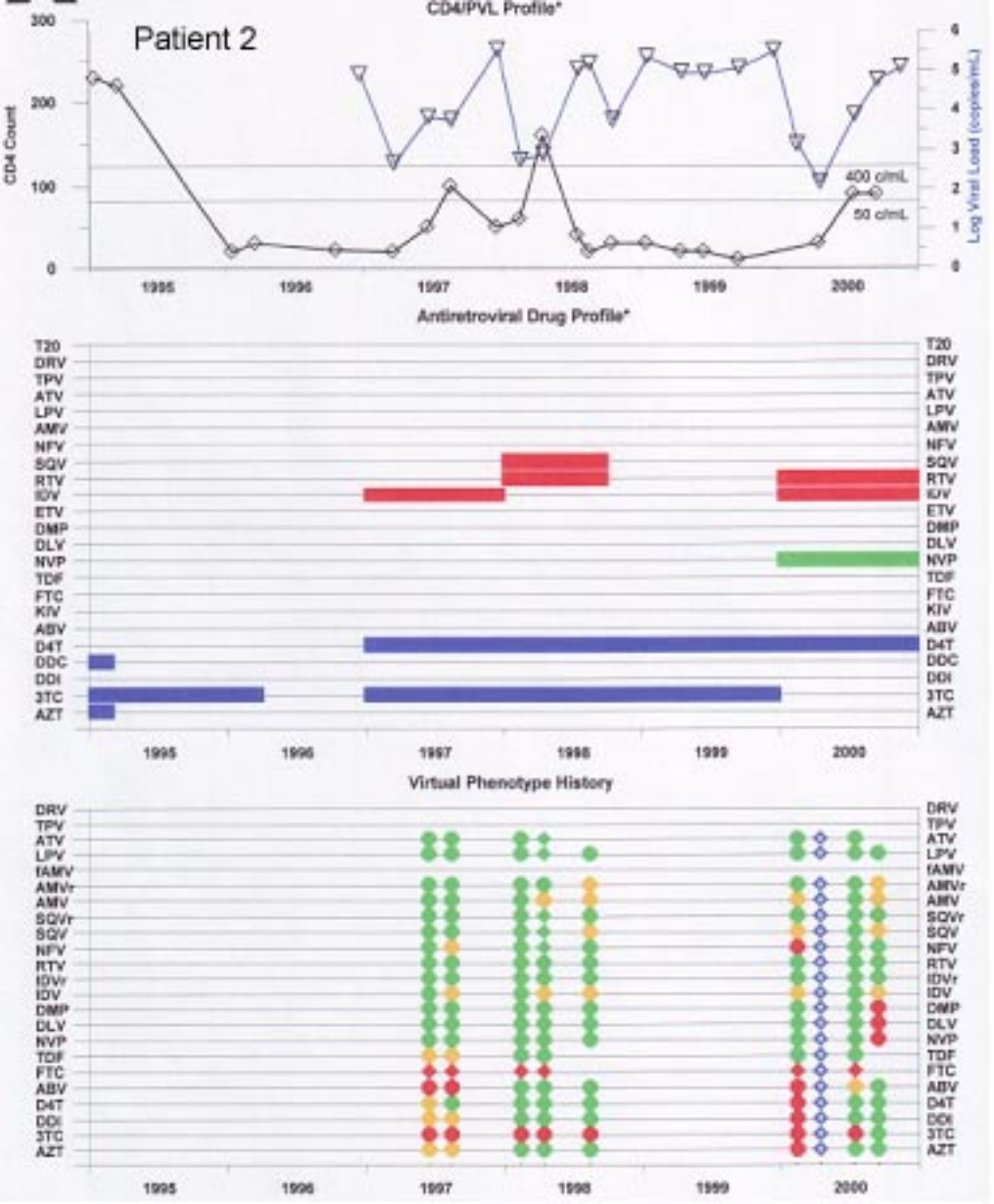


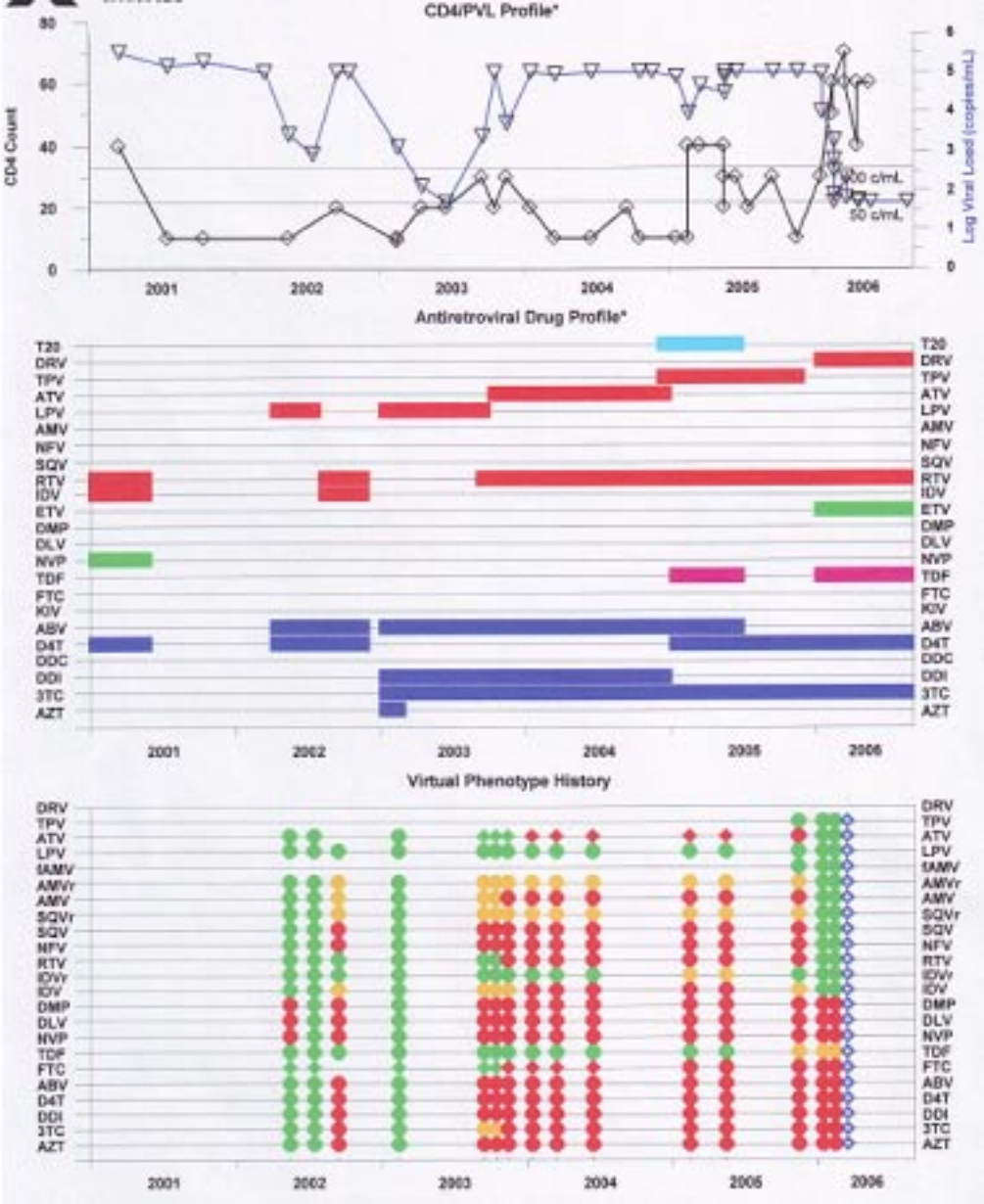


Virtual Phenotype History

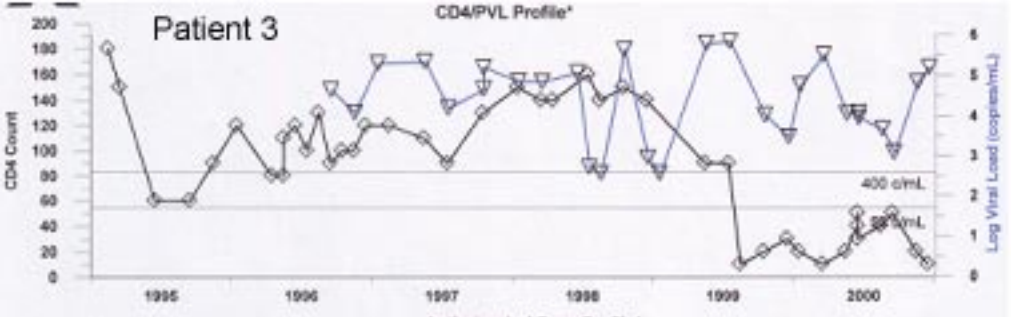


