The third 95: Recognizing and managing HIV treatment failure (Interactive-case discussion)

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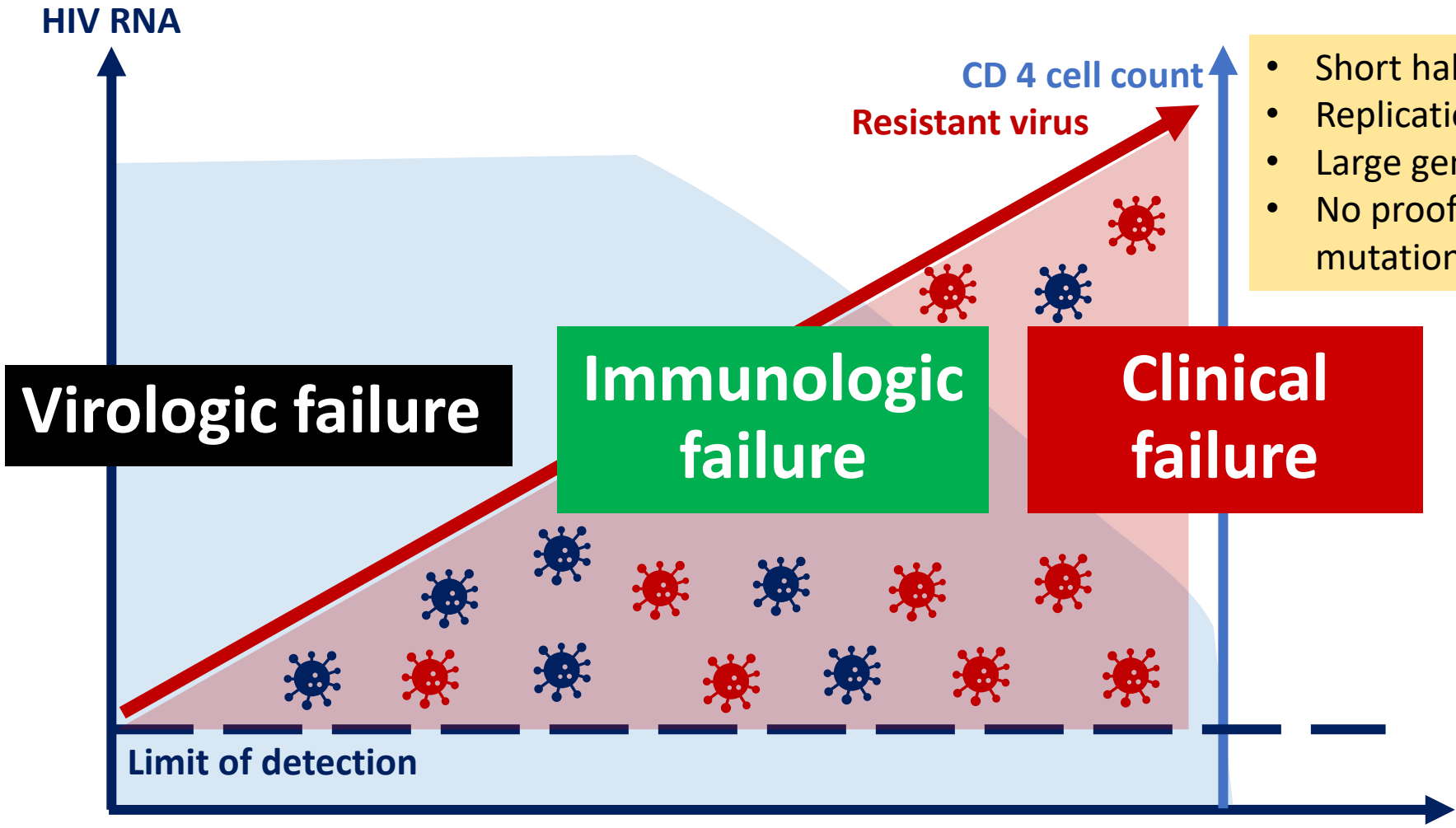
24 สิงหาคม 2566

Treatment failure and HIV drug resistance



- Short half life (<2h): increase turn over rate
- Replication >1010 viral particles/day for 5-10y
- Large genome 1000 nucleotide
- No proof reading of reverse transcriptase: mutation 3*10-5 basepair/replication cycle

