HIV Resistance: The Basics

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Consultant - Sexual Health/HIV
Objectives

• Describe the principles of antiretroviral treatment in current usage
• Evaluate the use of resistance testing in clinical practice
• Explain the issues which can lead to the development of drug resistance
• Interpret resistance tests and develop new treatment strategies as a result
Resistance

- What is resistance?
- Why does it matter?
- What strategies do we use to reduce development of resistance?
HIV - replication and mutation

- Approx 5000 new virions per ml of blood per day (30 million+ virions)
- No checking mechanism
- Rapid mutation rate
- Viral escape mutants

A replicating virus is a mutating virus - lead to theory of HAART
What is a mutation?

- HIV enzymes (reverse transcriptase, protease...) are made up of proteins
- The subunits of proteins are amino acids
- Each amino acid is coded for by a triad of nucleosides
  - A, C, T, G
  - Hence AZT, 3TC, d4T etc
- 1 mutation = change in 1 nucleoside that may or may not change the amino acid
How does HIV mutate?

- A mutation is a change in the genetic code of an organism, which may change the way in which the organism looks and behaves.
- Organisms mutate under pressure:
  - drugs
  - (host immune system)
Species

- In the face of drug selection pressure, "minority" (mutated) species may become dominant.
- In the absence of drug pressure, HIV may revert to wild type as dominant species.
  - Resistance mutations not lost but "archived" and become rapidly dominant species again when drug reintroduced.
Discussion

- Why does treatment failure occur?
- Why does resistance occur?
Why do resistance and treatment failure occur?

• Commonly for 4 reasons:
  - A random occurrence
  - Drug interaction decreasing effectiveness
  - Malabsorption
  - Nonadherence to the treatment regimen
    • Patient choice
    • Side effects
    • Life events
HIV Drugs and Resistance

- Some drugs have a “low genetic barrier” to resistance
  - One “point” mutation may confer resistance to a particular drug or entire drug class
    - e.g. some nucleoside drugs (NRTIs) or non-nucleosides (NNRTIs)
- Some drugs have “high genetic barrier”
  - Step wise accumulation of resistance mutations need to develop resistance
    - e.g. boosted protease inhibitors (PIs)
Barriers to resistance

Single PI
- Small change per mutation
- BUT
- Low drug levels

NNRTIs
- High drug levels
- BUT
- Large change per mutation

Boosted PIs
- Small change per mutation
- AND
- High drug levels

Increasing number of mutations
- Low trough
- High trough
- $EC_{50}$

Increasing $EC_{50}$
Minimizing Resistance

- Use combination therapy (HAART)
- Use boosted PIs
- Maximise adherence (>95%)
  - Tolerable
  - Simple
  - Alarms/other adherence support
- Use drugs with long/matched half lives
- Don’t interrupt therapy
When is resistance testing recommended?

• At baseline (as near to infection as possible
  - Why?
• When drugs stop working
• When drugs don’t work well enough
• For pregnant women starting treatment
• Chronic infection, treatment naive
Types of resistance

- **Clinical resistance**
  - HIV multiplies in your body even though you are taking antiviral drugs

- **Genotypic resistance**
  - The genetic code of HIV has mutations that are linked to drug resistance

- **Phenotypic resistance**
  - HIV multiplies in a test tube when antiviral drugs are added
Genotypic testing

- Genetic code of sample virus compared to wild type
- Each codon defines an amino acid used to build a new virus
- Currently sequence genes coding for reverse transcriptase (RT) and protease enzymes
- Letters and numbers are used to describe mutations
3TC Resistance

- ATG to ATA
- ATG = methionine
- ATA = valine
- Hence **M184V**

Position of mutation
- Old amino acid
- New amino acid
- ie. 184th amino acid
- Along chain
Phenotypic testing

- Sample of HIV grown in the laboratory
- Dose of an antiretroviral drug is added
- Growth rate of HIV is then compared to wild type virus
- If sample grows more than normal it is resistant to the drug
- Results reported as “fold” resistance
- This is a direct measure of *in vitro* resistance
Virtual phenotype

- Perform genotype
- Compare results to phenotypes of viruses with similar pattern
- Less expensive
- Faster
- Dependent on database
Current Rx: ZDV/3TC, ATV
CD4+ 424, HIV RNA 14,000

