The History of HIV Treatment: Antiretroviral Therapy and More

Md.S.Kalantari

HIV history timeline

- 1981:

  The first cases of severe immunodeficiencies were reported to the CDC.

- 1982:

  The CDC used the term AIDS, or acquired immune deficiency syndrome, for the first time.

- 1983:

French scientists at the Pasteur Institute discovered the virus that causes AIDS.

- 1986:

The virus causing AIDS was officially named HIV, or human immunodeficiency virus.

- 1987:

The FDA approved Zidovudine (AZT), the first antiretroviral drug used to treat HIV.

- 1996:

Highly active antiretroviral therapy (HAART) hit the market, boosting the life expectancy of someone with HIV by 15 years.

- 2007:

Timothy Ray Brown, known as the “Berlin patient,” got a bone marrow transplant to treat his leukemia. A few months later, doctors could no longer detect HIV in his blood despite no longer being on ART. He is the first person thought to be “cured” of cancer. (Though, there is no proven cure for HIV.)

- 2010:

A study found evidence that pre-exposure prophylaxis (PrEP) works. Researchers found that taking a daily dose of antiretrovirals not only helped those with HIV but also protected people without HIV from getting the virus.

- 2012:

The FDA approved the first at-home HIV test and the drug Truvada, a once-daily PrEP pill.

- 2021:

The FDA approved cabotegravir and rilpivirine (Cabenuva), the first long-acting shot used as a complete HIV treatment regimen.

NRTI`S

- Zidovudine (AZT, Retrovir): 1987
- Lamivudine (3TC, Epivir): 1995
- Abacavir (Ziagen): 1998
- Tenofovir disoproxil fumarate (Viread): 2001
- Emtricitabine (Emtriva): 2003

NNRTI'S

- Nevirapine (Viramune): 1996
- Efavirenz (Sustiva): 1998
- Etravirine (Intelence): 2008
- Rilpivirine (Edurant): 2011
- Nevirapine extended-release (Viramune XR): 2011
- Doravirine (Pifeltro): 2018
- Rilpivirine for ages 2 and up (Edurant PED): 2024

PI'S

- Saquinavir (Invirase): 1995
- Ritonavir (Norvir): 1996
- Indinavir (Crixivan): 1996
- Nelfinavir (Viracept): 1997
- Lopinavir/ritonavir (Kaletratra): 2000
- Atazanavir (Reyataz): 2003
- Fosamprenavir (Lexiva): 2003
- Tipranavir (Aptivus): 2005
- Darunavir (Prezista): 2006

Integrase Inhibitors

- Raltegravir (Isentress, Isentress HD): 2007
- Dolutegravir (Tivicay, Tivicay PD): 2013
- Bictegravir : 2018
- Cabotegravir (Vocabria): 2021

Recommended Initial Regimens for Most People With HIV

For people who do not have a history of using CAB-LA as PrEP, one of the following regimens is 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)**

Recommended Initial Regimens:
INSTI + 2 NRTI regimen DTG plus (TDF or TAF) plus (FTC or 3TC) DTG /ABC/3TC
Alternative regimens:
Boosted PI + 2 NRTI regimen DRV/r plus (TDF or TAF) plus (FTC or 3TC) ATV/r plus (TDF or TAF) plus (FTC or 3TC) DRV/r plus ABC/3TC **INSTI + 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 400 mg/TDF/3TC EFV 600 mg plus TAF/FTC
Preferred Regimens for HIV/HBV coinfection
INSTI + 2 NRTI regimen DTG plus (TDF or TAF) plus (FTC or 3TC)

Long-acting drugs

FDA Approves Cabenuva and Vocabria for the Treatment of HIV-1 Infection

- CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use.
- VOCABRIA (cabotegravir) 30 mg tablets which should be taken in combination with oral rilpivirine for one month prior to starting treatment with Cabenuva to ensure the medications are well-tolerated before switching to the extended-release injectable formulation.