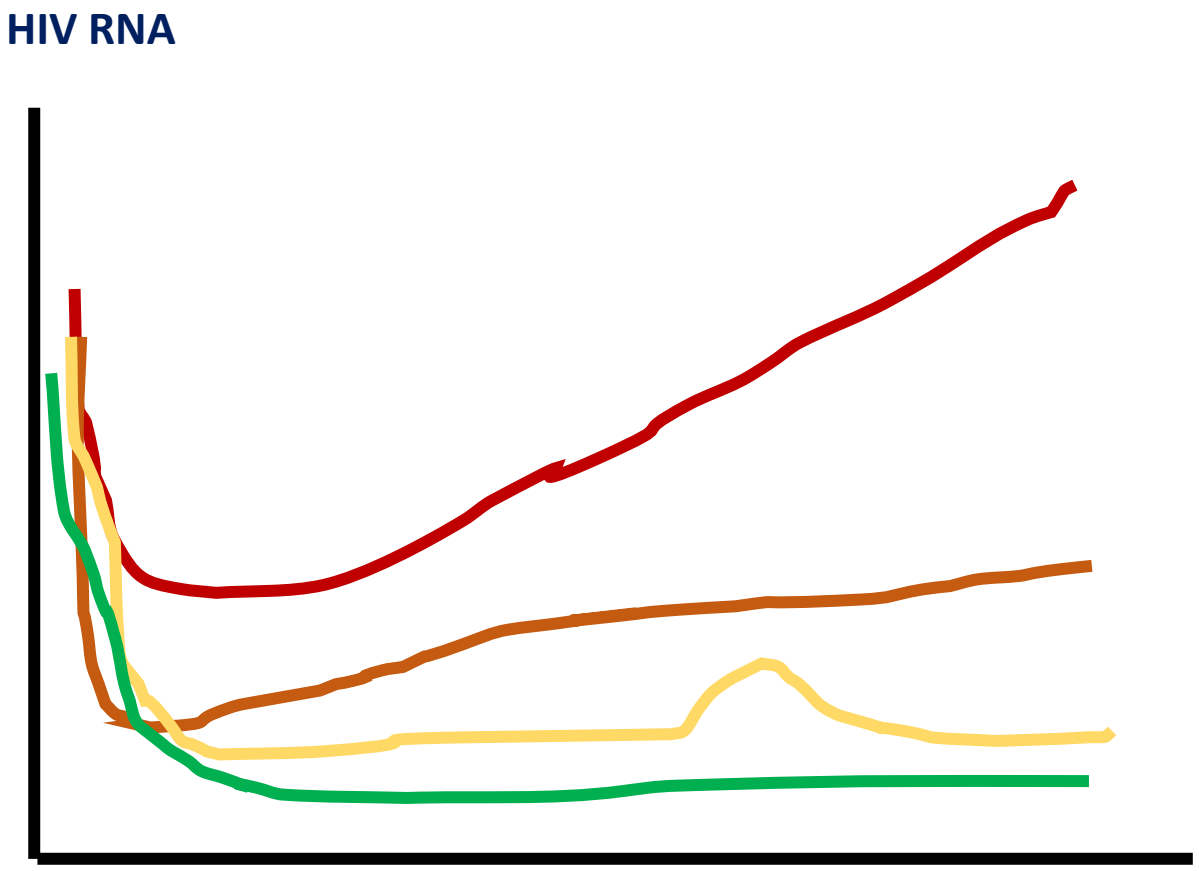
Case 1 A 40-year-old-woman, maid

HIV with HBV coinfection

- Presented with multiple cervical LN 4/45,
  - Anti-HIV+, HBsAg+,CD4 1048
  - Anti-HCV-,TPHA-, VDRL-NR,CXR normal
  - Pathology: chronic inflammation, AFB –
  - Loss to f/u
- Revisit 7/55 for ANC (G2 GA 18wk)
  - เป็นบุตรของสามีคนที่สาม ลูกคนแรกอายุ 23 ปีแข็งแรงดี
  - Oral hairy leukoplakia, CD4 224(10%)
  - **1/8/55 TDF+3TC+EFV**
  - **10/8/55 TDF+3TC+LPV/r**
    - HIV VL <40, HBV VL<10
  - 9/11/55 ลูกดิ้นน้อยลง DFIU at GA 36wk
  - **21/11/55 TDF+3TC+EFV**
- Good adherence, **TDF/FTC/EFV**
- HIV VL <40 (55-62)
- U/S UA normal every year
- HT in the young
  - On amlodipine, losartan
  - Normal PAC,PRA, U/S doppler
- **9/63 HIV VL 77** ยืนยันกินยาตรงเวลาทุกวัน

What is your management?

Various virological responses to ART: definition



Incomplete virologic response

- 2 consecutive HIV-RNA ≥200 copies/mL after 24 weeks of treatment in a patient who has not yet had documented virologic suppression
- baseline HIV-RNA level and regimens may affect the time course of response

Virologic failure

- inability to achieve or maintain suppression to HIV-RNA level <200 copies/mL

Low-level viremia:

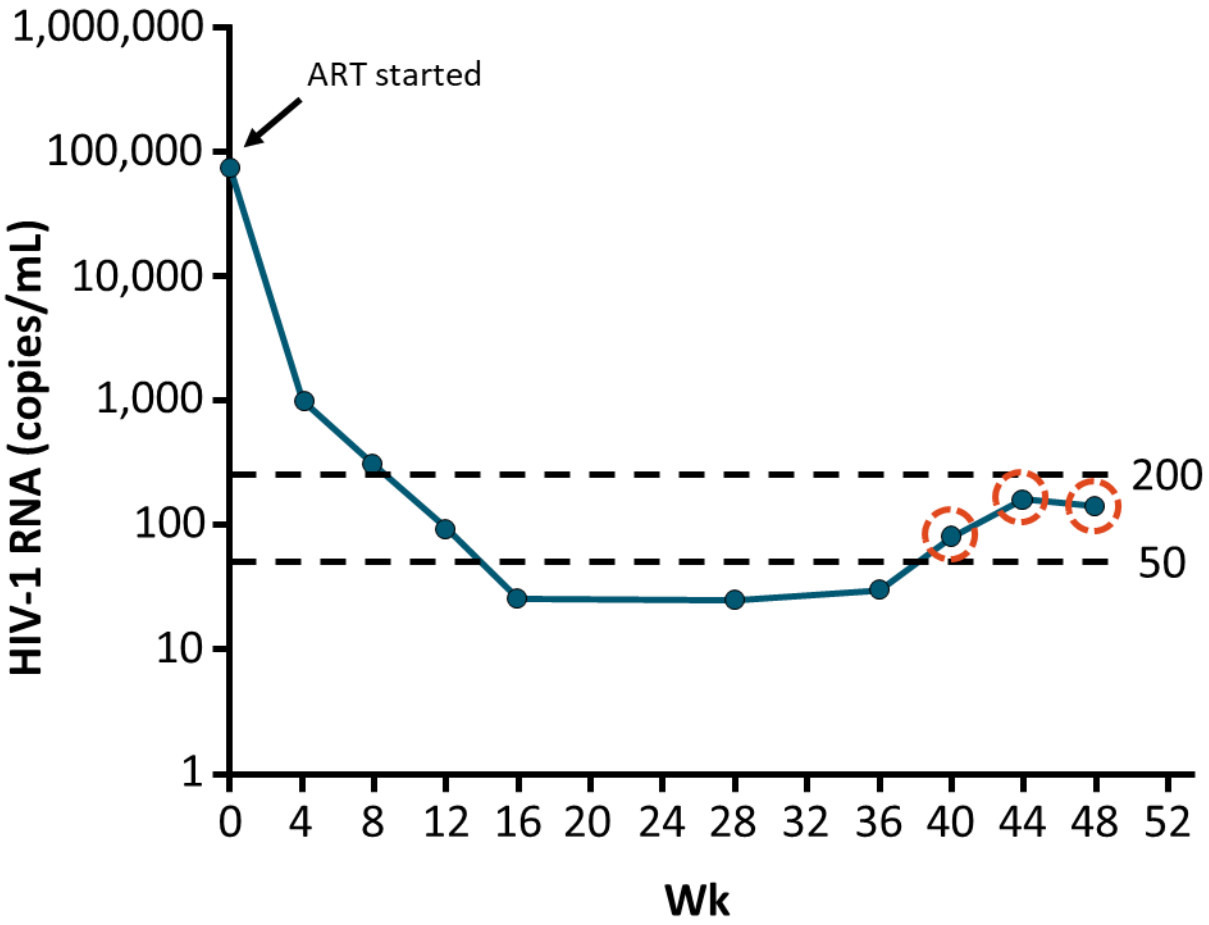
- Confirmed HIV-RNA level <200 copies/mL

