ANTIRETROVIRAL TREATMENT IN ADULTS WITH HIV

Shabnam Tehrani M.D.

Associate Professor of Infectious Diseases

Shahid Beheshti University of Medical Sciences

Clinical HIV/AIDS Fellowship

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Virologic Failure on the NNRTI plus NRTI regimen

Case presentation

- 38 -year-old male
- Diagnosis: HIV-1 infection (diagnosed 12 years ago)
- ART history: TDF+ FTC+ Efavirenz
- Hepatitis status: HBSAg:-, HBSAb:-, HCV:-

Lab Results

CD4 count :256-335-317-465- 80 (today)

HIV viral load (today):12,500 copies/mL
(6 months ago): undetectable

Serum Biochemistry tests: Normal

Case presentation

Next step??

Case Presentation

Genotype :	***sample***	***serum***
	RT-NRTI	***k70E, M184V, K219Q***
	NNRTI	***K103N, V179L,P225H***
	PR	***------***
	other	***T69N,V90I***

Case presentation

How would you interpret these resistance mutations ?

1. RT:M184V+RT:K70R+RT:K219Q+RT:K103N+RT:V179L+RT:P225H+RT:T69N+RT:V90I

Drug resistance interpretation: RT

NRTI Mutations:	**K70R** • **M184V** • **K219Q**
NNRTI Mutations:	**K103N** • **V179L** • **P225H**
RT Other Mutations:	T69N • V90I

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Intermediate Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	Intermediate Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Potential Low-Level Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Low-Level Resistance

RT comments

NRTI

- **K70R** is a TAM that confers intermediate resistance to AZT and contributes to reduced ABC and TDF susceptibility in combination with other TAMs.
- L74V causes intermediate ABC resistance. **L74I** causes low-level ABC resistance.
- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low/intermediate resistance to ABC (3-fold reduced susceptibility). **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT and TDF and are associated with clinically significant reductions in HIV-1 replication.
- **K219E/Q/N/R** are accessory TAMS that usually occur in combination with multiple other TAMs.

NNRTI

- **K103N** is a non-polymorphic mutation that confers high-level reductions in NVP and EFV susceptibility. It is the most commonly transmitted DRM.
- **V179L** is a rare non-polymorphic mutation listed as a RPV-associated resistance mutation by the FDA package insert. Its effects on NNRTI susceptibility have not been well studied.
- **P225H** is a non-polymorphic EFV-selected mutation that usually occurs in combination with K103N. The combination of **P225H** and K103N synergistically reduces NVP, EFV and DOR susceptibility.

Other

- **T69N/S/A/I/E** are relatively non-polymorphic mutations weakly selected in persons receiving NRTIs. They may minimally contribute reduced AZT susceptibility.
- **V90I** is a polymorphic accessory mutation weakly selected by each of the NNRTIs. It is associated with minimal, if any, detectable reduction in NNRTI susceptibility.

- This virus is predicted to have low-level reduced susceptibility to **RPV**. The use of the combination of CAB/**RPV** should be considered to be relatively contraindicated.

K103N is a nonpolymorphic NNRTI-resistance mutation selected in persons receiving NVP and EFV .It reduces NVP and EFV susceptibility about 50 and 20-fold.

Major Non-Nucleoside RT Inhibitor (NNRTI) Resistance Mutations

Consensus	100 L	101 K	103 K	106 V	138 E
DOR	I	EP		AM	
EFV	I	EP	NS	AM	
ETR	I	EP			AGKQ
RPV	I	EP			AGKQ
NVP	I	EP	NS	AM	

What combination would you recommend?

- TDF+ FTC+DTG ???
- TDF+ FTC+DRV/r ???
- TDF+AZT+DTG ??
- TDF+AZT+DRV/r ??
- DRV/r + DTG ?