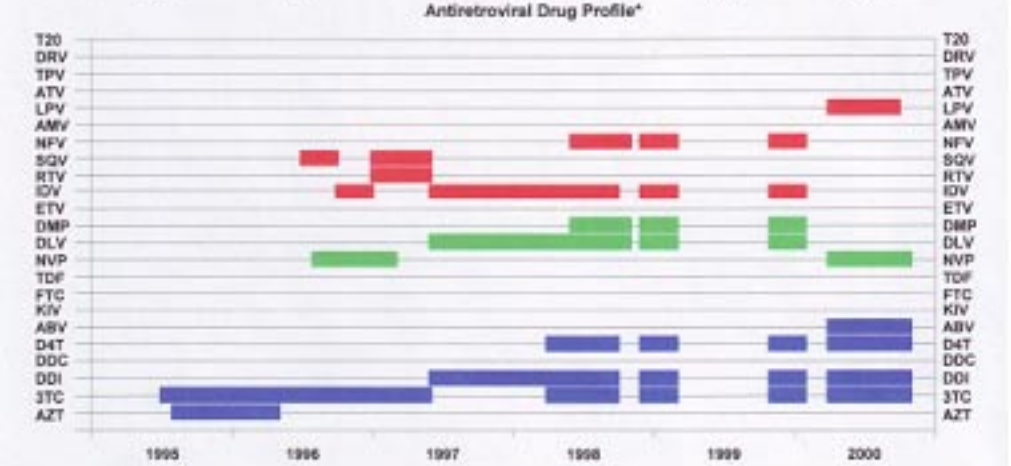


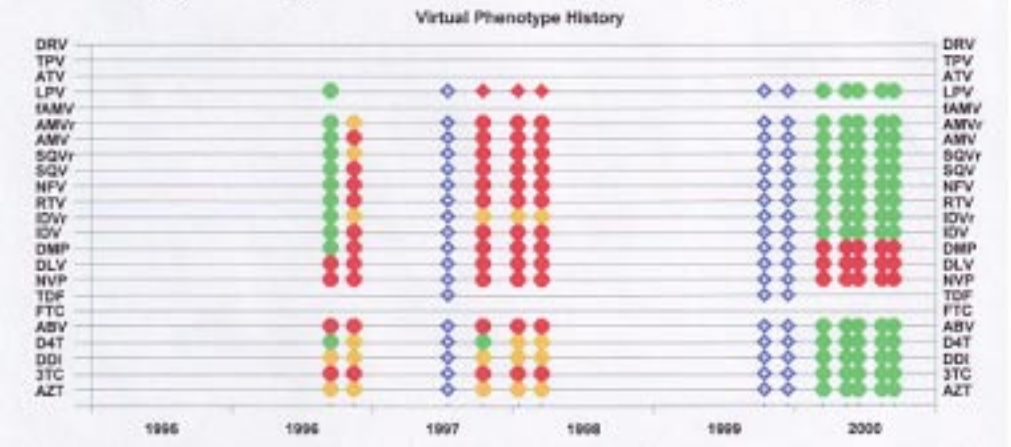

CD4/PVL Profile*
Patient 2
CD4 Count
Log Viral Load (copies/mL)
400 c/mL
50 c/mL
1995
1996
1997
1998
1999
2000
Antiretroviral Drug Profile*
T20
DRV
TPV
ATV
LPV
AMV
NFV
SQV
RTV
IDV
ETV
DMP
DLV
NVP
TDF
FTC
KIV
ABV
D4T
DDC
DDI
3TC
AZT
Virtual Phenotype History