Virologic blip:

- After virologic suppression, an isolated detectable HIV-RNA level that is followed by a return to virologic suppression

DHHS ART Guidelines. September 2022.

Managing Low-Level Viremia, Blip



- **Assess:**
  - Adherence
  - Drug–drug interactions
  - Drug–food interactions
  - New partners and condom use
- Recheck HIV-1 RNA **at least 3 mo**
- Do **not typically require an ART change** with HIV-1 RNA <200 copies/mL

hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all#approach-to-detectable-hiv-rna-levels
DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. September 2022.

Case 1 A 40-year-old-woman, maid

HIV with HBV coinfection

- Presented with multiple cervical LN 4/45,
  - Anti-HIV+, HBsAg+,CD4 1048
  - Anti-HCV-,TPHA-, VDRL-NR,CXR normal
  - Pathology: chronic inflammation, AFB –
  - Loss to f/u
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- **9/63 HIV VL 77** ยืนยันกินยาตรงเวลาทุกวัน
- **8/64 HIV VL 475**

What is your management?

Approach of treatment failure

Assessment

- Check adherence, drug tolerability
- Drug-drug or food interactions
- Review ART history and current treatment
- Co-medication
- Signs of clinical progression
- HIV RNA and CD4 counts over time
- All prior and current resistance test results
- Identify treatment option

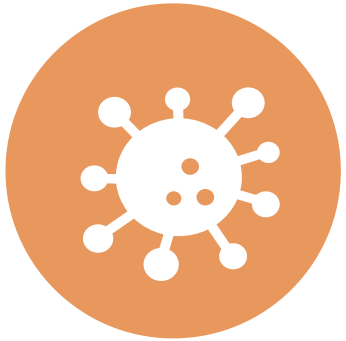
Drug Resistance Testing

- Perform before discontinuing regimen
  - At least prefer on prior ART 2-4 wk
- Drug resistance is **cumulative**
  - Consider all previous resistance test results
- **Do not interrupt** therapy in patients with overt or low-level viremia
  - Rapid HIV VL increase, CD4+ cell count decrease, clinical progression

DHHS ART Guidelines. September 2022.

Causes of Virologic Failure

- Comorbidities
- Unstable housing
- Psychosocial factors
- Missed clinic appointments
- Interruption, or intermittent access ART
- Incomplete adherence
- Cost and affordability
- Adverse drug effects
- High pill burden
- Dosing frequency



- Drug-resistant(transmitted or acquired)
- Prior ARV treatment failure
- Higher pre-treatment HIV-RNA level
- HIV-2

- Adverse events
- Suboptimal PKs
- Suboptimal potency
- Low barrier to resistance
- Prior exposure to suboptimal regimens
- Food requirements
- Drug–drug interactions
- Prescription errors

DHHS ART Guidelines. September 2022.

Case 1 A 40-year-old-woman, maid

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  - Anti-HCV-,TPHA-, VDRL-NR,CXR normal
  - Loss to f/u
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  - OHL, CD4 224(10%)
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- **9/63 HIV VL 77** ยืนยันกินยาตรงเวลาทุกวัน
- **8/64 HIV VL 475**
  - **Psychosocial problems**
  - **Missed 1-2 doses/week**
- **2/65 HIV VL 4660**

Which of the following regimens is the most appropriate for this patient?

1. Continue previous regimens+ wait for DRM
2. TLD
3. AZT/3TC+DTG
4. TDF/FTC+ DRV+RTV
5. DTG+DRV+RTV+3TC

Case 1 A 40-year-old-woman, maid

HIV/HBV with virological failure

O-9 susceptible	10-14 Potential low-level	15-29 low-level	30-59 Intermediate	≥60 High-level

Genotypic resistance assay (2/65)	
TDF/FTC/EFV, HIV VL 4660	
NRTIs	**L74I, M184V**
NNRTIs	**K103N, P225H**
PIs	**-**

NRTI
- 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.

NNRTI
- K103N is a non-polymorphic mutation that confers high-level reductions in NVP and EFV susceptibility. It is the most commonly transmitted DRM.
- 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.

