ARV Resistance and why it still matters

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North Manchester General Hospital
Resistance...
Outline

• Theory
• Relevance
• How to manage without a resistance test

• Please interact....
What is resistance..
What happens..
How does it occur?

- A mutation of the *viral genetic material*
And in HIV....

- A mutation of the *viral genetic material* that results in the drug no longer being able to block viral replication
What happens...
What happens…
What happens…
What happens…
Why does it occur?

• High mutation rate
  • HIV is ‘poor’ at replicating itself accurately
    • Many mistakes occur
  • Therefore lots of potential to develop resistance
    • In untreated patient: >1 billion viral particles made/day, with at least one mutation per 1000 viruses → 1-10 million mutations/day.
    • In a patient with a moderate viral load, every single mutation is possible in the HIV genome, every single day...

• Low barrier to resistance
  • It doesn’t take many resistance mutations to knock out a drug
  • These mutations not ‘lethal’ or significantly hampering for the virus
Why does it occur?

- Viral replication in presence of detectable drug(s)
  - Inadequate combination of drugs
    - Not potent enough
Resistance will develop with suboptimal treatment
Inevitable consequence of pre-ART therapy
At a time when treatment was for survival
And mistakes were being made.
2NRTI therapy failed

Relative viral load suppression with mono- and combination therapies


HIV-1 RNA, log_{10} copies/ml

Week 0  Week 24  Week 52

Adapted from Facui, AS. Nat. Med 2003. 6: 839–843
Resistance testing became available…

Nucleotide sequencing
Consequences were significant.

<table>
<thead>
<tr>
<th>Year</th>
<th>Virological failure</th>
<th>Peripheral neuropathy</th>
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Log c/ml

- ZDV/DDI
- ZDV/3TC/RIT
- ZDV/3TC/SAQ/EFV
- ZDV/3TC/SAQ/NFV
- ZDV/3TC/SAQ
- ZDV/DDI/SAQ
- D4T/DDI/NFV
- D4T/3TC/IND
- NFV/NVP/DDI

RESISTANCE TEST
GT resistance test

Gag  Pro  Reverse Transcriptase

67N  41L  74V  74V  103N  103N  181C  190A  184V  210W  215Y
Why does it occur?

• Viral replication in presence of detectable drug(s)
  • Inadequate combination of drugs
    • Not potent enough
    • Pre-existing resistance
Case 1

• 33 year old heterosexual male
• Presents with oropharyngeal and oesophageal candidiasis
• CD4 142 cells/mL
• Viral load 37,567 copies/ml
• Started on Septrin
So what are you going to choose..

1. AZT and 3TC
2. TDF and FTC
3. TDF and 3TC
4. TDF and AZT
5. Other
So what are you going to choose..

1. NVP
2. EFV
3. ATAZ/r
4. LOP/r
5. Other
Case 1

- 33 year old heterosexual male
- Presents with oropharyngeal and oesophageal candidiasis
- CD4 142 cells/mL
- Viral load 37,567 copies/ml
- Started on Septrin

Options:
- ZDV or TDF
- 3TC
- EFV or NVP
Ask professor for help in getting/interpreting a resistance test...
He tells you he is busy...
And he is!
His football club need him
Man Utd 2 Chelsea 1
Response to therapy – case 1
Resistance-associated mutation identified on baseline test
So what happens when resistance is present? Selective Pressure of Therapy
Selective Pressure of Therapy

Incomplete suppression
- Inadequate potency
- Inadequate drug levels
- Inadequate adherence
- Pre-existing resistance

Viral load

Time

Drug-susceptible quasispecies
Drug-resistant quasispecies
Patient – CD4 falls to 230 from 501 – what would you do?

1. Carry on with NVP/AZT/3TC
2. Switch to EFV/TDF/FTC
3. Switch to ATAZ/r/TDF/FTC
4. Persuade Dr Nelson to organise another resistance test
5. Repeat CD4 and wait till fall further
6. Other
Response to therapy – case 1

![Graph showing Viral Load over Time](image)

- **K103N=NNRTIs**
- **K103N/Y181C=NNRTIs**
- **M184V=3TC**
What do these mean.....
Before 3TC

“M” is the “wild type” amino acid

“184” is the codon position

“M” is the wild type amino acid
After 3TC and resistance…

• How do we identify a resistance mutation?

