Genotyping and Drug Resistance in Clinical Practice

Case Studies
12/02

- 40 year old Hispanic male
- Dx with HIV 1995
- + Hx of PCP > 1x, HepC

Medication history:
- AZT, Crixivan, Videx EC, Sustiva, Zerit, Ziagen, and Kaletra
- Currently not on any medications
- CD4 = 210; VL = 5916
- HCV < 10 copies
- Resumed most recent regimen of Zerit, Ziagen, and Kaletra
8/03

- Genotype done
- PI Mutations: 10V, 20T, 36I, 54V, 71V, 74S, 77I
- Virtual phenotype revealed resistance to AZT, Viramune, Sustiva, Norvir, and Viracept. Kaletra was above normal susceptible range, but below clinical cut-off.
What Would You Do?

Meds changed to
Lexiva, Norvir, Emtriva and Viread
3/04

- CD4 = 128, VL = 655,000
- Repeated genotype
- PI Mutations: 10V, 20T, 36I, 54V, 71V, 74S, 77I, 82F
- Phenotype revealed resistance to AZT, Crixivan, Norvir, Viracept, Invirase, Kaletra, and Reyataz
Now What??

Medication regimen stayed the same
3/05

- **CD4** - 63, **VL** = 167,063

- Genotype done

- **NRTI and NNRTI Mutations**: M41l, M184V, L210W, T215Y

- **PI Mutations**: L10I, L33F, M36I, F53L, A71V, V82F
Phenotype showed resistance AZT, Videx, Hivid, Epivir, Zerit, Ziagen, Viread, Crixivan, Norvir, Viracept; “Possible” resistance to Agenerase, Kaletra, Reyataz, Inverase

Patient Taking: Truvada, Norvir & Tipranavir
3/06

- CD4 = 36, VL - 123,573
- Genotype done
- NRTI and NNRTI mutations: M41L, M184V, H208Y, T215Y
- PI Mutations: I13V, L33F, M36I, Q58E, A71V, T74S, V77I, V82F, L89M
- Phenotype revealed resistance AZT, Videx, Hivid, Epivir, Emtriva, Zerit, Ziagen, Viread, Crixivan, Norvir, Viractpt, Kaletra, Reyataz, Inverase, and “possible” resistance to Tipranavir.
What *NOW??*

Medications changed to Tipranavir, Norvir, and Truvada
7/06

CD4 = 16, VL = 43,036

NOW What?????
Changed medication regimen to Prezista, Norvir, Truvada
History

- 44 year old Black male, seen in clinic 1/97
- Dx HIV+ - 1994; contracted virus through men who have sex with men
- Hospitalized in 1997 with crypto and histo
- CD4 - 44, VL = 392,497
- Currently taking AZT and 3TC
- Dx with Crypto with titer 1:4096 and Histo with titer of 1:8192
- Hospitalized and treated for infections
- Stayed on AZT and 3TC until March 1998
- Highest CD4 = 130 and lowest VL = 4800
Case Study - CM

3/98

- **CD4 = 91, VL = 88,000**
- Started on Zerit, Combivir and Viramune
- Crypto titer now at 1:512
- Stayed on this regimen until 1/99
- Highest CD4 = 203, lowest VL = 55,236, and it continued to rise while on this regimen
## Case Study - CM

### March, 2003

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Resistance-associated Mutations Identified:

Case Study - CM
2/99

- Switched to 3TC, Zerit and Viracept.
  - Too many side effects and only stayed on this regimen for 3 months
- CD4 = 212, VL = 71,991

5/99

- Changed again to Ziagen, Sustiva, and Hivid, then changed to Ziagen, Sustiva and Videx the next month. Stayed on this regimen until December 2000.
- Lowest VL = 22,259, highest CD4 = 208
1/00

- Changed to Kaletra, Videx, Sustiva, and Ziagen
- CD4 = 193, VL = <400

10/01

- Diagnosed with large cell lymphoma (B cell); treatment by oncologist
- Stayed on regimen listed above, no changes in HIV medications
3/03

- Obtained genotype due to VL = >100,000 and CD4 = 260
- Virtual phenotype showed resistant to AZT, NNRTIs
- No PI mutations

What to Do?
We Did This...

- Regimen changed to Videx EC, Tenofovir, Ziagen, Kaletra

- Responded well with CD4 = 288, but VL still detectable at 82,152
CD4 dropped to 126
VL = 169,000
### Case Study - CM

**2/04 - Another genotype done**

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Mutations: 41L, 106L, 118L, 188L, 211K, 215Y

No PI mutations

Virtual phenotype revealed same resistance pattern – AZT and NNRTIs
Medication Changed to...

