HIV DRUG RESISTANCE

THE ULTIMATE EVASION

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Why is HIV Drug Resistance important?

Pretreatment NNRTI Resistance >10%

- HIV Resistance
- AIDS deaths: 16% 890,000
- New infections: 9% 450,000
- ART costs: 8% $6.5 billion

Impacting UNAIDS 90-90-90 Target by 2020 and Elimination of the AIDS pandemic by 2030

Phillips AN et al, J Infect Dis 2017
Discussion Points

• What is HIV Drug Resistance

• What is study data telling us about the current state of adult HIV Drug Resistance
  • Pretreatment HIV drug resistance patterns
  • HIV drug resistance in first-line failures
  • HIV drug resistance in second-line failures
  • Third-line outcomes
**HIV Lifecycle and Drug Targets**

**Fusion and entry inhibitors**
e.g. Maraviroc

**Monoclonal antibody**

**Protease inhibitors**
e.g. LPV/r, ATV/r, DRV/r

**Capsid inhibitor**

**Maturation inhibitor**

**NRTI**
e.g. AZT, 3TC, FTC, ABC, TDF

**NNRTI**
e.g. NVP, EFV

**Integrase inhibitors**
e.g. RAL, DTG

https://www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle
How does HIV Drug Resistance occur?

• High HIV replication rate

• HIV Reverse Transcriptase lacks proof reading ability

• These two factors can contribute to the development of drug resistance mutations at or around the gene targeted by the ARV

https://www.hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all#hiv-drug-resistance-assays
Illustration by David Spach, MD and David Ehlert, Cognition Studio
Possible Causes of Therapy Failure

- Toxicity
- Drug-drug interactions
- Poor adherence
- Insufficient ARV potency
- Insufficient ARV drug levels

HIV DRUG RESISTANCE
HIV Viral Dynamics and Resistance

Sensitive virus (wildtype)

Resistant virus (mutant)

Drug interruption

Start treatment

“Bottleneck”

- Sensitive virus (wildtype)
- Resistant virus (mutant)
How to test for HIV Drug Resistance

Genotypic Assay
Determined which mutations are present compared to a reference HIV sequence using an algorithm e.g. Stanford HIVDR database, and scores drug susceptibility.

Phenotypic Assay
Test what effect the mutation will have on the virus in the laboratory.

Genotypic Assay
- Population Based (Sanger) Assays
  (>20-30% of a population)
  - Gold Standard
- Minority Variant (NGS) Assays
  (>1% of a population)
  - Research use
This is how you name a mutation

**N13F**
- **Wildtype Letter**: N
- **Mutant Letter**: F
- **Letter Number**: 13

**K103N**
- **Wildtype Amino Acid (consensus)**: K
- **Mutant Amino Acid**: N
- **RT Codon**
  - PR 1-99 Amino Acids
  - RT 1-540 Amino Acids
  - INT 1-288 Amino Acids

**K103KN**
Types of HIV Drug Resistance

**Acquired HIV Drug Resistance**
HIV drug resistance mutations emerging while taking ARVs

- PMTCT
- PrEP
- PEP
- ART Regimes

**Transmitted HIV Drug Resistance**
HIV drug resistance mutations detected in ARV naïve individuals

**Pretreatment HIV Drug Resistance**
HIV drug resistance mutations detected in individuals before starting ART

- Previous exposure to ARV
- ARV Naïve
PRETREATMENT
HIV DRUG RESISTANCE
Prevalence of Pretreatment HIV Drug Resistance

Meta-analysis of adult pretreatment data

Estimated annual incremental increase

LEVELS OF RESISTANCE LINKED
NNRTI NEAR OR ABOVE
CRITICAL 10%

7.2% 9.4% 10.1% 11%

2016

Gupta RK et al, Lancet Infect Dis 2018
Prevalence of Pretreatment HIV Drug Resistance