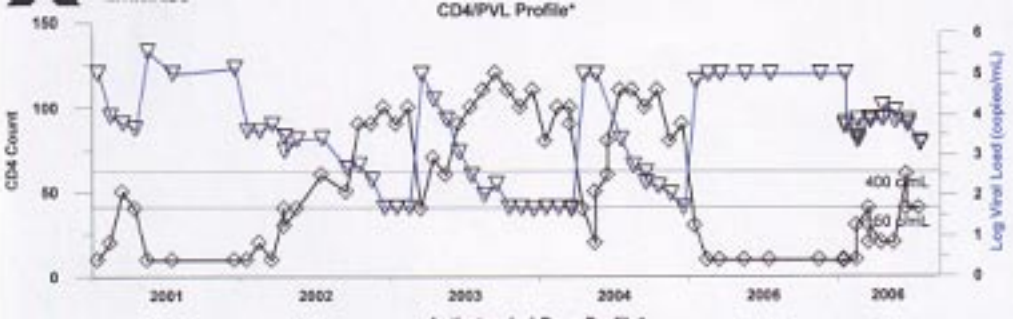

CD4/PVL Profile*
CD4 Count
Log Viral Load (copies/mL)
400 c/mL
50 c/mL
2001
2002
2003
2004
2005
2006
Antiretroviral Drug Profile*
T20
DRV
TPV
ATV
LPV
AMV
NFV
SQV
RTV
IDV
ETV
DMP
DLV
NVP
TDF
FTC
KIV
ABV
D4T
DDC
DDI
3TC
AZT
Virtual Phenotype History

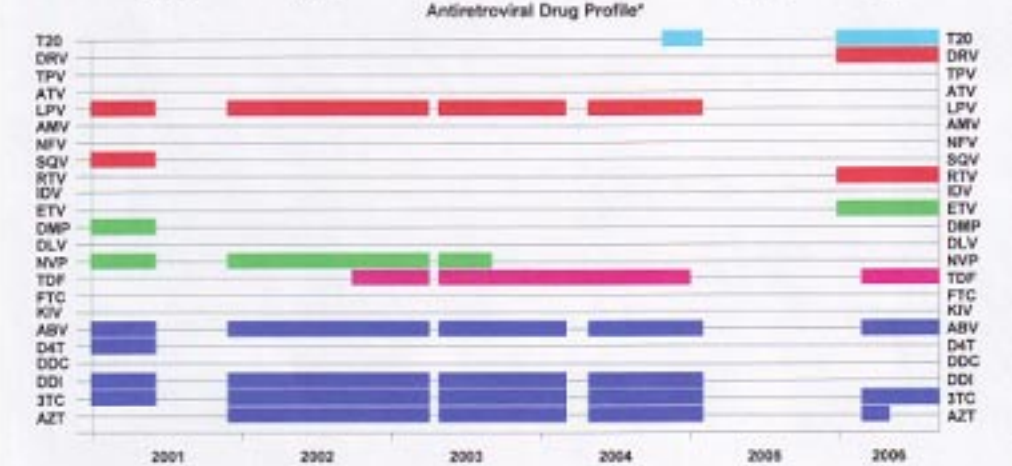
Patient 3


CD4/PVL Profile*
CD4 Count
Log Viral Load (copies/mL)
400 c/mL
1995
1996
1997
1998
1999
2000