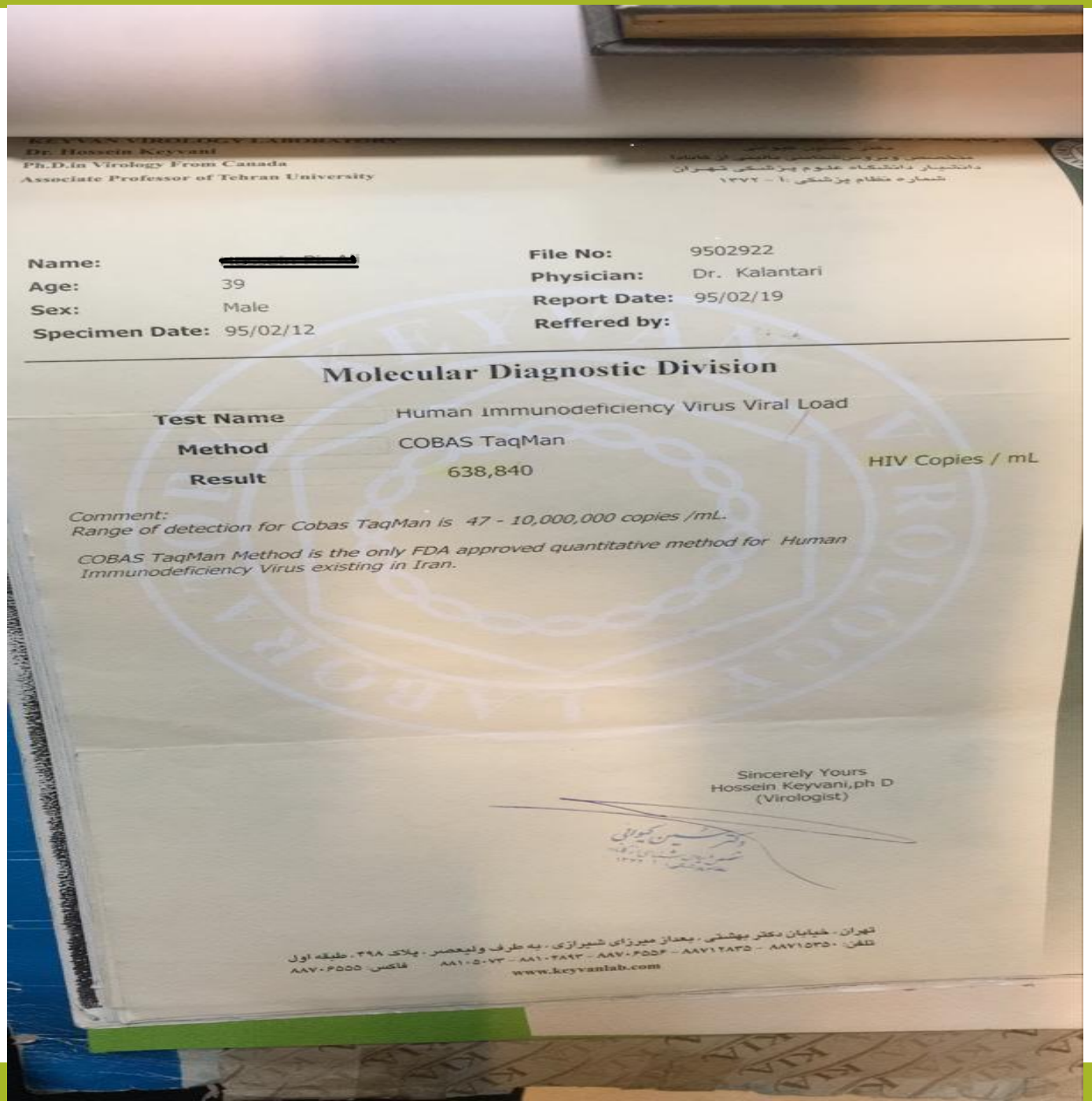
- in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

Sunlenca: The HIV medicine lenacapavir

- Sunlenca is the first of a new class of drugs called capsid inhibitors to be FDA-approved for treating HIV-1. Sunlenca works by blocking the HIV-1 virus' protein shell (the capsid), thereby interfering with multiple essential steps of the viral lifecycle

- **Ibalizumab (IBA) :**

is a long-acting CD_4 post-attachment inhibitor that is given intravenously every 2 weeks. A single-arm, multicenter clinical trial enrolled 40 heavily ART-experienced participants who had multidrug-resistant HIV-1 and who were experiencing virologic failure on an ARV regimen.