Reyataz
Norvir
Videx EC
Viread
Ziagen
7/04

- Diagnosed with Hepatitis B with VL = >10,000,000
- No change in HIV medications; no hyperlipidemia at this time
- Lowest VL on this regimen = 3,475, highest CD4 = 203
8/05

- **VL = 84,288**
- **Another genotype ordered**
- **Mutations: 41L, V118I, Y188L, T215Y**
- **PI Mutations: L10I, L63P, I84V**
- **Phenotype showed resistance to AZT, Zerit, Viread, and Viracept**
Changes??

No changes made
Patient admits to poor adherence due to too many medications and too many pills
Regimen changed to Kaletra and Epizcom; continues on this
Most recent CD4 = 146, VL = 23,577
Case Study - JR

- White 55 year old male
- Contracted virus by men who have sex with men
- HIV diagnosis made May 1989
- Positive history for syphilis and herpes simplex
- Started AZT monotherapy in 1990
- 10/95 – started on AZT and Hivid
- 2/96 – changed to AZT and 3TC
- 11/96 – changed to AZT, 3TC and Zerit
- 1/97 – started on Remune Study; continued on same other HIV medications
12/97
- Changed antiviral meds to Epivir, Zerit and Viramune
- CD4 = 324, VL = 16,685

5/99
- Closed Remune study but patient stayed on same HIV meds
- Never obtained undetectable VL on this combination
- VL range = 15,051 – 57,697; CD4 = 272 – 489

4/00
- VL increased so changed to Videx, Zerit, Agenerase and Norvir; hard for patient to tolerate
- CD4 range - 315 - 493; VL range = 1770 - 30,474
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Resistance-associated Mutations Identified:

PI Mutations: 32I, 33F, 47V, 90M
Virtual phenotype showed resistance to AZT, Viramune and Rescriptor
All protease inhibitors were listed as “resistance likely.”
Case Study - JR

What Changes Should Be Made??...

- Changes Made...

- Changed to Sustiva, Kaletra, and Videx EC

- CD4 = 273, VL = 43,333

- Within 2 months CD4 = 290, VL = 9,217
Case Study - J R

5/02

- Tenofovir substituted for Sustiva; stayed on Kaletra and Videx EC
- CD4 = 360, VL = 3,676
- Tolerating medications well
- Triglycerides 1060 and started on Tricor
- Stayed on this regimen until VL went up to 8,728, CD4 = 253

8/03

- Diagnosed with Type II Diabetes
12/03

- Genotype done


- PI Mutations: 32I, 46I, 47V, 82A

- Virtual phenotype revealed resistance to AZT, Viramune, Sustiva, Crixivan, Norvir, Viracept, Agenerase, Kaletra
12/03

- Medicines changed to Viread, Ziagen, Reyataz, boosted with Norvir
- CD4 jumped to 300
- VL dropped to 1510
- Stayed on regimen until VL went up to 240,000 and CD4 dropped to 286
9/04

- Another genotype done
- Mutations to NNRTIs and NRTIs, same as above with addition of 135T and 215Y
- PI mutations: 33M, 50L, 63P, 90M, 93L, plus all those listed on 12/03 genotype
- Virtual phenotype showed resistance to AZT, Viread, Viramune, Norvir, Lexiva, Reyataz
9/04

- Medications changed to Kaletra, Ziagen, Videx EC, Fuzeon

12/04

- Viread added to this regimen
  - Highest CD4 = 370
  - Lowest VL = 7,875
Started on Pfizer’s CCR5 research protocol

Inverase
Norvir
Ziagen
Tenofovir
Placebo? (never un-blinded to us)
What OB Would You Pick??

Inverase, Norvir, Viread and Ziagen was picked
Genotype done


PI Mutations: 32I, 46I, 47V, 82A

Virtual phenotype revealed resistance to AZT, Viramune, Sustiva, Crixivan, Norvir, Viracept, Agenerase, Kaletra

What to DO?
Case Study - JR

Early termination from research study due to VL never decreasing to undetectable

Genotype done after persistent high VL (13,677)

Mutations:  M41L, D67N, V118I, L210W, T215Y

PI Mutations:  V32I, M46I, I47V, L63P, G73C/S, L90M

Resistance to AZT, Videx, Hivid, Zerit, Ziagen, Vired, Crixivan, Norvir, Viracept, Agenerase, Inverase, and possible resistance to Kaletra and Aptivus

Medications not changed at this time; awaiting Tibotec’s TMC 125
6/06

- Started on Tibotec’s study TMC 125
- Optimized Best Therapy picked was Viread, Ziagen, and Inverase
- Inverase then dropped per protocol in late June
- Started TMC125 & TMC114
- Last VL = 428, CD4 = 532