“M” is the “wild type” amino acid

“184” is the codon position

“V” is the mutant amino acid
Response to therapy – case 1

Viral Load

Time

ATAZ/r/TDF/FTC

K103N/Y181C=NNRTIs

M184V=3TC
Emergence and evolution of resistance

- Increasing number of mutations
- Accumulation of mutations on the same viral genome
- Initially reduced viral fitness
- Compensatory changes restore fitness
Response to therapy – case 1

Viral Load

Time

ATAZ/r/TDF/FTC

TAMS=AZT


K103N/Y181C=NNRTIs

M184V=3TC
Response to therapy – case 1

Viral Load

Time


TAMS=AZT

K103N/Y181C=NNRTIs

M184V=3TC
The more mutations the more resistance…

Accumulation of TAMs:


Susceptible  Partial Resistance  Resistance

0  1  2  3  4  5  6

Number of TAMs present
The more TAMS the LESS abacavir effect..

Data on file, GlaxoSmithKline
The more TAMs the LESS tenofovir effect...

Studies 902 & 907
What if case 1 had been treated differently..

- 33 year old heterosexual male
- Presents with oropharyngeal and oesophageal candidiasis
- CD4 142 cells/mL
- Viral load 37,567 copies/ml
- Started on Septrin

ZDV or TDF

and

FTC

and

EFV or NVP
Case 1 with TDF/FTC…

- Viral Load
- Time

- K65R
- K103N/Y181C=NNRTI
- M184V=3TC
Susceptibility to NRTIs if K65R develops

PhenoSense Results for K65R alone (n=50)

For tenofovir, all viruses were below the 4.0-fold cut off for no response.

Miller et al (2003) 43rd ICAAC #H-904 and presentation
Susceptibility to NRTIs if K65R and M184V develop

PhenoSense Results for K65R + M184V (n=58)

% of viruses

AZT 100% 100% 90% 55% 42% 18% 3%
d4T 3TC
TDF
ABC
ddi
ddC

Below cut-off
Above cut-off

Miller et al (2003) 43rd ICAAC #H-904 and presentation
Case 1 with TDF/FTC...

Viral Load

Time

K65R

K103N/Y181C=NNRTI

M184V=3TC

ATAZ/r/AZT/3TC
Hence sequencing Options: PI AND

- 3TC/FTC

184V

Resistance to 3TC/FTC

Options?

- AZT (yes, ↑ activity)
- ABC, d4T, ddI (yes)
- TDF (yes, ↑ activity)
Hence sequencing Options: PI AND

- **AZT/d4T + 3TC/FTC**
  - Resistance to 3TC/FTC
  - Maybe Broader NRTI-class Resistance
  - Options?
  - **184V +/- TAMs**
  - TDF, ABC (if <3-4 TAMs) and depending on pattern

- **3TC/FTC**
  - Resistance to 3TC/FTC
  - Options?
  - **184V**
  - AZT (yes, ↑ activity)
  - ABC, d4T, ddl (yes)
  - TDF (yes, ↑ activity)
Hence sequencing Options: PI
AND….

- **TDF + 3TC/FTC**
  - K65R +184V
  - Resistance to TDF/3TC/FTC/ ddl and ABC
  - Options?
  - Boosted PI +
    - AZT (yes, ↑ activity)
    - TDF (maybe)

- **AZT/d4T + 3TC/FTC**
  - 184V +/- TAMs
  - Resistance to 3TC/FTC
    - Maybe Broader NRTI-class Resistance
  - Options?
  - TDF, ABC (only if <3-4 TAMs) and depending on pattern

- **3TC/FTC**
  - 184V
  - Resistance to 3TC/FTC
  - Options?
  - AZT (yes, ↑ activity)
    - ABC, d4T, ddl (yes)
    - TDF (yes, ↑ activity)
So hands up who will start with…

1. AZT and 3TC

2. TDF and either FTC or 3TC
So hands up who will start with…

1. EFV or NVP

2. ATAZANAVIR boosted by ritonavir or KALETRA
So choice of NRTI backbone is important when sequencing after resistance develops.