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	Susceptible
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)	Susceptible
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Susceptible

Drug resistance mutation scores of NRTI: Copy to clipboard

Rule	ABC	AZT	FTC	3TC	TDF
L74V	30	0	0	0	0
L74V + M184V	15	0	0	0	0
M184V	15	-10	60	60	-10
Total	60	-10	60	60	-10

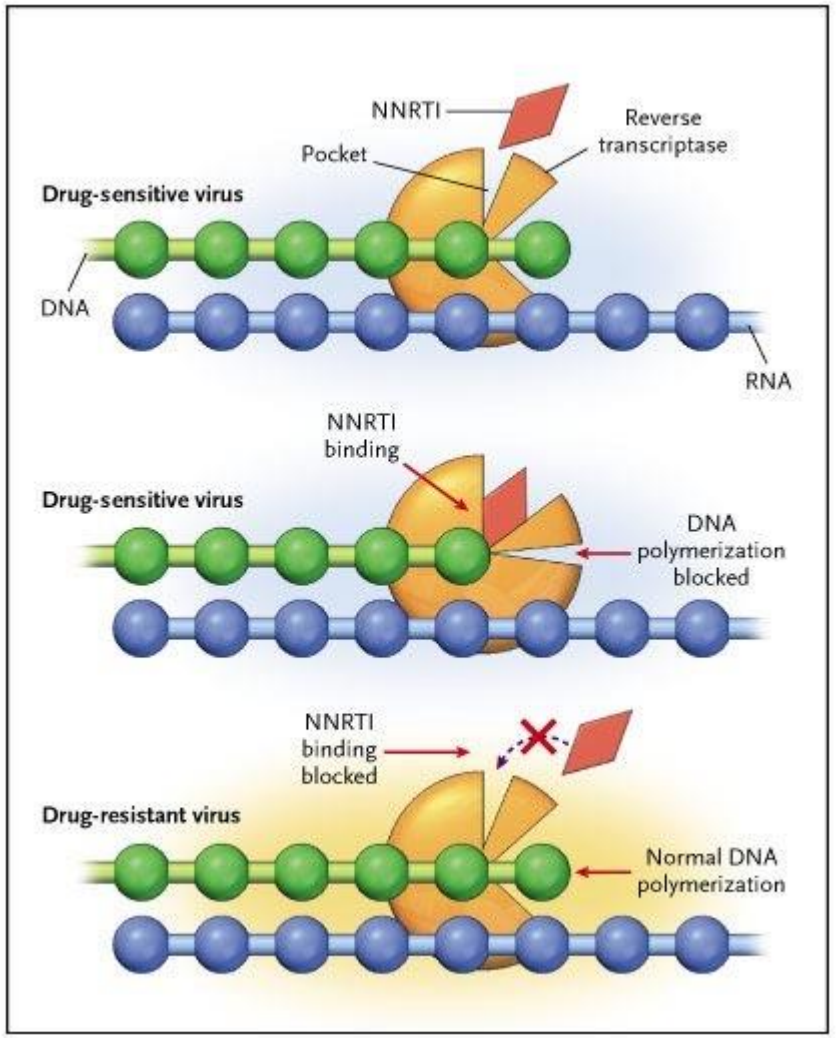
Drug resistance mutation scores of NNRTI: Copy to clipboard

Rule	DOR	EFV	ETR	NVP	RPV
K103N + P225H	10	0	0	0	0
P225H	20	45	0	45	0
K103N	0	60	0	60	0
Total	30	105	0	105	0

Which of the following regimens is the most appropriate for this patient?

1. TDF/FTC+RPV
2. TLD
3. TDF/FTC+ DRV+RTV
4. TLD+ DRV+RTV
5. TLD+ RPV

Designation for mutations

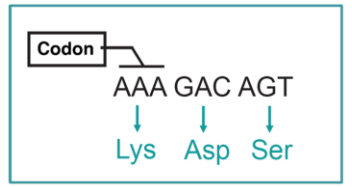


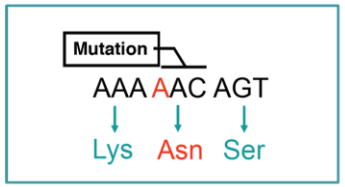
Clavel F, et al. NEJM 2004

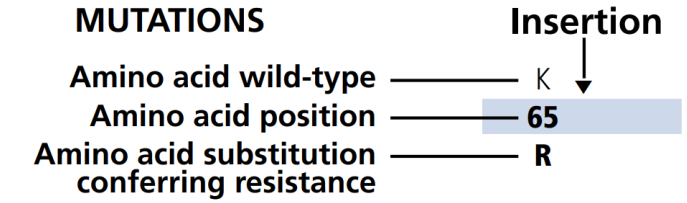
- Viral DNA is a code for RNA which codes for protein
- Each codon encodes a particular amino acid
- Changes in the codon may result in the incorporation of a different amino acid (mutation)
- Mechanism for HIV virus to escape the actions of an antiretroviral medications

Table 1. Amino acids and their abbreviations.

