NNRTI Resistance

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MTN 020

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Case 1

- A 28-year-old woman with a baseline CD4 count of 310 cells/mm^3 and HIV RNA level of 45,000 copies/mL initiates antiretroviral therapy with a regimen of efavirenz plus abacavir plus lamivudine. Within 5 months, she has an undetectable HIV RNA.

Case 1

- Six months later, however, she has intermittent problems with adherence and has an HIV RNA level of 5,340 copies/mL.
- A genotypic resistance assay is performed that shows a K103N mutation in reverse transcriptase and no significant mutations in protease.

Case 1

- The patient stops her antiretroviral medications.
- At a visit one year later, CD4 count has declined to 227 cells/mm^3 and she states she is interested in restarting antiretroviral therapy.

Case 1

- A second genotypic resistance assay is performed (not on therapy) and this resistance assay does not show any mutations in reverse transcriptase or protease. The patient has never taken nevirapine.

Case 1

- Which of the following is true?
  - A. the patient is NOT likely to have a response to efavirenz or nevirapine
  - B. K103N reflects resistance to efavirenz but NOT to nevirapine
  - C. K103N reflects resistance to efavirenz but NOT to delavirdine
  - D. If the patient is placed back on efavirenz and the K103N re-emerges, efavirenz should be continued because the K103N mutation reduces viral fitness

Case 1

- The K103N mutation is the most common non-nucleoside reverse transcriptase inhibitor (NNRTI) mutation to develop in association with virologic breakthrough in a patient taking efavirenz.
- EFV – long half life, low barrier of resistance. K103N is often the first mutation associated with efavirenz/emtricitabine/tenofovir failure

Stanford Database

Drug Resistance Interpretation: RT

NRTI Resistance Mutations: None
NNRTI Resistance Mutations: **K103N**
Other Mutations: None

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	Susceptible	**efavirenz (EFV)**	High-level resistance
abacavir (ABC)	Susceptible	**etravirine (ETR)**	Susceptible
zidovudine (AZT)	Susceptible	**nevirapine (NVP)**	High-level resistance
stavudine (D4T)	Susceptible	**rilpivirine (RPV)**	Susceptible
didanosine (DDI)	Susceptible		
emtricitabine (FTC)	Susceptible		
tenofovir (TDF)	Susceptible		

RT Comments

NNRTI

- K103N causes high-level resistance to NVP, and EFV. it has no effect on ETR or RPV susceptibility.