NNRTI – EFV & NVP

WHO Survey data 2014 - 2016

Prevalence of Pretreatment HIV Drug Resistance

HIVDR linked to treatment

HIVDR Mutation Frequency

Low level pretreatment HIV drug resistance to NRTIs and PIs

Prevalence of Pretreatment HIV Drug Resistance

Transmitted Drug Resistance two times higher in women than in men

12.2% 6.3%

HIV DRUG RESISTANCE IN FIRST-LINE TREATMENT FAILURE
Acquired Drug Resistance after First-Line failure

- Most common first line regimen

- NNRTI: EFV or NVP
- 1st NRTI: 3TC or FTC
- 2nd NRTI: TDF or AZT

Mean Pooled estimates of HIVDR in individuals failing NNRTI-based 1st line

73
350

Systematic literature review of studies published 2014 to 2017

Overview of First-line failure mutations

- M184V
- EFV/NVP
- 3TC/FTC
- Pattern differs
- TDF/d4T
- K65R
- TAMs (≥3)
- AZT/d4T

Time on a Failing Regimen
First-line failure mutations

- Y181C is selected by NVP more than EFV
- V106M is selected more by EFV (34%) than NVP (2%)
- Wider range mutations selected for by EFV rather than NVP

- TAMs associated with first line regimen containing d4T (blue) or AZT (red).
- The AZT containing regimen had a higher frequency of TAMs compared to d4T regimen.

Wallis et al., JAIDs 2010
• Subtype C development of V106M instead of V106A (Brenner et al, 2003; Morris et al, 2003)

• K103N at greater frequency and higher levels in women with subtype C and D rather than A (Flys et al, JAIDS 2006)

• Culture studies have revealed K65R occurs faster in HIV-1 subtype C (Brenner, AIDS 2006)

• 11% of patients infected with CRF02_AG majority failing a TNF based regimen in Nigeria developed K65R (Hawkins et al, JAIDS 2009)
Over four timepoints (T0=2008; T1=2011; T2=2013; T3=2015)

Level NRTI and NNRTI and dual resistance increased over time

Mulu et al., PlosOne 2017
HIV DRUG RESISTANCE IN SECOND-LINE TREATMENT FAILURE
What does the high frequency of NRTI resistance in First-line mean for Second-line options?

Studies performed to answer the following questions:

• Is LPV/r monotherapy an option?
• Should we use two new classes of drugs? Boosted PI with INSTI
• RAL versus DTG?
• INSTI versus boosted PI?
SECOND-LINE study outcome

- 97% of subjects had ≥1 NRTI or NNRTI mutation at start of the study

More AE in the PI arm compared to the RAL arm.

Non-inferiority of the RAL and LPV/r arm compared to control arm (LPV/r and 2/3 NRTIs)

At Week 48, difference 1.8%, 95% CI -4.7 to 8.3
Outcome of PI-based treatment by NRTI susceptibility

EARNEST study showed:
- boosted PI monotherapy was inferior at suppressing the virus
- integrase based second-line using RAL was non-inferior to a second-line PI-based regimen
- presence of NRTI resistance allowed for better treatment outcome – served as a measure of adherence.
The EARNEST, SELECT and SECOND-LINE studies all showed that integrase based second-line using RAL was non-inferior to a second-line PI-based regimen.

The use of an upfront resistance test to optimise the NRTI utilised did not have an impact on treatment outcome.

SPRING-2 showed DTG versus RAL non-inferior (88% vs 85%)

FLAMINGO showed DTG versus DRV/r was superior (90% vs 83%)
Meta-analysis of 649 participants across 13 Sub-Saharan studies receiving boosted PI plus 2 NRTIs

More than one third of patients did not achieve virological suppression defined as <400 copies/ml

Median 17% of participants acquired resistance associated with PI and frequency was found to increase over treatment duration.