- **So if AZT/3TC used 1\textsuperscript{st} line**
- **Sequencing harder**: toxicity greater
- **Boosted PI monotherapy +/- 1-2 new agents**
So choice of NRTI backbone is important when sequencing after resistance develops.

- So if TDF/FTC used 1st line
  - Sequencing easier: toxicity less
  - Boosted PI with AZT +/- new agent
How common is drug resistance in Myanmar?

In Europe around 8%

N=23,000 from 75 studies in 20 countries

Frentz 2012
Why are we so bothered?

Once that patient has resistance to a drug, they will always have resistance to that drug.
Limitations of resistance testing

• Archived resistance
  • May be so low they cannot be detected.... But they are still there.... and will rapidly re-emerge under drug pressure
  • So you need to look at all previous resistance test results too
  • And maybe make a guess on what might be there.....
Archived NNRTI Resistance Markedly Reduces Treatment Response

Why does it occur?

- Viral replication in presence of detectable drug(s)
  - Inadequate combination of drugs
    - Not potent enough
    - Pre-existing resistance
  - Low levels
    - Compliance
    - Absorption/metabolism
    - Interactions
Poor compliance often results from intolerance/toxicity to ARVs
...or too many tablets
The advent of STRs

1996
30+ Pills a Day

2006
the first STR
Drug-drug Interactions

with or without food?

take together?

What about my other drugs?
Drugs for HIV or non-HIV related issues
Age and illnesses of getting old
Why does it occur?

- Viral replication in presence of detectable drug(s)
  - Inadequate combination of drugs
    - Not potent enough
    - Pre-existing resistance
    - Low levels
      - Compliance
      - Absorption/metabolism
      - Interactions
  - Treatment interruption
    - Patient
    - Healthcare system/professional
Resistance - simple

- A single mutation may wipe out activity.....
  - M184V - lamivudine or emtricitabine
  - K103N – efavirenz or nevirapine
Response to therapy – case 1

Viral Load

Time

K103N/Y181C=NNRTIs
M184V=3TC

400
50
In these situations class cross-resistance is usual

Single point mutations in the NNRTI binding pocket (e.g. K103N) lead to VF

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<th>Nevirapine</th>
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<td>C I L S A H</td>
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</table>

- As EFV and NVP share similar binding sites, mutations often lead to cross resistance to the other agent\(^2\)
- NNRTI resistance accumulation can compromise the efficacy of second-generation NNRTIs\(^3\)

Resistance not always so simple - NRTIs

All or nothing;

• Nevirapine and 3TC

The more mutations the more resistance:

• AZT

Resistance: not always so simple – 2nd generation NNRTIs (etravirine).

The number of mutations required to substantially decrease the efficacy of an antiviral drug

First-generation NNRTI

One mutation correlates with reduced virological response

Next-generation NNRTI (ETR)

The presence of multiple NNRTI mutations at baseline is usually required to confer a reduced response

Increasing number of mutations at baseline

Resistant to resistance: boosted PI’s

Viral failures
No baseline resistance N= 76 63 54 48

Using resistance to your advantage

• Hypersusceptibility
  • A resistance to one ARV makes the virus even more susceptible to another.....

• Viral fitness
  • The resistance required to resist a drug interferes with other vital processes in the virus and it is not so ‘replication-competent’....
M184V Increases Susceptibility to d4T, ZDV, and TDF
Change in NRTI Susceptibility and Number of TAMs, ± M184V

Doing it without access to a resistance test

The principle aim of the RDI is to provide a treatment decision-making aid free of charge over the Internet such that physicians entering the genotype and other baseline data for a patient will receive a report containing predictions of virological responses to a range of alternative antiretroviral combinations.
No resistance test…

After failing NNRTI/2NRTIs

• Baseline viral load
• Treatment history
• Baseline CD4 count
• Time to follow-up

<table>
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<th>Resistance</th>
<th>Time</th>
<th>Accuracy (%)</th>
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<tr>
<td>Genotype</td>
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<tr>
<td>No genotype</td>
<td>24w</td>
<td>64</td>
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RDI models: Predicting treatment response without a genotype versus genotyping with interpretation

ANRS, Agence Nationale de Recherches sur le SIDA; RDI, Response Database Initiative; TCE, treatment change episode