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<thead>
<tr>
<th>DRUGS</th>
<th>FOLD CHANGE</th>
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| **NNRTI mutations: None** |
| Viramune®                | 1.7         | 5.5     | SUSCEPTIBLE         |                  |
| Sustiva®, Stocrin®       | 0.9         | 3.4     | SUSCEPTIBLE         |                  |

| **PI mutations: 50L** |
| Crixivan®               | 0.2         | 0.9     | 4.5                 | MAXIMAL RESPONSE |
| Crixivan ®; boosted      | 0.2         | 10.6    | 40.1                | MAXIMAL RESPONSE |
| Viracept®                | 0.3         | 1.3     | 7.3                 | MAXIMAL RESPONSE |
| Invirase®; boosted       | 0.2         | 7.1     | 26.5                | MAXIMAL RESPONSE |
| Agenerase®               | 0.7         | 0.9     | 2.0                 | MAXIMAL RESPONSE |
| Agenerase®; boosted      | 0.7         | 1.2     | 9.6                 | MAXIMAL RESPONSE |
| Lexiva®, Telzir®         | 0.7         | 2.2     |                     |                  |
| Kaletra®                 | 0.3         | 9.7     | 56.1                | MAXIMAL RESPONSE |
| Reyataz®                 | 4.6         | 2.4     |                     | RESISTANT Note 1 |
| Aptivus®; boosted        | 0.5         | 1.2     | 5.4                 | MAXIMAL RESPONSE |

Note 1: Note 2
When?

- First Treatment Failure
- Second Treatment Failure
- Subsequent Treatment Failure
- Primary Infection
- New diagnosis
- Pregnancy
Reverse Transcriptase Resistance

- NRTI
- NNRTI
NRTI Resistance

- Single mutation
- Accumulation of mutations
- Both pathways seen in some NRTI
- Often one pattern most prevalent in clinical practice
M184V

- Greatly reduces affinity of RT for 3TC (and FTC) - 1000-FOLD DECREASE
- M184V alone ABC resistance
- Minimal effect on ddl
- Increased susceptibility to TFV, AZT, d4T
- REDUCED FITNESS & TRANSMISSION
TAMs

TAMs = nucleoside associated mutations (NAMs) that are driven by thymidine analogues but impact most NRTIs

d4T or AZT

**Commoner**
- Higher level AZT & d4T resistance
- More NRTI X-resistance

**Combivir drives 41/215/184**
- 41L 210W 215Y*
- 67N 70R* 219Q/E

Common with dual therapy (AZT/ddI or AZT/ddC)

Common with AZT monotherapy
- Lower level AZT & d4T resistance
- Less NRTI X-resistance
AZT Mutations, TAMs, NAMs, etc...

- As they accumulate, resistance increases to NRTI’s
- Large numbers accumulate, broad cross-resistance to NRTI’s present
- Impact on 3TC much less than other NRTIs and clinical relevance uncertain
- Are greatly enhanced by the 69 insertion (6-bp insertion in RT gene)
Accumulation of NAMs and NRTI Resistance

ZDV
Accumulation of NAMs and NRTI Resistance
Accumulation of NAMs and NRTI Resistance

Number of NAMs

ZDV
D4T
ABC
ddI, TNF
3TC

Susceptible
Partial Resistance
Resistant

Resistance

Number of NAMs
NNRTI Resistance

- First generation NNRTIs have a LOW genetic barrier
- 1 mutation = cross-class resistance
- No benefit in continuing NNRTI in presence of resistance (ie no impact on viral fitness, unlike M184V)
Boosted PIs have a HIGH genetic barrier to resistance

- PI resistance is complex
- Most PIs require at least 3 mutations to have significant resistance
- Single mutations may confer high level resistance to:
  - nelfinavir and D30N
  - atazanavir and I50V
Current Rx: ZDV/3TC, ATV  
CD4+ 424, HIV RNA 14,000

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Case 1
Case 1

- Patient prescribed zidovudine, lamivudine and efavirenz 2002-2007
- Viral load rapidly undetectable when started treatment
- May 2007: viral load 3,560; CD4 450
Case 1

- What sort of drugs are:
  - AZT?
  - 3TC?
  - Efavirenz?
- Why type of failure is this?
- What should be done next?
- Why wasn’t resistance test performed in 2002?
- What would have been expected if a genotypic resistance test had been performed at baseline?
Case 1

- Why might patient have failed?
- What can doctors (and other professions) do to support patients and prevent failure?
- What can we not prevent?
Case 1

• Consider:
  - Pill burden
  - Number of doses per day
  - Lifestyle
  - Side effects
  - Effectiveness (potency and durability)
  - Preserving future drug options
  - Overall quality of life

• Offer adherence support
  - Specialist nurse support
  - Bleepers/alarms/pill boxes
Case 1

• Type of mutations expected:
  - Thymidine Associated Mutations (TAMs)
  - M184V  
    • Methionine replaced at position 184 by Valine  
    • Signifies 3TC (lamivudine) resistance  
  - K103N
Case 1

- **New drugs**
  - Given tenofovir, emtricitabine and lopinavir (boosted with low dose ritonavir)

- **Outcome**
  - Re-suppressed with undetectable viral load
Summary

• HIV mutates rapidly - especially under drug pressure
• We can tailor therapy according to resistance test result
  - usually genotype/virtual phenotype
• Triple therapy is a good way of minimizing risk of developing resistance
• We can help patient to reduce their risk in other ways
Acknowledgements

• Dr Laura Waters
• Deborah Flanagan
• Linda Connor

• Contact:
  - tristan.barber@chelwest.nhs.uk
Questions