Stockdale AJ et al, Clin Infect Dis 2018
A5288 Second-line Resistance Patterns

- 665 participants across 10 countries
- Confirmed viral failure on a boosted PI-based second-line regimen
- NRTI resistance: 3TC/FTC (100%), TDF (84%), AZT (76%)
- NVP (63%) and EFV (56%)

69% remained susceptible to the second line regimen

Wallis et al, CROI 2016
• What have we learnt from the second-line studies:
  • The majority of individuals failing a second-line regimen do not have resistance to the regimen.
  • Therefore we need to find a way to improve second-line outcome:
    • Studies have shown resistance testing to optimise NRTI selection doesn’t impact outcome
    • Adherence remains the main leader to treatment failure; although we are starting to see an increase in protease resistance
  • New studies starting to look at the use of DTG in protease suppressed and unsuppressed individuals (ACTG A5381).
THIRD-LINE TREATMENT OUTCOMES
Overview of A5288 Study Cohorts

Screening Process up to 120 days
Cohort allocation based on ARV History and Genotype; Initiation of Study Regimen

All Cohorts: At participating sites, randomize 1:1 to CPI+SOC or SOC

Cohort A
No LPV/RTV resistance and susceptible to at least one NRTI regardless of NNRTI resistance or prior RAL exposure
Continue PI backbone; NRTIs may be modified. If taking RAL prior to start; must discontinue

Cohort B
Resistance to LPV/RTV but susceptible to DRV/RTV and ETR and with no prior RAL exposure and regardless of NRTI resistance
OR
Resistance to all NRTIs (susceptible to none) but susceptible to DRV/RTV and ETR and with no prior RAL exposure
Randomized 1:1 to Cohort B1 or B2 (if HepB +, assigned to B3)

Cohort B1
Best available NRTIs, RAL and DRV/RTV

Cohort B2
ETR, RAL and DRV/RTV

Cohort B3
RAL, DRV/RTV, and TDF/FTC, or TDF+3TC

Cohort C
Resistance to LPV/RTV and ETR but susceptible to DRV/RTV and with no prior RAL exposure and regardless of NRTI resistance
OR
Resistance to ETR and to all NRTIs (susceptible to none) but susceptible to DRV/RTV and with no prior RAL exposure
Best available NRTIs, RAL and DRV/RTV

Cohort D
Not eligible for Cohorts A, B or C
Best available regimen, includes study-provided and any locally-available drugs
A5288 Outcomes

- Of the participants without LPV resistance who were assigned to continue their second-line ART (Cohort A), less than 50% achieved viral suppression and this cohort also had the most participants with AE.

- Across all cohorts, 10% of participants experienced VF with new drug resistance mutations (NRTI=6%, NNRTI=4% and PI=2%)

- Third-line ART regimens assigned by algorithm and containing new drugs were highly effective in participants with LPV resistance.

- Similar outcome data has been published on a South African third-line public sector cohort with 79% viral suppression however the level of PI resistance at 2\textsuperscript{nd} line treatment failure was up to 93% (Moorhouse M., et al JAIDs 2019).

Overall, 64% (95% CI 60, 68%) of participants achieved viral load suppression.

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**Graph:**

- X-axis: Weeks from Enrollment
- Y-axis: % Viral Failure
- Legend:
  - A
  - B1
  - B2
  - B3
  - C
  - D
  - Total

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Phenotypic analysis different from genotypic prediction in subtype C samples

The predicted genotype and phenotype were concordant for NVP, EFV and 3TC -> used in first-line treatment

However TDF, RPV and ETR misclassified 17%, 30% and 30% respectively of the isolates -> demonstrating phenotypic susceptibility despite estimated genotypic resistance.

This may result from the presence of compensatory and/or epistatic mutations in RT which increase susceptibility
Conclusions from third-line outcome data

• No clinical indicator for resistance

• The resistant profiles are divergent and therefore there is a place for resistance testing for third-line selection.

• The use of next generation NNRTIs requires that resistance algorithms be addressed.

• Mutations that have accumulated from first and second-line may impact third-line treatment outcome.
Overall Conclusions

• To achieve 90:90:90 we need U=U.

• Modify treatment strategies to keep up ahead of HIV drug resistance.

• The level of NNRTI resistance is concerning and has prompted the move to a new first-line regimen using DTG.

• More tolerable second-line regimens are needed as resistance is not always the driver for failure although higher levels of PI resistance are emerging over time.

• Currently the best third-line approach is some level of individualised regimens using resistance testing and historic treatment information to guide selection.
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