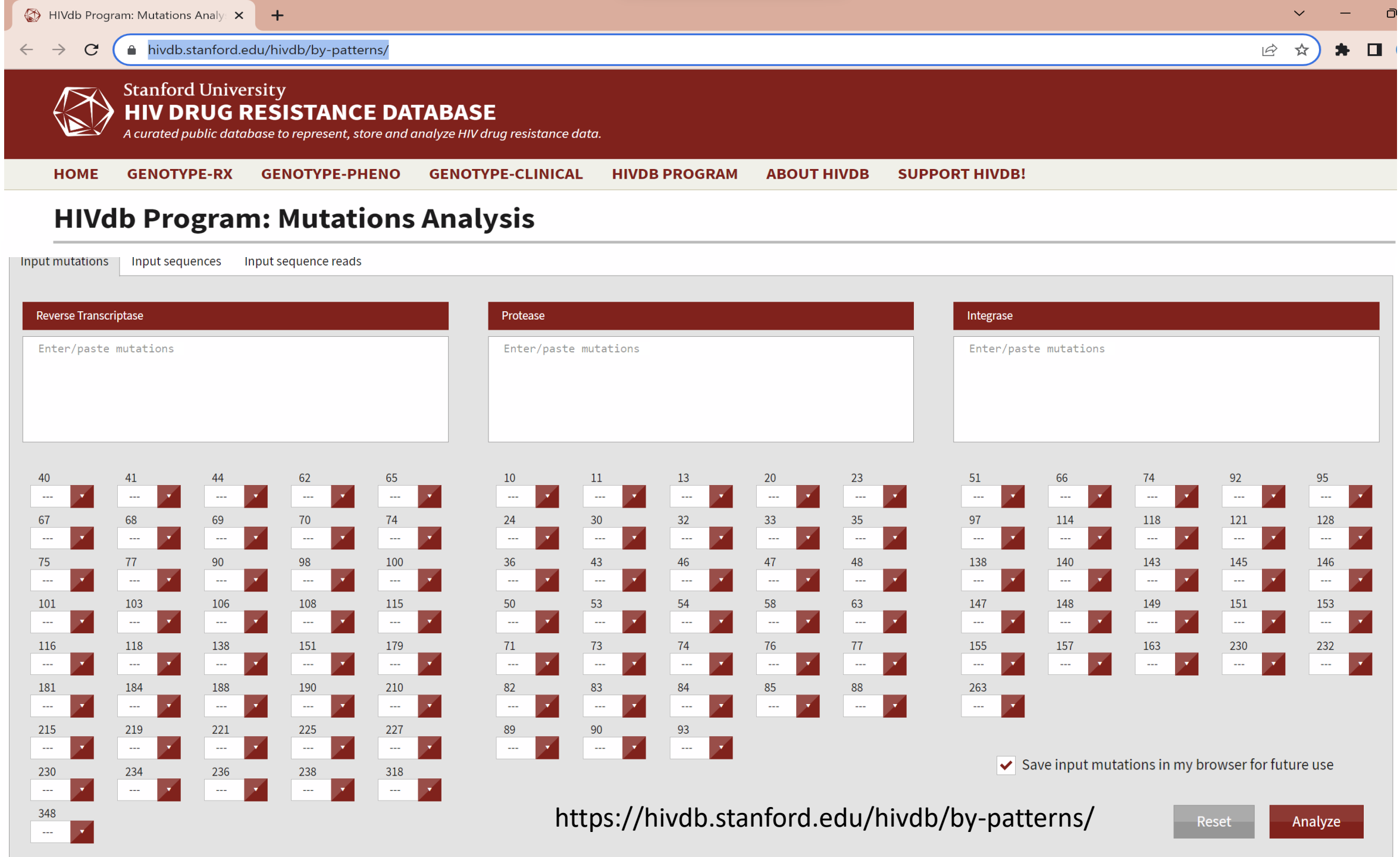
Alanine	A	Methionine	M
Cysteine	C	Asparagine	N
Aspartate	D	Proline	P
Glutamate	E	Glutamine	Q
Phenylalanine	F	Arginine	R
Glycine	G	Serine	S
Histidine	H	Threonine	T
Isoleucine	I	Valine	V
Lysine	K	Tryptophan	W
Leucine	L	Tryosine	Y







https://www.iasusa.org/resources/hiv-drug-resistance-mutations/


HIVdb Program: Mutations Analy
hivdb.stanford.edu/hivdb/by-patterns/
Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.
HOME
GENOTYPE-RX
GENOTYPE-PHENO
GENOTYPE-CLINICAL
HIVDB PROGRAM
ABOUT HIVDB
SUPPORT HIVDB!
HIVdb Program: Mutations Analysis
Input mutations
Input sequences
Input sequence reads
Reverse Transcriptase
Protease
Integrase
Enter/paste mutations
Save input mutations in my browser for future use
https://hivdb.stanford.edu/hivdb/by-patterns/
Reset
Analyze

- The Stanford University HIV Drug Resistance Database also provides helpful guidance for interpreting genotypic resistance test results
- HIVdb program mutation penalty scores
  - Estimated ARV activity by adding the penalties for each DRM in a sequence and converting the total score to 5 interpretations:
  - Score: multiples of 5
    - from -15 (increased activity) to 60 (loss activity)
  - Some have negative penalty scores for certain drugs
    - M184I/V have scores of -10 for AZT, d4T, and tenofovir (TDF)
  - Some combinations of DRMs receive more penalty scores
    - L74I/V and M184I/V have 30 and 15, for abacavir (ABC)
    - L74I/V + M184/V has 15 for ABC. A total penalty score of 60 (30 + 15 + 15): high-level ABC resistance

Susceptible	0-9
Potential low-level resistance	10-14
Low-level resistance	15-29
Intermediate resistance	30-59
High-level resistance	≥60

https://hivdb.stanford.edu/hivdb/by-patterns/

Case 1 A 40-year-old-woman, maid

HIV with HBV coinfection with VF after TDF/FTC/EFV

- Presented with multiple cervical LN 4/45,
  - Anti-HIV+, HBsAg+,CD4 1048
  - Anti-HCV-,TPHA-, VDRL-NR,CXR normal
  - Loss to f/u
- Revisit 7/55 for ANC (G2 GA 18wk)
  - OHL, CD4 224(10%)
  - **1/8/55 TDF+3TC+EFV**
  - **10/8/55 TDF+3TC+LPV/r**
    - HIV VL <40, HBV VL<10
  - **21/11/55 TDF+3TC+EFV**
  - Good adherence
  - HIV VL <40 (55-62)
- HT in the young
  - On amlodipine, losartan
  - Normal PAC,PRA, U/S doppler

- 9/63 HIV VL 77 ยืนยันกินยาตรงเวลาทุกวัน
- 8/64 HIV VL 475
  - Psychosocial problems
  - Missed 1-2 doses/week
- 2/65 HIV VL 4660

Genotypic resistance assay (2/65)	
TDF/FTC/EFV, HIV VL 4660	
NRTIs	**L74I, M184V**
NNRTIs	**K103N, P225H**
PIs	-

- **2/65 TLD+ATV+RTV, can't tolerate N/V**
- **3/65 TLD+RPV, HIV VL<40 (2/65)**
- **12/65 TLD, HIV VL (2/66)<40**