Dr. Hossein Keyvani
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دانشیار دانشگاه علوم پزشکی تهران
شماره نظام پزشکی : ۱۰ - ۱۳۷۲

Name: [redacted]
Age: 39
Sex: Male
Specimen Date: 95/02/12

File No: 9502922
Physician: Dr. Kalantari
Report Date: 95/02/19
Reffered by:

Molecular Diagnostic Division

Test Name	Human Immunodeficiency Virus Viral Load
Method	COBAS TaqMan
Result	638,840 HIV Copies / mL

Comment:
Range of detection for Cobas TaqMan is 47 - 10,000,000 copies /mL.

COBAS TaqMan Method is the only FDA approved quantitative method for Human Immunodeficiency Virus existing in Iran.

Sincerely Yours
Hossein Keyvani,ph D
(Virologist)

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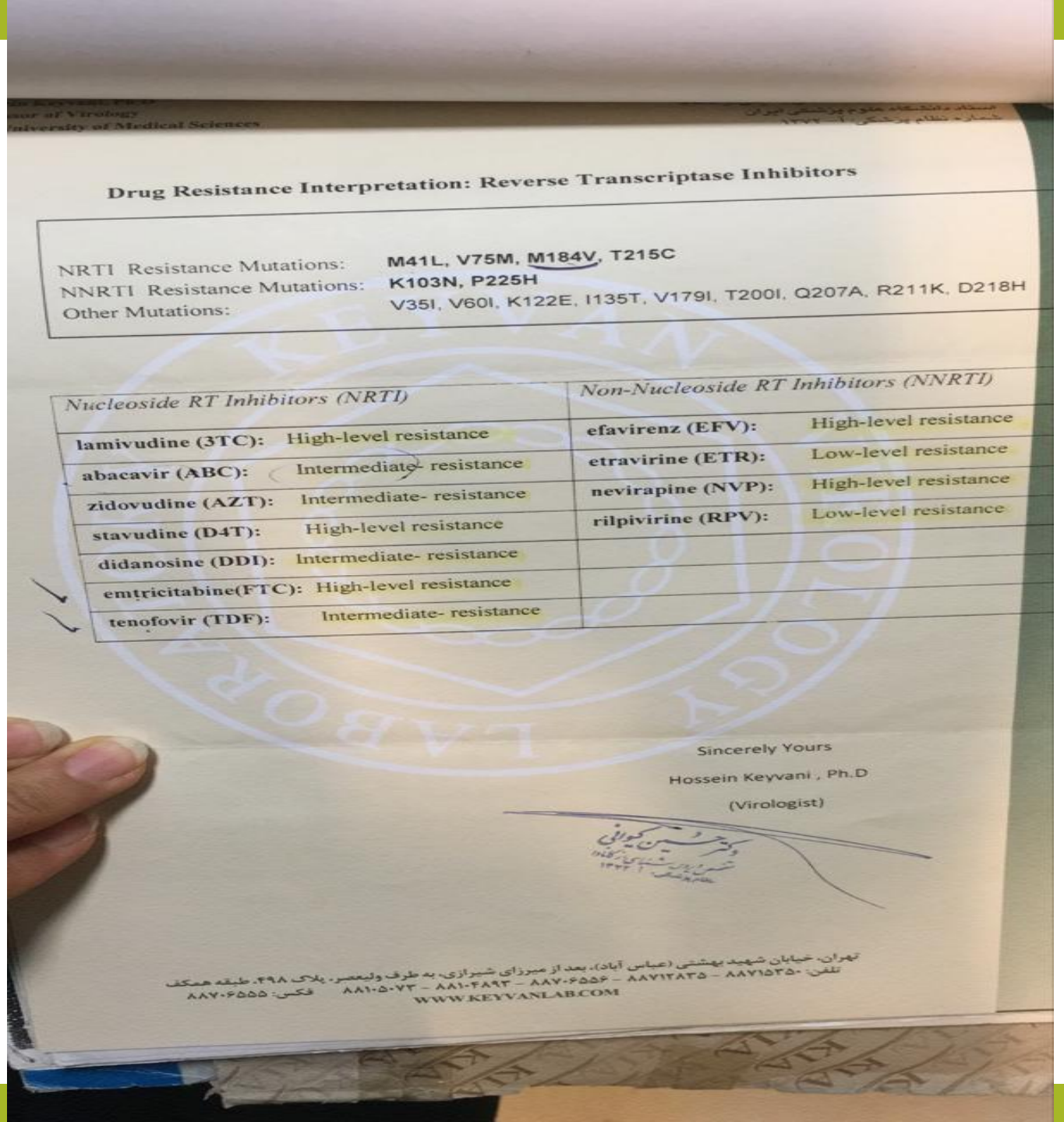