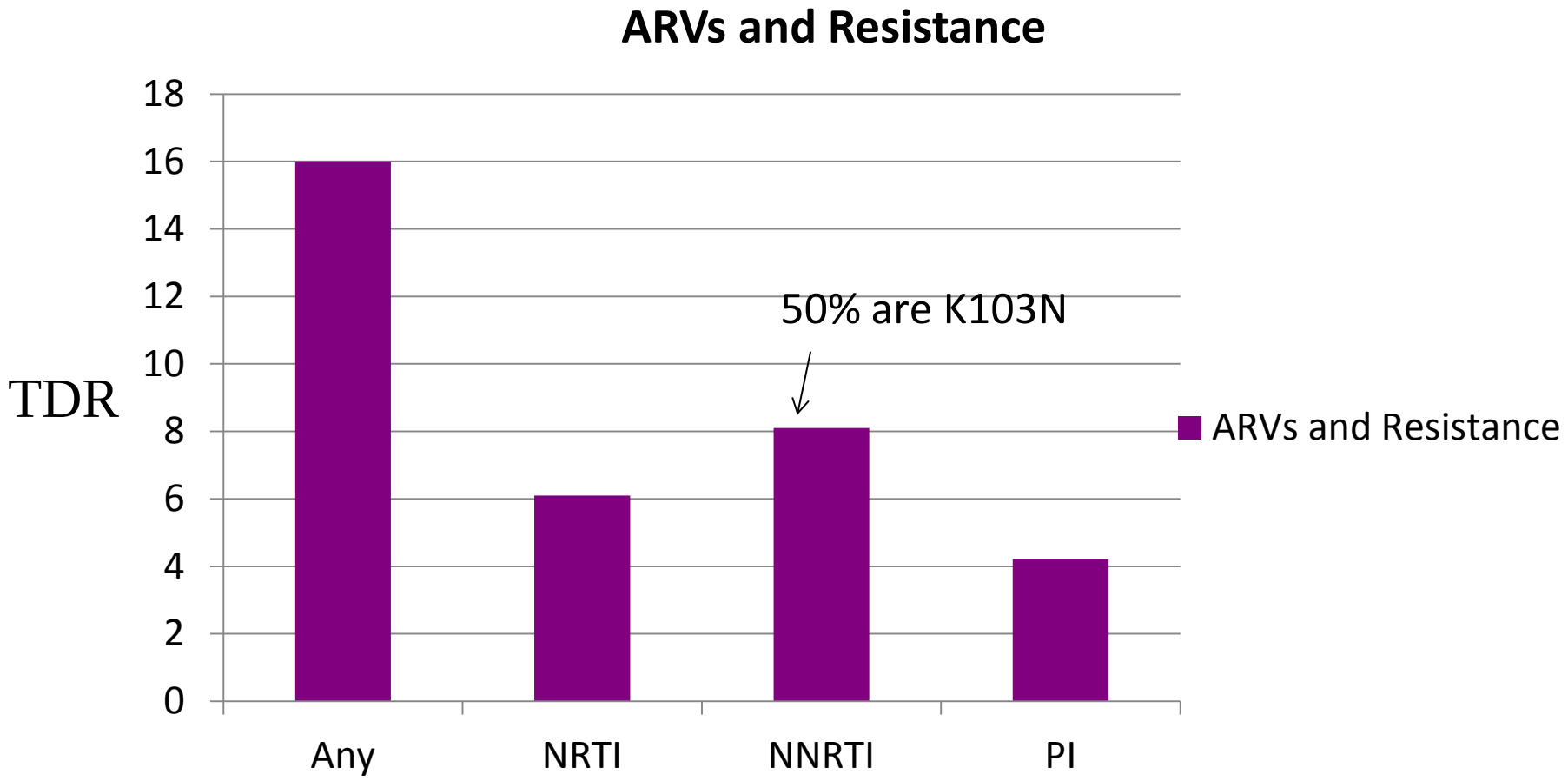
Mutation Scoring

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
K103N	-	-	-	-	-	-	-	60	0	60	0
Total:	0	0	0	0	0	0	0	60	0	60	0

Case 1

- Because the K103N mutation is archived, it will likely reemerge if the patient is challenged with any of the NNRTI drugs, making a sustained virologic response to efavirenz or nevirapine unlikely.

U.S. Transmitted Drug Resistance



NEXT CASE

Case 2

- Participant seroconverted on 03 Oct 2014.
  - CD4 count of 427 cells/mm^3
  - viral load was 476,690 copies/ml
- Time to start anti-retroviral therapy?

South African 2015 HIV Guidelines

Box 19: ART eligibility criteria

Eligible to start ART
CD4 count ≤500 cells/µl irrespective of clinical stage (Prioritise those with CD4 <350 cells/µl) OR Severe or advanced HIV disease (WHO clinical stage 3 or 4), regardless of CD4 count OR Irrespective of CD4 count or clinical stage: • Active TB disease (including drug-resistant and EPTB) • Pregnant and breastfeeding women who are HIV-positive • Known hepatitis B viral (HBV)co-infection • Prioritise those with CD4 ≤350 cells/µl or advanced HIV disease

HIV Drug Resistance Results and Counseling Messages

PTID	Visit	Specimen Date	Resistance Detected	Interpretation
311-50216-9	17.0	03 OCT 2014	K101E, E138G (RT)	Intermediate NNRTI resistance

RT = reverse transcriptase

NNRTI = non-nucleoside reverse transcriptase inhibitor

TO SITE CLINICIAN:

This participant is infected with HIV that may have intermediate resistance to the NNRTI class of drugs. The resistance may not be strong enough to affect first line therapy, but the participant should be monitored when possible, and it is important to consult the PSRT for treatment guidance.