Revell AD et al. J Antimicrob Chemother 2013; [Epub ahead of print]
Managing without a resistance test

• Predict virological response to salvage ART accurately (approximately 80%) without the use of a genotype\(^1\)

• Significantly more accurate predictors of response than genotyping with rules-based interpretation \((P<0.001)\)\(^1\)

• As accurate for cases from southern Africa as for other regions\(^1\)

• Identify alternative regimens that are predicted to be effective for the majority of cases where the new regimen in the clinic failed\(^1,2\)

• Identified cost-saving alternatives for most cases of failure in a study of second-line therapy in India\(^2\)

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Preventing resistance

1. Choose a good combination
   • (= 3 active drugs)
2. Ensure good levels
   • Compliance
   • Absorption
   • Interactions
3. Monitor for viral control & react quickly to failure
4. Build a robust new regimen on virological failure
   • Known resistance now
   • All previous resistance
   • Guesstimate other resistance
5. Go back to 2....
Case 1

• 49yr old woman diagnosed 1995 (then 32)
  • PCP, CD4 50
  • Weight loss, OPC
• HBV/HCV –ve
• No significant co-morbidity
• CVD risk factors:
  • Non-smoker, No FHx, BMI 19
  • BP 120-5/80
  • TC 4.2, HDL-C 0.9
• Started ZDV/DDI
Genotypic resistance test
Case 1

<table>
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<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Mutations</th>
<th>Interpretation</th>
<th>Additional Information</th>
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<tbody>
<tr>
<td>Retrovir®</td>
<td>Zidovudine</td>
<td>✓</td>
<td>Evidence of Resistance</td>
<td>AZT resistance may be reversed</td>
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<td>Epivir®</td>
<td>Lamivudine</td>
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<td>184: Characteristic mutation</td>
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<td>Videx®</td>
<td>Didanosine</td>
<td>✓</td>
<td>Evidence of Resistance</td>
<td>103: Characteristic mutation</td>
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<td>HiVas®</td>
<td>Zalcitabine</td>
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<td>108I: Characteristic mutation</td>
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<td>Abacavir</td>
<td>✓</td>
<td>Evidence of Resistance</td>
<td>156N: Characteristic mutation</td>
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<td>Viramune®</td>
<td>Nevirapine</td>
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<td>B решил®</td>
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Viral loads

- ZDV/DDI/SAQ
- D4T/DDI/NFV
- D4T/3TC/IND
- ZDV/3TC/SQA/NFV
- ZDV/3TC/SQA/EFV
- D4T30/DDI/HU/LOP/r/ABC
- ZDV/3TC/RIT
- NFV/NVP/DDI
- D4T30/DDI/LOP/r/ABC
- ZDV/DDI
- LOP/r/ABC/TDF
- ZDV/3TC/SAQ
- Neutropenia
- Virological failure
- Peripheral neuropathy

Time (years): 1996 to 2011
Most likely cause?
Taking only 25% tablets

• Depressed
  • Life in a mess

• Diarrhoea
  • I’ve had enough!!!

• Aware of new agents
  • Wants to take fewer tablets

• Fed up with current combination
  • CD4 224, viral load 60,000
  • Tropism R5
Going back to resistance test
So what’s available?

• Definitely active:
  • RAL
  • T-20
  • MRV
  • BENCHMMRK
  • TORO
  • MOTIVATE
Where do these act - life cycle of HIV
So what’s available?

• Reduced activity:
Increasing predictive accuracy to DRV score by weighting mutations

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Add mutations up for fold-change

Example: ≈ 5–7 fold-change = Intermediate activity

Increasing predictive accuracy to TPV score by weighting mutations

Add mutations up for fold-change

Example: = ~ 4 fold-change = Intermediate activity

De Meyer S, et al. IHDRW 2006;Abstr. 73.
### HIVdb: Genotypic Resistance Interpretation Algorithm

**SeqID:** Feb 2011

| PI Major Resistance Mutations: | V32I, M46I, I84V, L90M |
| PI Minor Resistance Mutations: | L10I, ATVV |
| Other Mutations:               | K20R, M36I |

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<th>Drug Resistance Interpretation</th>
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<td>atazanavir/r (ATV/r)</td>
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<td>fosamprenavir/r (FPV/r)</td>
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<td>tipranavir/r (TPV/r)</td>
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Increasing predictive accuracy to ETR score by weighting mutations