Drug Resistance Interpretation: Reverse Transcriptase Inhibitors

NRTI Resistance Mutations:	**M41L, V75M, M184V, T215C**
NNRTI Resistance Mutations:	**K103N, P225H**
Other Mutations:	V35I, V60I, K122E, I135T, V179I, T200I, Q207A, R211K, D218H

Nucleoside RT Inhibitors (NRTI)		*Non-Nucleoside RT Inhibitors (NNRTI)*	
lamivudine (3TC):	High-level resistance	**efavirenz (EFV):**	High-level resistance
abacavir (ABC):	Intermediate- resistance	**etravirine (ETR):**	Low-level resistance
zidovudine (AZT):	Intermediate- resistance	**nevirapine (NVP):**	High-level resistance
stavudine (D4T):	High-level resistance	**rilpivirine (RPV):**	Low-level resistance
didanosine (DDI):	Intermediate- resistance		
emtricitabine(FTC):	High-level resistance		
tenofovir (TDF):	Intermediate- resistance		

Sincerely Yours

Hossein Keyvani , Ph.D

(Virologist)

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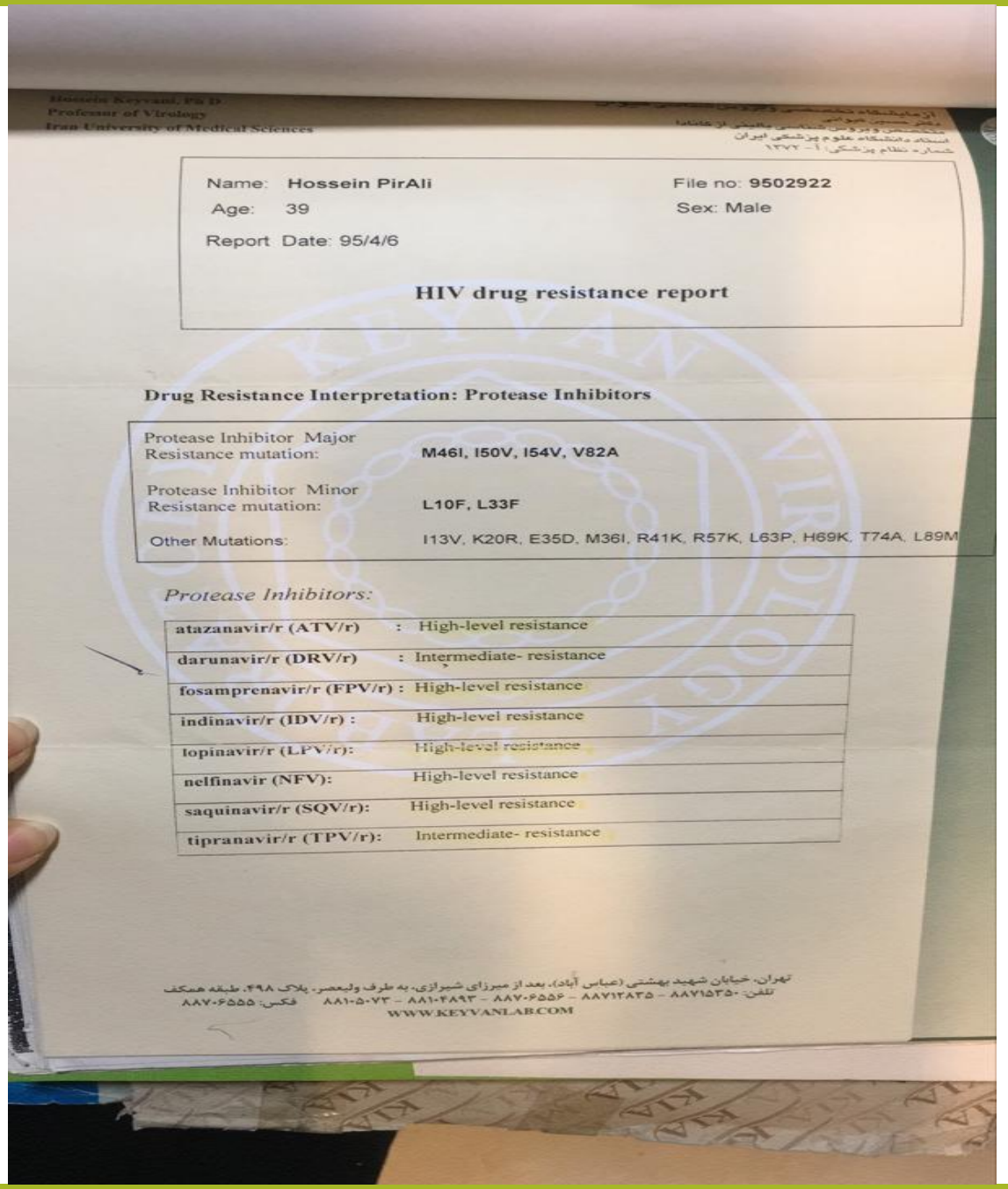