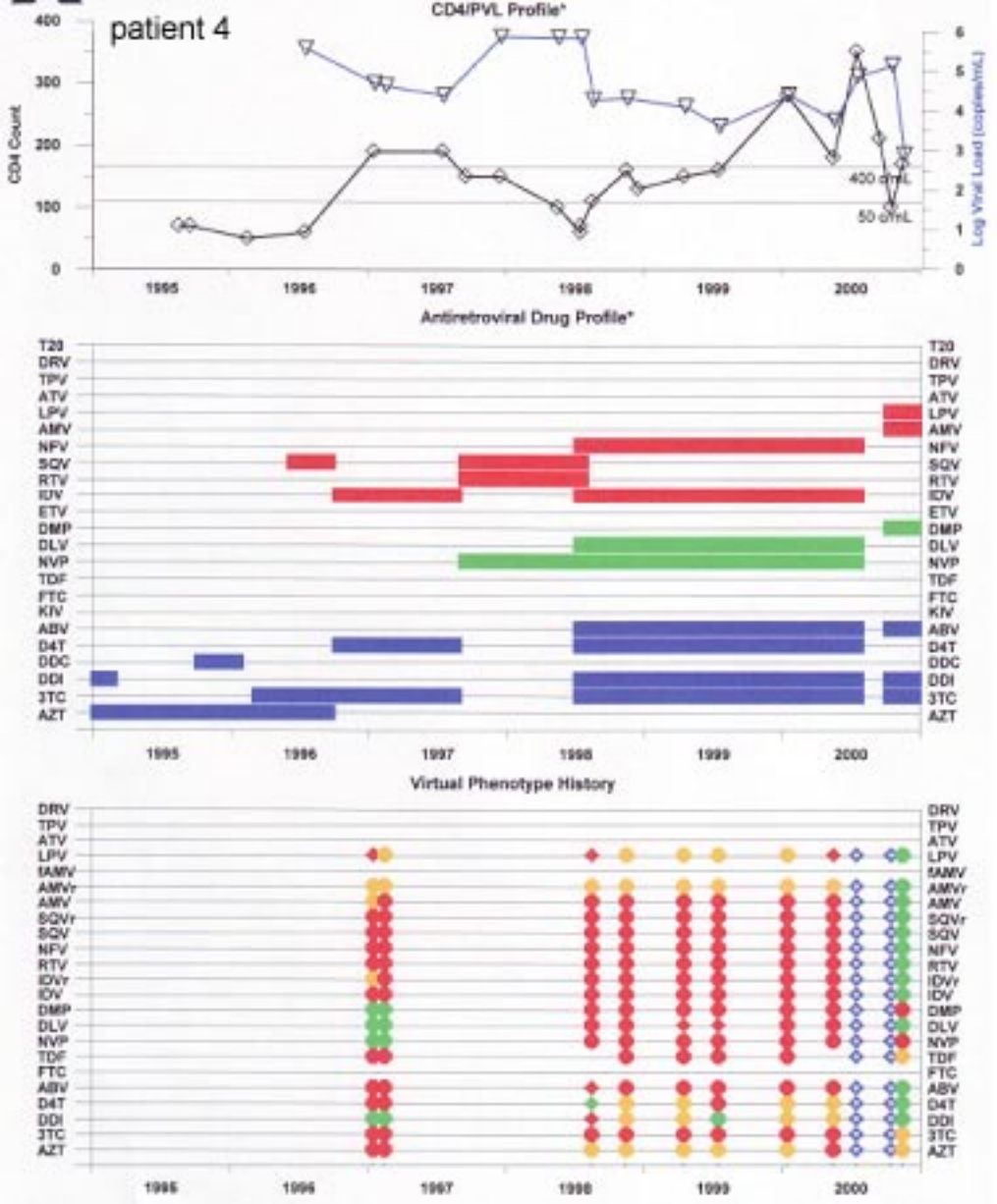

Antiretroviral Drug Profile*
T20
DRV
TPV
ATV
LPV
AMV
NFV
SQV
RTV
IDV
ETV
DMP
DLV
NVP
TDF
FTC
KIV
ABV
D4T
DDC
DDI
3TC
AZT
1995
1996
1997
1998
1999
2000