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Adapted from Vingerhoets J et al. Oral Presentation IHDRW 2008
### HIVdb: Genotypic Resistance Interpretation Algorithm

#### Drug Resistance Interpretation:

<table>
<thead>
<tr>
<th>NRTI Resistance Mutations</th>
<th>NNRTI Resistance Mutations</th>
<th>Other Mutations</th>
</tr>
</thead>
</table>

**Nucleoside RTI**

<table>
<thead>
<tr>
<th>Nucleoside</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine (3TC)</td>
<td>Potential low-level resistance</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>Stavudine (D4T)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>Didanosine (Ddi)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>Potential low-level resistance</td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>Intermediate resistance</td>
</tr>
</tbody>
</table>

**Non-Nucleoside RTI**

<table>
<thead>
<tr>
<th>Non-Nucleoside</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine (DLV)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>Etravirine (ETR)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>High-level resistance</td>
</tr>
</tbody>
</table>

SeqID: Date Feb 2011
So what’s available?

• Definitely active:
  • RAL, MRV, T-20

• Reduced activity:
  • DAR/r & TIP/r

• Some benefit or not?
  • NRTI’s, 3TC/FTC
Partial treatment interruption studies
Maintain NRTIs

Week 2 viral load increase after drugs in one class interrupted; other ARVs maintained

Deeks et al. 12th CROI 2005; Poster 680.
OPTIONS: NRTIs vs No NRTIs in Regimens for Highly ART-Experienced

- Randomized, noninferiority, multicenter trial (ACTG A5241)
  - Primary endpoint: regimen failure (VF or divergence from NRTI assignment, whichever occurred first)

Treatment-experienced pts failing on PI-based regimen with NRTI, NNRTI experience and/or resistance (N = 360)

- Stratified by choice of MVC-containing regimen and previous enfuvirtide or integrase inhibitor experience

Yr 1
Primary Endpoint

NRTI-Omitting
Individualized Optimized Regimen*
(n = 179)

Yr 2
Secondary Endpoint

NRTI-Including
Individualized Optimized Regimen*
(n = 181)

*20 potential 3- to 4-drug combinations including DRV/RTV, ENF, ETR, MVC, RAL, TPV/RTV. Individualized selection of regimens with PSS > 2.

OPTIONS: Pt-Specific Regimen Selected Then Randomized to ± NRTI

Chosen Regimen and NRTI Combinations

- Add NRTIs
  - TDF + FTC (3TC)
  - ZDV + TDF + FTC (3TC)
  - Other

- Omit NRTIs
  - 6%
  - 12%
  - 82%
  - 6%
  - 56%
  - 7%
  - 8%
  - 14%
  - 9%
  - 14%

Regimen
- RAL + DRV/RTV + ETR + MVC
- RAL + DRV/RTV + ETR + ENF
- RAL + DRV/RTV + MVC
- RAL + DRV/RTV + ETR
- RAL + DRV/RTV
- RAL + ETR + MVC
- RAL + DRV/RTV + ETR + MVC

OPTIONS: Omitting NRTIs Non-inferior to Adding NRTIs to Optimized Regimen

Primary Efficacy Outcome Comparisons

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Omit NRTIs (n = 179)</th>
<th>Add NRTIs (n = 181)</th>
<th>Omitting NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen failure</td>
<td>53 (30)</td>
<td>48 (26)</td>
<td>3.2 (-6.1 to 12.5)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>44 (25)</td>
<td>45 (25)</td>
<td>-0.4 (-9.4 to 8.7)</td>
</tr>
<tr>
<td>Stop NRTI assignment</td>
<td>19 (8)</td>
<td>10 (6)</td>
<td>3.6 (-1.7 to 9.0)</td>
</tr>
</tbody>
</table>

- Similar virologic suppression (HIV-1 RNA < 50 c/mL) in each arm (~ 65%)
- Similar CD4+ cell count increases in each arm (90-106 cells/mm³)
- No significant difference in any safety outcome when globally evaluating symptoms and laboratory abnormalities
  - However, mortality significantly higher in NRTI-added arm (P < .001)
  - 6 deaths in NRTI arm, 2 possibly due to ART drug