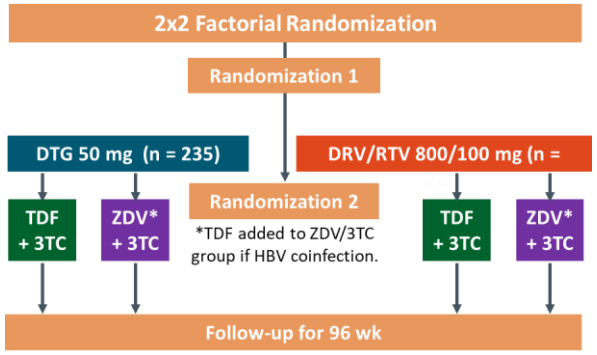
Data in Patients with NRTI Resistance: INSTIs or PIs

DAWNING[1]

- Response rates consistently high with **DTG + 2 NRTIs** regardless of baseline NRTI RAMs to the second-line NRTI
  - HIV-1 RNA <50 copies/mL at Wk 48
    - In patients with BL M184V/I ± other NRTI RAMs receiving 3TC or FTC: 85%
    - In patients with K65R receiving TDF: 86%

NADIA[2,3]

- High response rates with both **DTG and DRV/RTV + 2 NRTIs** regardless of BL NRTI RAMs
- At Wk 96, superiority of TDF vs ZDV2
  - DR: **n = 9 in DTG arm**; **n = 0 in DRV/RTV arm** (P = .0023)
  - **DTG and DRV/RTV both effective, even with no fully active NRTIs**
  - **3TC/TDF** contributed to high levels of efficacy even with **K65R/N, M184V/I**



1. Brown. CROI 2019. Abstr 144. 2. Paton. CROI 2021. Abstr 94LB. 3. Paton. NEJM. 2021;385:330.

Case 2 A 53-year-old-man

HIV with HBV coinfection

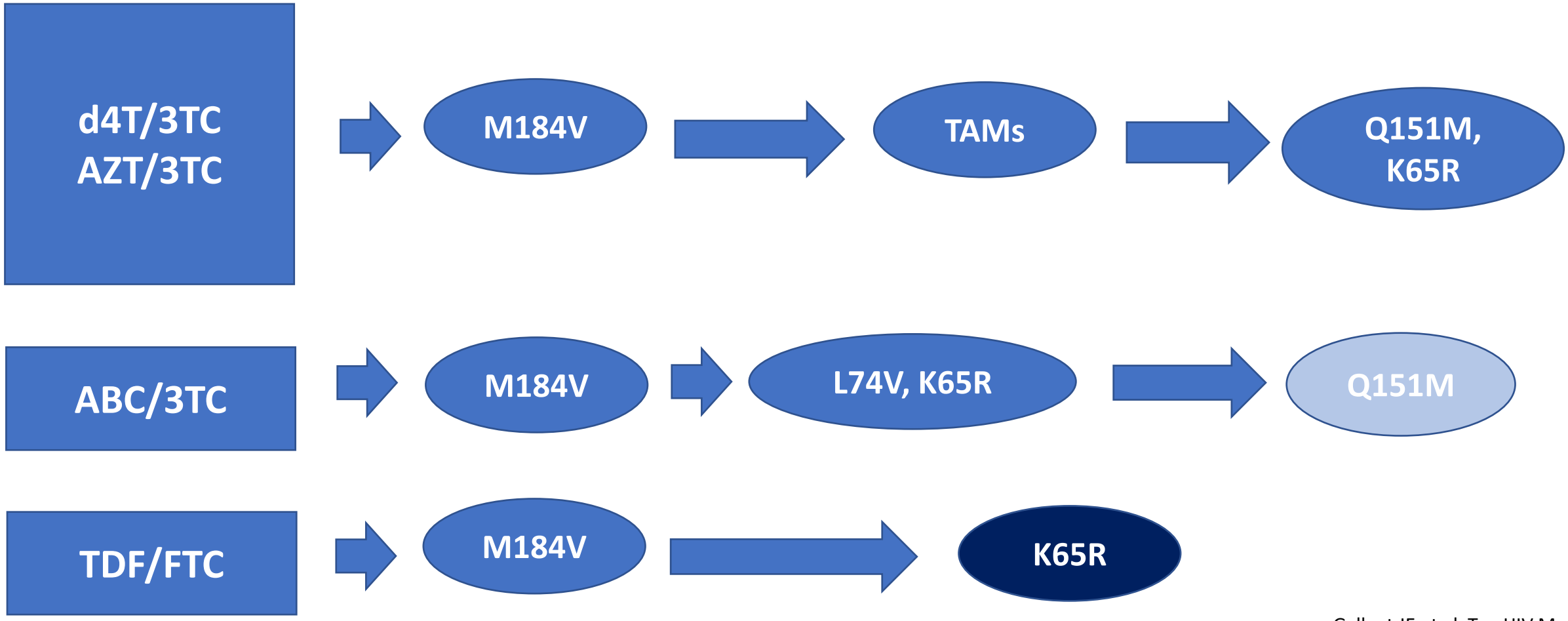
- Presented with pulmonary TB 4/49, treated
  - Multiple heterosexual partners, Tattoo, IDUs
  - Anti-HIV+, CD4 71(3%)
  - HBsAg+, HBeAg-, AntiHBe+
  - Anti-HCV-,TPHA-, VDRL-NR,CXR normal
  - SCrAg-, no CMVR
  - **5/49 GPOvir S**
    - CD4 398(14%),HIV VL<40 (12/49-51)
    - Peripheral neuropathy
  - **8/51 GPOvir Z**
    - Peripheral neuropathy
    - 5/52 HBV VL <6
- **5/52 TDF/FTC+NVP**
  - (5/51-11/61), CD4 597(26%),HIV VL <40
  - HBV VL <10(53-60), normal U/S UA yearly
  - 12/62 CD4 596(26%), HIV VL 67
  - 12/63 CD4 517(22%), HIV VL 156
  - 11/64 CD4 517(22%), HIV VL 1260
  - ยืนยันกินยาตรงเวลาทุกวัน มีช้า 1-3 ชั่วโมงนานๆครั้ง

Which of the following regimens?