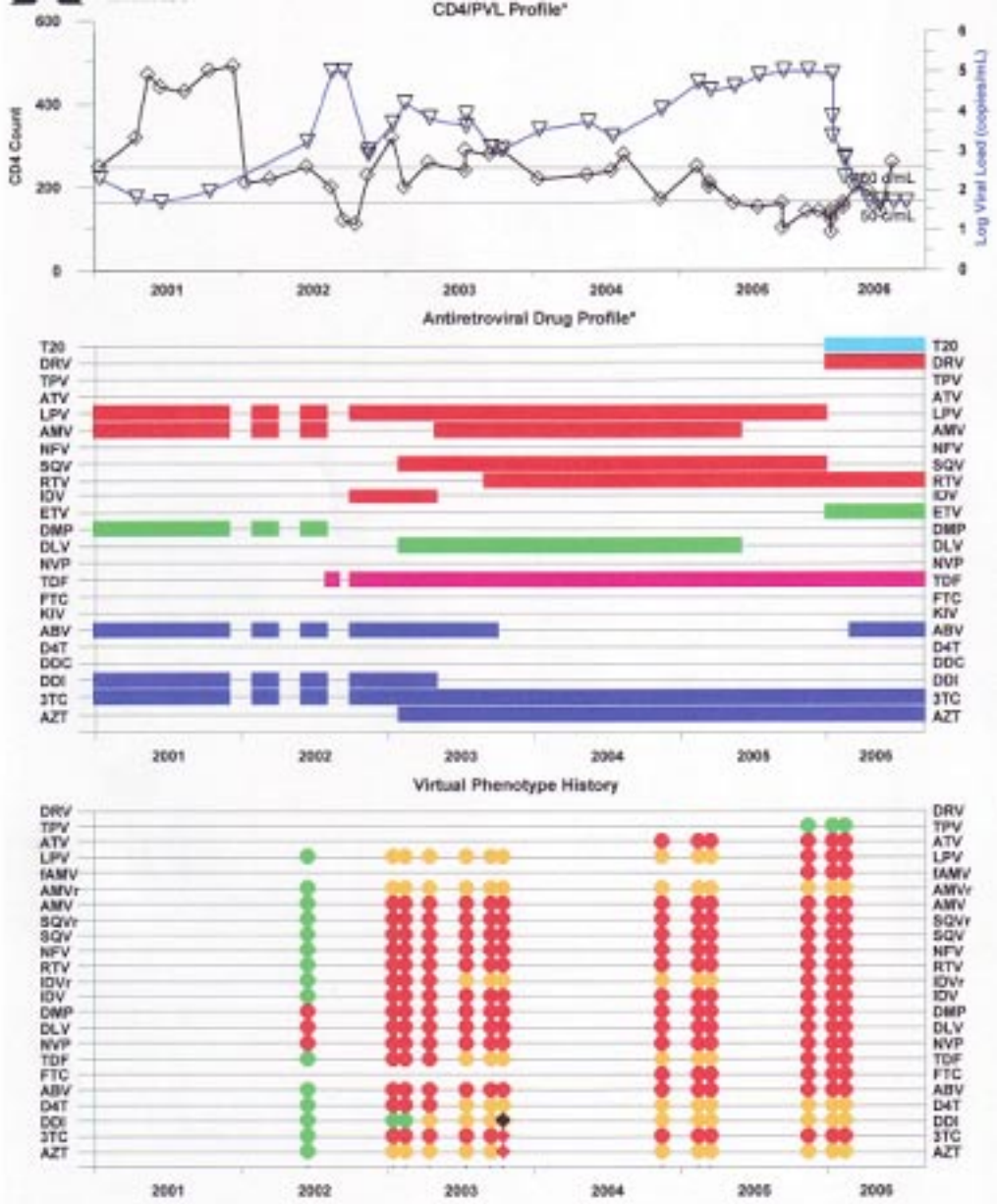

Virtual Phenotype History
DRV
TPV
ATV
LPV
fAMV
AMVr
AMV
SQVr
SQV
NFV
RTV
IDVr
IDV
DMP
DLV
NVP
TDF
FTC
ABV
D4T
DDI
3TC
AZT
1995
1996
1997
1998
1999
2000