Partial treatment interruption: 3TC monotherapy benefits over STI

- **Prospective, randomized study** (n = 29 in both groups);
- Open label; on 3TC-containing regimen

- **Mean change** in CD4 count (cells/mm³)
  - 0%
  - 4%
  - 8%
  - 12%
  - 16%
  - 20%
  - 24%
  - 28%
  - 32%
  - 36%
  - 40%
  - 44%
  - 48%
  - 52%
  - 56%
  - 60%

- **Mean change** in HIV RNA (log₁₀ copies/mL)
  - p = 0.122

- HIV RNA > 1000 copies/mL
- CD4 > 500 cells/mm³
- Have M184V mutation

*Castagna et al. AIDS 2006 20(6):795-803*
What are you going to do?

She is currently on LOP/r/TDF/ABC

She wants to change her ART
## Choices?

<table>
<thead>
<tr>
<th>Fully active</th>
<th>Partially active</th>
<th>Some benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL</td>
<td>DAR/r</td>
<td></td>
</tr>
<tr>
<td>MRV</td>
<td>TIP/r</td>
<td>3/FTC</td>
</tr>
<tr>
<td>T-20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Data for >1 active drug + OBR in triple-class failure

Overall Efficacy Data

Efficacy by ARTs in OBT

Enfuvirtide  Darunavir

+ +

+ -

- +

- -

447 230

44 23 42 24 80 47 191 90

43 43 63 55 74 74 87 87

79 98 90 90

New drug = 1  = 2  =3

+ : First Use in OBT
- : No Use in OBT

* Virological failures carried forward

Cooper D et al., 14th CROI, Los Angeles 2007, #105aLB, Steigbigel R et al., 14th CROI, Los Angeles 2007, #105bLB
Patient

• Received adherence support

• DAR/r
• RAL/MAR
• TDF/FTC

• Has been undetectable since
Summary

• Antiretroviral resistance can seem confusing and complex
• A lot of it is actually quite simple
• People might bluff you with lots of numbers
  • You don’t really need to know them as there are programmes to help

• It is important to understand:
  • How resistance develops
  • That it is archived forever
  • That you may not detect resistance even if it is there (look at previous regimens and if failed)
If time for discussion
Case 1

• 49 yr old MSM
• HIV diagnosed 2006
  • CD4 = 95

•Commenced on Nevirapine and Truvada (Tenofovir/FTC)
  • Poor compliance  →  virologic failure

• Resistance testing:
  • K103N  –  NNRTI resistance
  • M184V  –  3TC/FTC resistance
Case 1 cont.

- Intensive counselling
  - Compliance issues addressed

-Commenced on Atazanavir/ritonavir & Truvada
  - Remains undetectable since, good CD4

- Wants a single tablet regimen....
  - We have:
    - Atripla = Efavirenz, Tenofovir, FTC
    - Eviplera = Rilpivirine, Tenofovir, FTC
    - QUAD in the future (Elvitegravir, Cobicistat, Tenofovir, FTC)

- Can he have any of these?
- What are the issues?
Case 2

• 37 year old woman
• HIV positive, CD4 157
  • Referred from elsewhere
  • Diagnosed 6 weeks before, all other tests and baselines ‘normal’

• Commenced on Atripla (Efavirenz, Tenofovir, FTC)

• Viral load decreased from 780,000 to 12,000 over 6 weeks but then rebounded...

• Why?
Case 2 cont.

• Possibilities:
  • Poor compliance
  • Poor absorption / PK interactions
  • Virus was resistant already....
  • Something else

• In fact baseline resistance test was abnormal
  • Primary K103N resistance...
    • Which knocked out Efavirenz
Case 3

• 47 yr MSM
• HIV positive since 1991
  • Regimens:
    • AZT 1992 for two years
    • D4T, 3TC and Indinavir Oct ’97 to Nov ’97
    • D4T, 3TC and Saquinavir Nov ’97 to March ’98
    • DDI, Nevirapine, AZT and Indinavir Oct ’98 to Feb ’99
    • DDI, Nevirapine, AZT, Nelfinavir and Ritonavir Feb ’99 to Apr ’99
    • DDI, Nevirapine, AZT and Nelfinavir Apr ’99 to Dec 2000
    • AZT, 3TC and Abacavir Feb ’01 to Aug ’02
    • Lopinavir/ritonavir, 3TC and Abacavir till 1 month ago, when stopped treatment

• Resistance test now wild-type
• What more do I need to know and what can I use?
Case 3 cont.