1. TLD
2. AZT/3TC+DTG+ entecavir
3. AZT/3TC/TDF+ DTG
4. TLD+ DRV+RTV
5. DTG+DRV+RTV+3TC+ entecavir

Development of resistance patterns after initial failure of NRTI

- Early detection of treatment failure allows more options for the next regimen



Gallant JE,et al. Top HIV Med. 2005

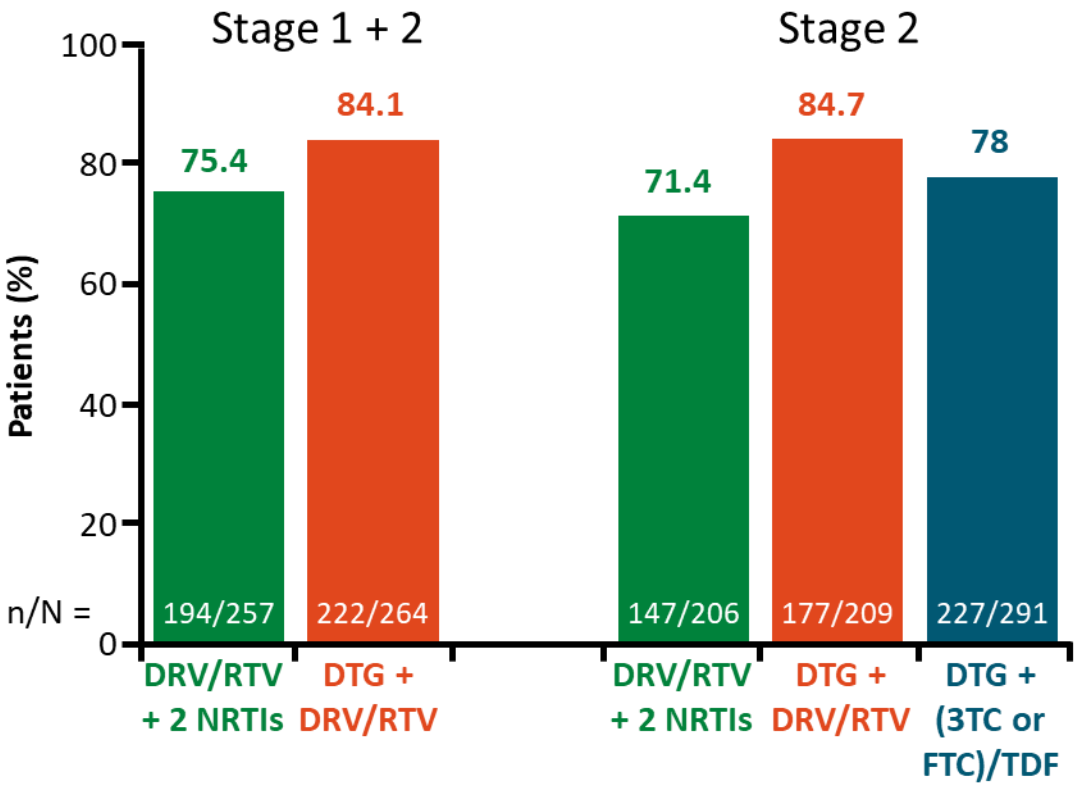
Antiretroviral Options for Patients with VF

Type of Failing Regimen	Resistance Considerations	New Regimen Options
NRTIs + DTG	NRTIs RAMs	2 active NRTIs + DTG or boosted PI Boosted PI + DTG
NRTIs + NNRTI	NNRTIs RAMs	2 active NRTIs + DTG or boosted PI
	NNRTIs RAMs + M184V/I	2 active NRTIs + DTG or boosted PI
	NNRTIs RAMs + multiple NRTIs RAMs	Boosted PI + DTG
NRTIs + Boosted PI	NRTIs RAMs Most likely no resistance or only M184V/I	2 active NRTIs + DTG Boosted PI + NRTIs Boosted PI + DTG

DHHS ART Guidelines. September 2022.
THAI HIV/AIDS Guidelines 2020/2021.

D²EFT: After First-line NNRTI Failure
DTG or DRV/RTV + 2NRTIs, or DRV/RTV + DTG

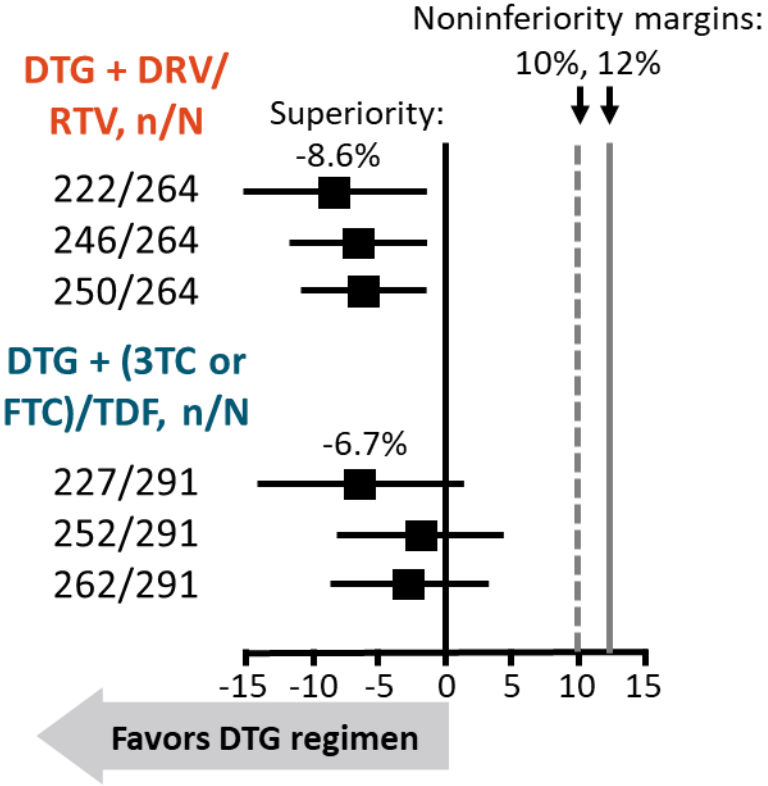
HIV-1 RNA <50 copies/mL at Wk 48



Undetectable HIV-1 RNA at Wk 48 (Available Data)