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Name: Hossein PirAli
File no: 9502922
Age: 39
Sex: Male
Report Date: 95/4/6

HIV drug resistance report

Drug Resistance Interpretation: Protease Inhibitors

Protease Inhibitor Major Resistance mutation:	M46I, I50V, I54V, V82A
Protease Inhibitor Minor Resistance mutation:	L10F, L33F
Other Mutations:	I13V, K20R, E35D, M36I, R41K, R57K, L63P, H69K, T74A, L89M

Protease Inhibitors:

atazanavir/r (ATV/r) :	High-level resistance
darunavir/r (DRV/r) :	Intermediate- resistance
fosamprenavir/r (FPV/r) :	High-level resistance
indinavir/r (IDV/r) :	High-level resistance
lopinavir/r (LPV/r):	High-level resistance
nelfinavir (NFV):	High-level resistance
saquinavir/r (SQV/r):	High-level resistance
tipranavir/r (TPV/r):	Intermediate- resistance

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

HIV-1 integrase drug-resistance mutations in Iranian treatment-experienced HIV-1-infected patients

- Arezoo Marjani1 · Farah Bokharaei-Salim1 · Fatemeh Jahanbakhshi2 · Seyed Hamidreza Monavari1 ·Maryam Esghaei1 · Saeed Kalantari3 · Seyed Jalal Kiani1 · Angila Ataei-Pirkooh1 · Atousa Fakhim4 · Hossein Keyvani1

- Archives of Virology (2020) 165:115–125 https://doi.org/10.1007/s00705-019-04463-y

- From June 2012 to December 2018, a total of 655 treatment-experienced HIV-1-infected patients enrolled in this cross-sectional survey.

- Following amplification and sequencing of the HIV-1 integrase region of the pol gene, DRM and phylogenetic analysis were successfully carried out on the plasma samples of patients who had a viral load over 1,000 IU/ml after at least 6 months of ART.

- Out of the 655 patients evaluated, 62 (9.5%) had a viral load higher than 1,000 IU/ml after at least 6 months of ART

- Phylogenetic analysis showed that all of the 62 HIV-1 patients experiencing treatment failure were infected with CRF35_AD, and one of these patients (1.6%) was infected with HIV-1 variants with DRMs. The DRMs that were identified belonged to the INSTI class, including E138K, G140A, S147G, and Q148R.

- If the above option are not feasible, a new ARV regimen can also include a fully active drug with a high resistance barrier plus two partially active NRTIs—particularly TAF or TDF with lamivudine (3TC) or emtricitabine (FTC)—though this is less well-defined and close monitoring is advised

salvage regimen

- These drugs may include NRTIs, PIs, and second-generation INSTIs, although dosing of some drugs (e.g., DRV and DTG) may need to be increased when treating people with relevant resistance mutations to achieve drug concentrations necessary to be at least partially active against a less sensitive virus

- **discontinue:**
  - NNRTIs (especially efavirenz, nevirapine, and rilpivirine [RPV]), the first-generation INSTIs raltegravir (RAL) and elvitegravir (EVG)

thanks for your attention