Case Presentation

- TDF + FTC+ DTG

- After a further 12 weeks, the viral load was <50 copies/ml and the CD4 cell count was 150 cells/µl


DISCUSSION

Discussion

When Should a Resistance Assay be Ordered?

Clinical Setting/ Recommendation	Rationale
Recommended: •Virologic failure during ART	Determine role of resistance in drug failure and maximize the number of active drugs in the new regimen
•HIV infection before starting ART	Assays may not detect minor resistant species, but some resistance mutations may persist for years. Consider testing early after diagnosis of HIV infection.
Usually not recommended: **•After discontinuation of drugs**	Resistance mutations may become minor species in the absence of selective drug pressure
•Plasma VL <1,000 copies/mL	Resistance assays unreliable if VL is low

Indications for Genotype Resistance Testing

Indication #1: all treatment naïve patients at entry into care

Patients should be assessed for transmitted drug resistance with a genotype assay for (PI), (NNRTI), and (NRTI) mutations upon initiation of care.

Integrase resistance testing not routinely indicated at baseline.

Indications for Genotype Resistance Testing

Indication #2: Virologic failure

Drug-resistance testing should guide ARV regimen design and should be performed while the patient is still taking the failing regimen or within 2- 4 weeks of discontinuation of a non–longacting regimen.

Discussion
(Managing Patients with Virologic Failure)

- When designing a new ARV regimen for a patient with virologic failure, it is important to consider the factors outlined above on causes of virologic failure

- A new regimen should be selected based on the patient's ART history, a review of their current and previous drug-resistance test results, and whether a fully susceptible ARV drug with high barrier to resistance and other fully active drugs are available.

Discussion
(Managing Patients with Virologic Failure)

- A new ARV regimen can include two fully active drugs if at least one has a high resistance barrier, such as the second-generation INSTI DTG or the boosted-PI DRV

- ARV agents with high barrier to resistance are those in which emergent resistance is uncommon in patients experiencing virologic failure. These include boosted darunavir (DRV), dolutegravir (DTG), and bictegravir (BIC).

Discussion
(Virologic Failure on the NNRTI plus NRTI regimen)

- In this setting, patients often have viral resistance to the NNRTI, with or without the M184V/I mutation, which confers high-level resistance to 3TC and FTC. Additional NRTI mutations also may be present. Below are some treatment options:

1-DTG plus NRTIs: recommends that fully active DTG plus two NRTIs, at least one of which is fully active, can be a treatment option after failure of a first-line NNRTI-based therapy.

Discussion
(Virologic Failure on the NNRTI plus NRTI regimen)

2- Boosted PI plus NRTIs: recommends that a boosted PI (**preferably boosted DRV**) plus two NRTIs, at least one of which is fully active, can be an option after failure of a first-line NNRTI-based therapy .

-However, if full activity of at least one NRTI in the regimen cannot be assured, fully active boosted DRV plus two NRTIs estimated to be only partially active (particularly TAF or TDF with 3TC or FTC) can be considered .

Discussion
(Virologic Failure on the NNRTI plus NRTI regimen)

3- Boosted PI plus an INSTI:

- a boosted PI (e.g., DRV) that is a preferred option combined with DTG would be a viable option in this setting.

Virologic Failure On The PI Plus NRTI Regimen

Case presentation

- 42-year-old male
- Diagnosis: HIV-1 infection (diagnosed 9 years ago)
- **ART history:**
  - 2016–2018: TDF + FTC + EFV → switched due to CNS side effects
  - 2018–present: Atazanavir/ritonavir (ATV/r) + TDF/FTC

Case presentation

- **Adherence history: Generally good, though he reports “missing doses on weekends” in the last year**
- **Current Presentation (2025)**
- **presents for routine HIV monitoring.**

- **Symptoms:**
  Fatigue for 3–4 months
- **No fever, no opportunistic infections**
- **Vital Signs :Stable; afebrile**

Lab Results

HIV viral load (today):21,000 copies/mL
(6 months ago):undetectable

CD4 count : 310 cells/mm^3
(previously 450)

Serum Biochemistry tests: Normal

Medication review

States he takes ATV/r “sometimes without food because of work”

Taking pantoprazole 40 mg daily for chronic reflux started 4 months ago

Genotype Resistance Testing

Genotype :	***sample***	***serum***
	RT-NRTI	***E40F, A62V, V118I***
	NNRTI	***none***
	PR	***I50L , A71V, L10I***
	other	***----***

Case presentation

How would you interpret these resistance mutations ?