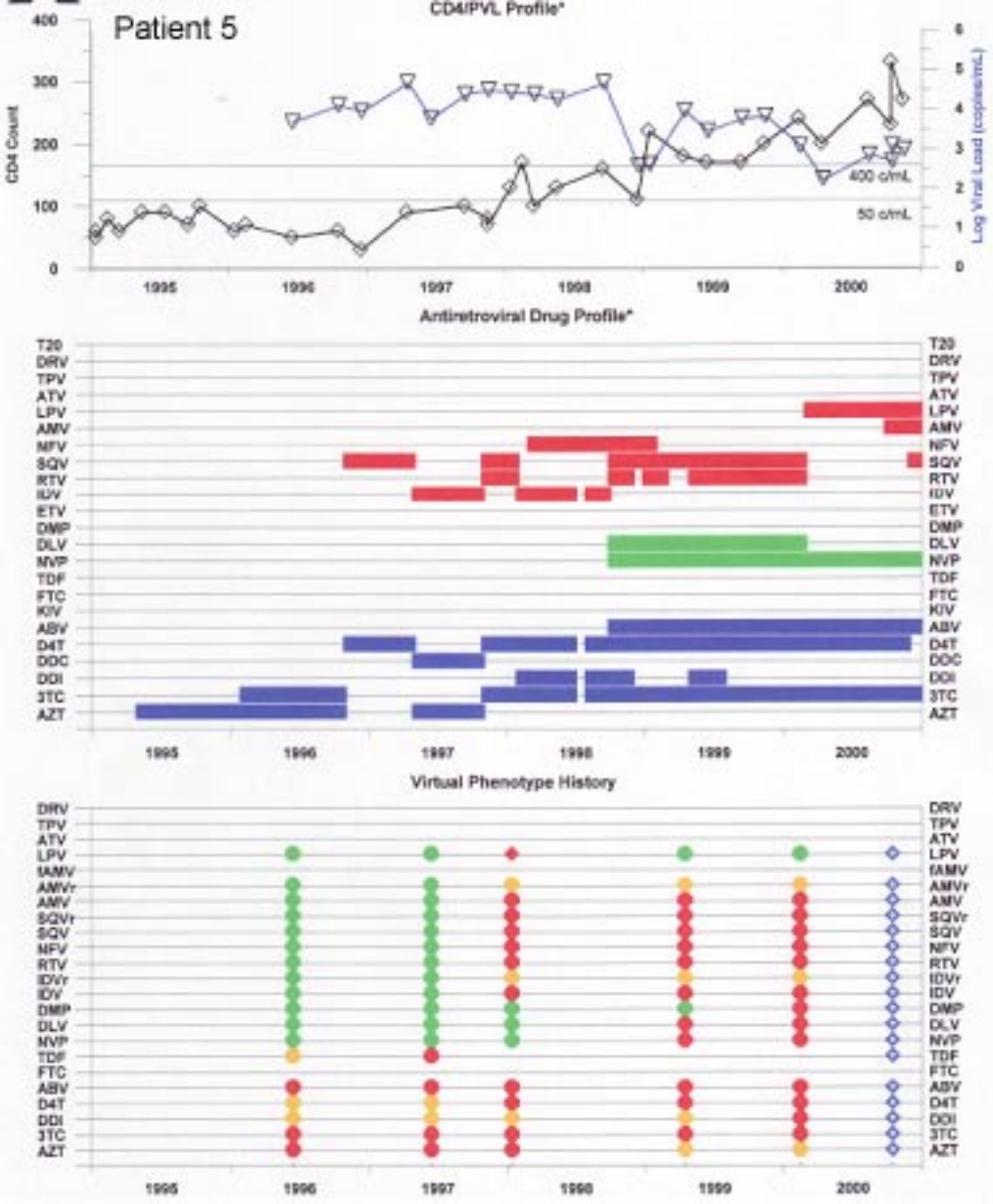

CD4/PVL Profile*
CD4 Count
Log Viral Load (copies/mL)
400 c/mL
2001
2002
2003
2004
2005
2006