• Any previous resistance tests?
  • No

• Why did they switch previously - ?intolerance ? AEs
  • Generally from failure

• Therefore have to guesstimate resistance...
  • Multiple NRTI resistance
  • First-line NNRTI resistance
  • (Possible some PI resistance)
Case 4

- 27 yr woman
  - HIV positive 2009

- Commenced Efavirenz, AZT, 3TC
  - Complied and was undetectable for 2 years

- Then lost job, got fed up etc. and stopped therapy
  - Now off therapy for 1 year
  - Resistance test wild-type

- Do I have to be wary of any resistance?

- May have had a ‘functional monotherapy’ for a while...
Data was limited
And ART was still a pipedream

Relative viral load suppression with mono- and combination therapies

- Dual class combination therapy: nucleoside + protease inhibitor (1996)

Adapted from Facui, AS. Nat. Med 2003. 6: 839–843
You request a resistance test - how does it work?
And how do you interpret?

• **Genotypic Testing**: Prediction of phenotype based on sequence
Limitations of resistance testing

- Population sequencing
  - Standard resistance testing will only detect mutations that are in >20% of the circulating virus
Kaplan-Meier curves for the proportion of patients without virologic failure

Proportion without virologic failure

Days

Minority variants not detected

Minority variants detected

$p < 0.001$
Drugs still main reason to switch…

- 452 switches due to toxicity/perceived toxicity

Boyle A et al. HIV11 Glasgow 2012, UK - abstract O312
Adherence benefits of STR/FDC

Meta-analysis of 9 clinical trials in 4 therapeutic areas (TB, HTN, HIV, DM)
11,925 FDC patients and 8317 non-FDC patients

Effect of FDCs versus non-FDC on risk of non-adherence

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dezii CM et al, 2000</td>
<td>0.74 (0.65, 0.84)</td>
<td>17.5</td>
</tr>
<tr>
<td>Dezii CM et al, 2000</td>
<td>0.71 (0.62, 0.80)</td>
<td>17.6</td>
</tr>
<tr>
<td>Eron JJ et al, 2000</td>
<td>0.78 (0.55, 1.11)</td>
<td>4.3</td>
</tr>
<tr>
<td>Geiter LJ et al, 1987</td>
<td>0.88 (0.55, 1.42)</td>
<td>2.5</td>
</tr>
<tr>
<td>Melikian C et al, 2002</td>
<td>0.50 (0.35, 0.71)</td>
<td>4.2</td>
</tr>
<tr>
<td>Melikian C et al, 2002</td>
<td>0.47 (0.22, 1.01)</td>
<td>1.0</td>
</tr>
<tr>
<td>NDC Dataset, 2003</td>
<td>0.81 (0.77, 0.86)</td>
<td>29.0</td>
</tr>
<tr>
<td>Su WJ et al, 2002</td>
<td>0.89 (0.51, 1.57)</td>
<td>1.8</td>
</tr>
<tr>
<td>Taylor AA et al, 2003</td>
<td>0.74 (0.67, 0.81)</td>
<td>22.1</td>
</tr>
</tbody>
</table>

Overall | 0.74 (0.69, 0.80) | 100.0

FDC regimens reduce risk of non-adherence by ~25% (compared to dosing with individual pills)
Drugs associated with ageing

Projected Proportion of those 50+ Years of Age* Living With HIV in United States 2001-2017

US VA in 2003

As of 2008:
• San Francisco
• NY City

17% 19% 21% 22% 25% 27% 27% 29% 33% 35% 37% 39% 41% 44% 45% 47% 50%


HIV lifecycle and where ARVs act....