PI Resistance Notes

Major Protease Inhibitor (PI) Resistance Mutations

Consensus	30 D	32 V	33 L	46 M	47 I	48 G	50 I	54 I	76 L	82 V	84 I	88 N	90 L
ATV/r		**I**	F	IL	V	**VM**	**L**	VTALM		ATFS	**V**	D**S**	**M**
DRV/r		**I**	F		VA		**V**	**LM**	**V**	F	**V**		
LPV/r		**I**	F	IL	V**A**	VM	**V**	**VTALM**	**V**	**AFTS**	**V**		M

Drug resistance interpretation: PR

PI Major Mutations:	**I50L**
PI Accessory Mutations:	None
PR Other Mutations:	L10I • A71V

Protease Inhibitors	
atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	Susceptible
lopinavir/r (LPV/r)	Susceptible

PR comments

Major

- **I50L** is a non-polymorphic mutation selected by ATV. It causes high-level resistance to ATV and increases susceptibility to LPV and DRV.

Other

- **L10I/V** are polymorphic, PI-selected accessory mutations that increase the replication of viruses with other PI-resistance mutations.
- **A71V/T** are polymorphic, PI-selected accessory mutations that increase the replication of viruses with other PI-resistance mutations.

PI Resistance Notes

I50L

- **I50L : is a nonpolymorphic mutation selected by ATV .**
- **It confers high-level resistance to ATV and increases susceptibility to the remaining PIs .**

- **In a weighted genotypic score, I50V was one of 11 mutations associated with a reduced virological response to treatment with a DRV-containing regimen when combined with other DRV-resistance mutations**

Drug resistance interpretation: RT HIVDB 9.8 (20

NRTI Mutations: E40F · A62V
NNRTI Mutations: None
RT Other Mutations: V118I

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Susceptible
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	Susceptible
lamivudine (3TC)	Susceptible
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Susceptible
efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

RT comments

NRTI

- **E40F** is a non-polymorphic accessory mutation selected by AZT and d4T. It usually occurs in combination with M41L, L210W and T215Y. In this context it is associated with reduced susceptibility to each of the NRTIs.
- **A62V** is an accessory mutation that often occurs in combination with the multi-NRTI resistance mutations K65R or Q151M. **A62V** is widespread in subtype A viruses in former Soviet Union countries but A62 is otherwise non-polymorphic.

Other

- **V118I** is a polymorphic accessory NRTI-resistance mutation that often occurs in combination with multiple TAMs.

Clinical Decision-Making

- **What combination would you recommend ?**

Treatment Strategies

Treatment Strategies

- Switch failing regimen
- Reinforce adherence
- Ensure future PIs taken with food
- Recheck VL in 4–8 weeks

- Recommended Salvage Regimens
  - Darunavir/r + TDF/FTC
  - Dolutegravir + Darunavir/r (dual therapy option in treatment-experienced patients)

Key Teaching Points

- I50L = hallmark ATV resistance
- PPIs ↓ ATV absorption
- ATV failure often preserves DRV activity


DISCUSSION

ATV resistance prevalence

- In a large meta-analysis of HIV-1 protease sequences from patients who experienced virological failure on ATV (mostly boosted ATV/ritonavir), 18% of sequences had at least one (PI) drug-resistance mutation (DRM). (2022 May 5;11(5):546. doi: 10.3390/pathogens11050546)

- In a more recent broader review (combining many datasets), among sequences with PI DRM, the most frequent major mutations (with prevalence > 5%) included I50L (34%), M46I (33%), V82A (22%), L90M (19%), I54V (16%), N88S (10%), among others. (2022 May 5;11(5):546. doi: 10.3390/pathogens11050546)

ATV resistance prevalence

- Ritonavir-boosted atazanavir is an option for second-line therapy in low- and middleincome countries (LMICs).