Treatment guidance: Please consult the PSRT to determine if first line ART may be used. The participant should be monitored when possible for success of first line treatment.

Case 2 Question

- Okay to start first line ARVs?
  - A. Yes, but avoid efavirenz
  - B. Yes, but avoid nevirapine
  - C. No, do not start an NNRTI based regimen
  - D. Send a query to the PSRT

Nucleoside RTI	
lamivudine (3TC)	Susceptible
abacavir (ABC)	Susceptible
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
didanosine (DDI)	Susceptible
emtricitabine (FTC)	Susceptible
tenofovir (TDF)	Susceptible

Non-Nucleoside RTI	
efavirenz (EFV)	Low-level resistance
etravirine (ETR)	Low-level resistance
nevirapine (NVP)	Intermediate resistance
rilpivirine (RPV)	Intermediate resistance

RT Comments

NNRTI

- K101E is a nonpolymorphic mutation that causes intermediate resistance to NVP (~5-fold reduced susceptibility) and low-level resistance (~2-fold reduced susceptibility) to EFV, ETR and RPV. It has a weight of 1.0 in the Tibotec ETR genotypic susceptibility score. In combination with M184I it reduces RPV susceptibility by about 5-fold.
- E138Q/G are nonpolymorphic accessory mutations frequently selected in patients receiving ETR and RPV and occasionally in patients receiving NVP and EFV. E138Q/G are associated with 2 to 3-fold reduced susceptibility to ETR and RPV.

First Line Regimens – SA Guidelines

Individuals >15 yrs (weighing > 40 kg), Hep B co-infected, MTB co-infected

- Tenofovir + lamivudine (or emtricitabine) + efavirenz (in a fixed dose combination)

Individuals on stavudine

- Change stavudine to tenofovir

Adolescents < 15 yrs (or less than 40 kg)

- Abacavir, lamivudine, efavirenz

First Line Regimens – SA Guidelines

Contraindication to efavirenz (psychiatric, intolerance, “impairment of daily function”)

- Tenofovir + emtricitabine (or lamivudine) + nevirapine or lopinavir/ritonavir

Tenfovir contraindication

- Abacavir + lamivudine + efavirenz (or nevirapine)

PSRT Response

- “We support initiation of an efavirenz based ARV regimen, noting that the mutations observed have minimal effect on its susceptibility.”

- “Please be in touch with us in case she exhibits signs of virologic failure (ongoing viremia, intolerance to efavirenz, etc.)”

BUT…

Resistance Concerns?

Resistance Mechanisms

- Most NNRTI-resistance mutations reduce susceptibility to two or more NNRTIs

- The genetic barrier to NNRTI resistance is low. Typically, efavirenz and nevirapine require only a single mutation to reduce clinical efficacy.

Resistance – Schader et al.

- HIV-1 primary isolates of different subtypes and different baseline resistance profiles were used to infect primary cells *in vitro* in the presence of dapivirine

Schader et al. Antimicrobial Agents and Chemotherapy, 2012

Resistance – Schader et al.

- Suboptimal concentrations of dapivirine alone facilitated the emergence of common non-nucleoside reverse transcriptase inhibitor resistance mutation
  - The most common NNRTI resistance-associated mutation selected in the presence of dapivirine alone in subtype C viruses selected for mutations at positions 138 (E138K) and 181 (Y181C)

Schader et al. Antimicrobial Agents and Chemotherapy, 2012

Discussion

- Does demonstration of low-moderate level resistance pose real risk to treatment failure?
- Should we encourage second line ARVs in the setting of NNRTI resistance?
- What are barriers to patients/participants receiving protease inhibitor based ARVs in South Africa?

Discussion

- What challenges, if any, do you anticipate if a participant is started on a second line ARV regimen following her participation in MTN 020?