- **Fusion**
- **NRTIs/NNRTIs**
- **Integration**
- **R5 binding**
- **PIs**

- Genomic RNA
- Double stranded DNA
- Proviral RNA
- Viral proteins
- Viral mRNA
- Genomic RNA
- Cell membrane
- Cell nucleus
Resistance: not always so simple – NRTIs. Dichotomous Pathways to Resistance

TAMs emerge sequentially with ZDV- and d4T-containing regimens after M184V


Higher-level ZDV resistance
More NRTI cross-resistance
Less effect of M184V

Lower-level ZDV resistance
Less NRTI cross-resistance
Greater effect of M184V
**Resistance not always so simple – NNRTIs**

**Weighting mutation system helps predict response**

<table>
<thead>
<tr>
<th>Relative weight* for individual ETR</th>
<th>Total weighted genotypic score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAMs</strong></td>
<td>0–2</td>
</tr>
<tr>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>V901</td>
<td>V106I</td>
</tr>
<tr>
<td>A98G</td>
<td>E138A</td>
</tr>
<tr>
<td>K101E</td>
<td>V179F</td>
</tr>
<tr>
<td>K101H</td>
<td>G190S</td>
</tr>
<tr>
<td>V179D</td>
<td></td>
</tr>
<tr>
<td>V179T</td>
<td></td>
</tr>
<tr>
<td>G190A</td>
<td></td>
</tr>
</tbody>
</table>

Example: K101H + G190A = Weighted score of 2 = Highest response

*When the genotype report shows a mixture of two or more different substitutions at the same position, only the highest of the individual weight factors for these substitutions is counted when calculating the weighted genotypic score.*

Resistant to resistance: boosted PI’s

<table>
<thead>
<tr>
<th>Subjects Analyzed for Resistance, n (%)</th>
<th>Quad (n=353)</th>
<th>ATV/r + FTC/TDF (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with Resistance to ARV Regimen, n (%)</td>
<td>12 (3)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Any Primary Integrase-R, n</td>
<td>5 (1)</td>
<td>0</td>
</tr>
<tr>
<td>E92Q</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>T66I</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Q148R</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>N155H</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Any Primary PI-R, n</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Any Primary NRTI-R, n</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>M184V/I</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>K65R</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

DeJesus E, et al., CROI 2012; Seattle. Poster 627.
Boosted PIs protect against emergence of drug resistance after 1st line ART

- Combination ARV therapy started Jan 1999 – Dec 2005 (n=1323)
  - Boosted PI (n=518)
  - NNRTI (n=805)
- Viral failure (defined as HIV RNA >500 c/mL after more than 180 days of treatment) by third agent:
  - Boosted PI (n=4.6%); NNRTI (n=5.6%)
  - No difference by regimen but more resistance emerged with NNRTI-based regimens

Swiss Cohort Study

Mutations at time of virologic failure*

*Mann-Whitney p=0.005
But also differences…

Resistance not always so simple – PIs

DRV Weighting mutation system helps predict response

<table>
<thead>
<tr>
<th>Estimated increase in FC</th>
<th>&lt;2</th>
<th>2 to 3</th>
<th>3 to 4</th>
<th>&gt;4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V11I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I54L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G73S</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>L89V</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V32I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I54M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L76V</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I84V</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Add mutations up for fold-change
Example: ~ 5–7 fold-change = **Intermediate activity**

De Meyer S, *et al*. IHDRW 2006; Abstr. 73.
And for tipranavir....

<table>
<thead>
<tr>
<th></th>
<th>- 1</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L24I</td>
<td>L10V/I</td>
<td>V11L</td>
<td>I47V</td>
</tr>
<tr>
<td></td>
<td>D30N</td>
<td>I13V</td>
<td>V32I</td>
<td>I54A</td>
</tr>
<tr>
<td></td>
<td>I50L/V</td>
<td>K20R</td>
<td>A71L</td>
<td>V82T</td>
</tr>
<tr>
<td></td>
<td>154L</td>
<td>I54A</td>
<td>G73T</td>
<td>I84V</td>
</tr>
<tr>
<td></td>
<td>L76V</td>
<td>V82I</td>
<td>L89V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V82I</td>
<td>L90M</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Add mutations up for fold-change

Example: = ~ 4 fold-change = Intermediate activity

De Meyer S, et al. IHDRW 2006;Abstr. 73.
Single mutation leading to resistance – all or nothing

First-generation NNRTI

One mutation correlates with reduced virological response

Increasing number of mutations at baseline

Thank you

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