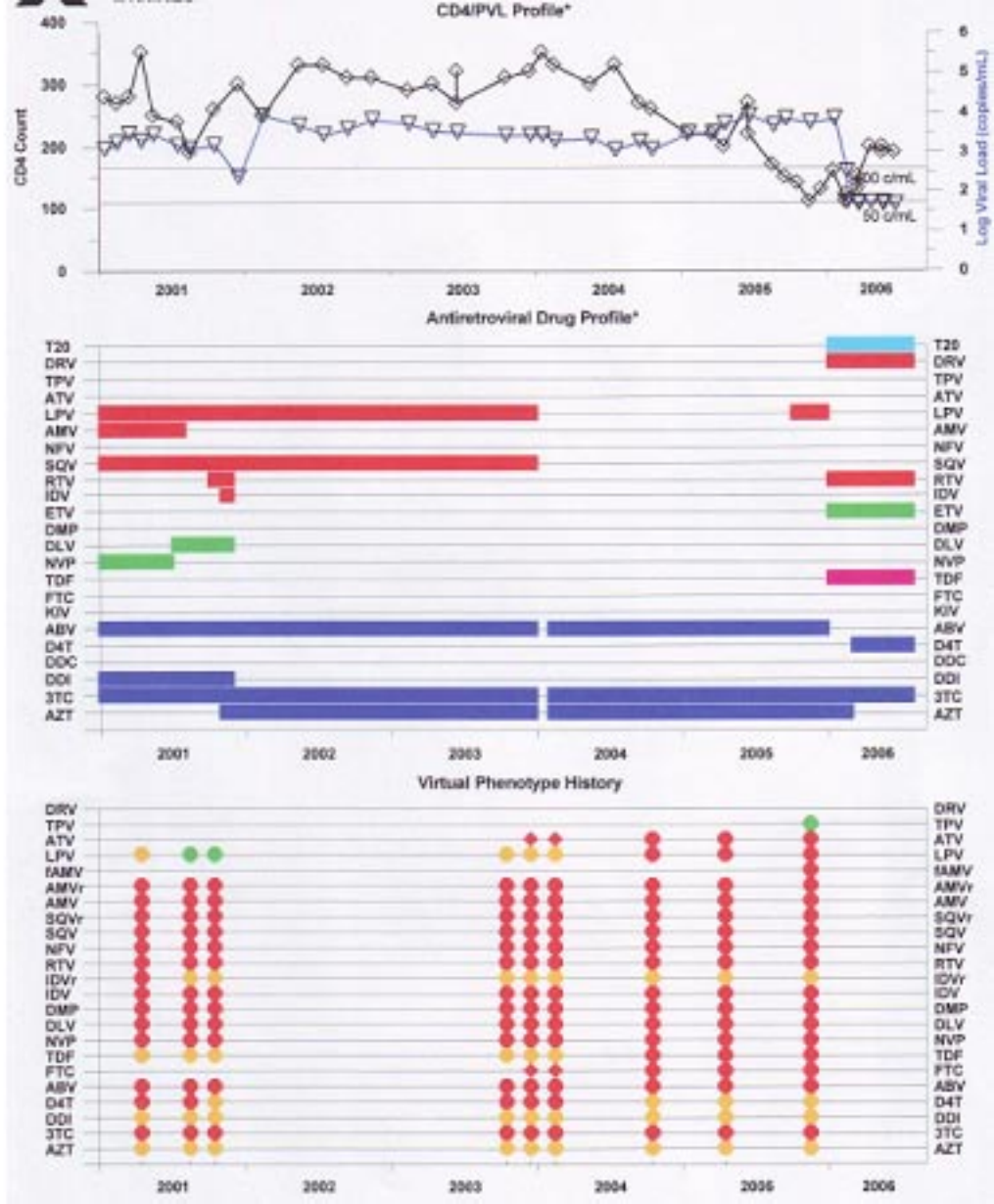

Antiretroviral Drug Profile*
T20
DRV
TPV
ATV
LPV
AMV
NFV
SQV
RTV
IDV
ETV
DMP
DLV
NVP
TDF
FTC
KIV
ABV
D4T
DDC
DDI
3TC
AZT
2001
2002
2003
2004
2005
2006


Virtual Phenotype History
DRV
TPV
ATV
LPV
fAMV
AMVr
AMV
SQVr
SQV
NFV
RTV
IDVr
IDV
DMP
DLV
NVP
TDF
FTC
ABV
D4T
DDI
3TC
AZT
2001
2002
2003
2004
2005
2006


patient 4
CD4/PVL Profile*
CD4 Count
Log Viral Load (copies/mL)
400 c/mL
50 c/mL
1995
1996
1997
1998
1999
2000
Antiretroviral Drug Profile*
T20
DRV
TPV
ATV
LPV
AMV
NFV
SQV
RTV
IDV
ETV
DMP
DLV
NVP
TDF
FTC
KIV
ABV
D4T
DDC
DDI
3TC
AZT
Virtual Phenotype History
DRV
TPV
ATV
LPV
fAMV
AMVr
AMV
SQVr
SQV
NFV
RTV
IDVr
IDV
DMP
DLV
NVP
TDF
FTC
ABV
D4T
DDI
3TC
AZT


CD4/PVL Profile*
CD4 Count
Log Viral Load (copies/mL)
2001
2002
2003
2004
2005
2006
Antiretroviral Drug Profile*
T20
DRV
TPV
ATV
LPV
AMV
NFV
SQV
RTV
IDV
ETV
DMP
DLV
NVP
TDF
FTC
KIV
ABV
D4T
DDC
DDI
3TC
AZT
Virtual Phenotype History
DRV
TPV
ATV
LPV
fAMV
AMVr
AMV
SQVr
SQV
NFV
RTV
IDVr
IDV
DMP
DLV
NVP
TDF
FTC
ABV
D4T
DDI
3TC
AZT


Patient 5
CD4/PVL Profile*
CD4 Count
Log Viral Load (copies/mL)
400 c/mL
50 c/mL
Antiretroviral Drug Profile*
T20
DRV
TPV
ATV
LPV
AMV
NFV
SQV
RTV
IDV
ETV
DMP
DLV
NVP
TDF
FTC
KIV
ABV
D4T
DDC
DDI
3TC
AZT
Virtual Phenotype History
1995
1996
1997
1998
1999
2000


CD4/PVL Profile*
CD4 Count
Log Viral Load (copies/mL)
400 c/mL
50 c/mL
Antiretroviral Drug Profile*
T20
DRV
TPV
ATV
LPV
AMV
NFV
SQV
RTV
IDV
ETV
DMP
DLV
NVP
TDF
FTC
KIV
ABV
D4T
DDC
DDI
3TC
AZT
Virtual Phenotype History
2001
2002
2003
2004
2005
2006