- Most mutations selected by atazanavir—especially I50L, its hallmark signature—do not strongly compromise darunavir susceptibility.

- ***DRV is the most widely used PI and has a high genetic barrier against the development of resistance by HIV-1.***
- ***The presence of multiple mutations is often needed for HIV to develop resistance against DRV.***
- ***This is why DRV/ritonavir is often recommended as a salvage PI after ATV failure.***

Initial Characteristics to Consider in All People With HIV

- Pre-treatment HIV RNA level (viral load)
- Pre-treatment CD4 count
- History of prior exposure to CAB-LA or oral TDF/FTC or TAF/FTC as PrEP, or use of INSTI-based post-exposure prophylaxis (PEP)
- Suspected drug resistance (prior to availability of genotypic testing results)
- HIV genotypic drug resistance test results

Initial Characteristics to Consider in All People With HIV

- Genotypic drug resistance testing in people without prior ARV exposure should focus on testing for mutations in the reverse transcriptase and protease genes.
- If transmitted INSTI resistance is a concern, providers should also test for resistance mutations to this class of drugs.
- Anticipated adherence to the regimen

Recommended Initial Regimens for Most People With HIV

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

For people who do not have a history of using CAB-LA as PrEP, one of the following regim recommended[a]:

- BIC/TAF/FTC **(AI)**
- DTG plus (TAF or TDF)[b] plus (FTC or 3TC) **(AI)**
- DTG/3TC **(AI),** except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

For people who have a history of CAB-LA use as PrEP, INSTI genotype resistance testing should be performed before starting ART. If ART is to be started before results of genotypic testing results, the following regimen is recommended:

- DRV/c[c] or DRV/r with (TAF or TDF)[b] plus (FTC or 3TC)—pending the results of the genotype test **(AIII)**

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

[a] Because of the current low rates of transmitted INSTI resistance in the United States, even when there is suspicion that HIV was acquired from a partner with virologic failure while on an INSTI, an INSTI-based regimen can be started pending the results of the INSTI genotype.

Recommended Initial Regimens for People With HIV in IRAN

جدول 5 – رژیم های آغازین ضد رتروویروسی در بیماران بالای 14 سال

Recommended Initial Regimens
INSTI + 2 NRTI regimen • DTG plus (TDF or TAF①) plus (FTC or 3TC) • DTG② /ABC③/3TC
Alternative regimens
Boosted PI + 2 NRTI regimen • DRV/r④ plus (TDF or TAF) plus (FTC or 3TC) • ATV/r plus (TDF or TAF) plus (FTC or 3TC) • DRV/r plus ABC/3TC • **INSTI⑤ + 2 NRTI regimen** • RAL plus (TDF or TAF) plus (FTC or 3TC) **NNRTI + 2 NRTI regimen** • EFV 600 mg plus TDF plus (FTC or 3TC) • EFV 400⑥ mg/TDF/3TC • EFV 600 mg plus TAF/FTC

Take Home Message

A new regimen should be selected based on the patient's ART history, a review of their current and previous drug-resistance test results.

Drug-resistance testing should guide ARV regimen design and should be performed while the patient is still taking he failing regimen or within 2- 4 weeks of discontinuation of a non–longacting regimen.

A new ARV regimen can include two fully active drugs if at least one has a high resistance barrier, such as the second-generation INSTI DTG or the boosted-PI DRV.

Thank You

Any questions?