HIV-1 RNA, c/mL	DRV/RTV + 2 NRTIs, n/N	DTG + DRV/RTV, n/N
<50	194/257	222/264
<200	222/257	246/264
<400	227/257	250/264

HIV-1 RNA, c/mL	DRV/RTV + 2 NRTIs, n/N	DTG + (3TC or FTC)/TDF, n/N
<50	147/206	227/291
<200	174/206	252/291
<400	179/206	262/291



- **DTG + DRV/RTV** and **DTG + (3TC or FTC)/TDF** **non-inferior** to DRV/RTV + 2 NRTIs: all may be effective options after NNRTI failure

Matthews. CROI 2023. Abstr 198.

Case 2 A 53-year-old-man

0-9 susceptible	10-14 Potential low-level	15-29 low-level	30-59 Intermediate	≥60 High-level

HIV/HBV with virological failure

Genotypic resistance assay (12/64)	
TDF/FTC+ NVP, HIV VL 1260	
NRTIs	**K65R, Y115F, M184V, K219E**
NNRTIs	**V90I, V106I, V108I, Y181C**
PIs	**L10I**

NRTI
- K65R confers intermediate reductions in susceptibility to TDF, ABC, and 3TC/FTC. It increases AZT susceptibility. In NRTI-experienced, INSTI-naive patients with K65R, TDF+3TC+DTG is usually highly effective and more effective than AZT/3TC/DTG. However, in patients receiving TDF+3TC+DTG, there is a risk of emergent DTG resistance that does not arise in NRTI-naive patients receiving TDF+3TC+DTG.
- Y115F causes intermediate resistance to ABC and low-level resistance to TDF.
- K219E/Q/N/R are accessory TAMS that usually occur in combination with multiple other TAMs.

NNRTI
- V106I occurs in 1% to 2% of viruses from untreated persons. It contributes to reduced NNRTI susceptibility only in combination with other NNRTI-resistance mutations.
- V108I is a relatively non-polymorphic accessory mutation selected in vitro and/or in vivo with each of the NNRTIs. It appears to contribute to reduced susceptibility to most NNRTIs only in combination with other NNRTI-resistance mutations.
- Y181C is a non-polymorphic mutation selected in persons receiving NVP, ETR and RPV. It confers high-level resistance to NVP, intermediate resistance to ETR and RPV, and low-level resistance to EFV. It does not significantly reduce DOR susceptibility.

Other
- 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

Nucleoside Reverse Transcriptase Inhibitors

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

Non-nucleoside Reverse Transcriptase Inhibitors

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

Rule	ABC	AZT	FTC	3TC	TDF
K65R	45	-10	30	30	50
Y115F	30	0	0	0	15
Y115F + M184V	15	0	0	0	5
M184V	15	-10	60	60	-10
K219E	5	10	0	0	5
Total	110	-10	90	90	65

Rule	DOR	EFV	ETR	NVP	RPV
V106I	10	0	10	10	10
V106I + Y181C	5	0	0	0	10
V108I	10	10	0	15	0
V108I + Y181C	5	0	0	0	0
Y181C	10	30	30	60	45
Total	40	40	40	85	65

Which of the following regimens is the most appropriate for this patient?

1. AZT/3TC+DTG+Entecavir
2. AZT/3TC+DRV+RTV+Entecavir
3. TDF/FTC+DRV+RTV
4. TLD+AZT
5. TLD+ DRV+RTV

DHHS: Selection of New ART Regimen

1 ✕

Adding only **1 ARV** to a failing regimen is **not recommended**

2 ✓

Can include **2 fully active ARVs** if **≥1** of them has a high resistance barrier (eg, **DTG, boosted DRV** or **possibly BIC**); In some instances, can consider 1 fully active ARV with a high resistance barrier with 2 partially active NRTIs

3 ✓

It is preferrable to include **3 fully active ARVs** if **none** of them has a high resistance barrier

- Definition of **fully active:**
  - No predicted resistance based on treatment history or resistance testing
  - Novel mechanism of action
  - May include newer members of existing drug classes that remain fully active against isolates that are resistant to older drugs (ETR, DRV, DTG, and possibly DOR and BIC)

DHHS ART Guidelines. September 2022.

Case 2 A 53-year-old-man

HIV with HBV coinfection with virological failure after TDF/FTC+NVP

- Presented with pulmonary TB 4/49, treated
  - Multiple heterosexual partners, Tattoo, IDUs
  - Anti-HIV+, CD4 71(3%)
  - HBsAg+, HBeAg-, AntiHBe+
  - Anti-HCV-,TPHA-, VDRL-NR,CXR normal
  - SCrAg-, no CMVR
  - **5/49 GPOvir S**
    - CD4 398(14%),HIV VL<40 (12/49-51)
    - Peripheral neuropathy
  - **8/51 GPOvir Z**
    - Peripheral neuropathy
    - 5/52 HBV VL <6
- **5/52 TDF/FTC+NVP**
  - (5/51-11/61), CD4 597(26%),HIV VL <40
  - HBV VL <10(53-60), normal U/S UA yearly
  - 12/62 CD4 596(26%), HIV VL 67
  - 12/63 CD4 517(22%), HIV VL 156
  - 11/64 CD4 517(22%), HIV VL 1260
  - ยืนยันกินยาตรงเวลาทุกวัน มีช้า 1-3 ชั่วโมงนานๆครั้ง

Genotypic resistance assay (12/64)	
TDF/FTC+ NVP, HIV VL 1260	
NRTIs	**K65R, Y115F, M184V, K219E**
NNRTIs	**V90I, V106I, V108I, Y181C**
PIs	**L10I**

- **11/64 AZT/3TC+DTG+TDF**
  - 3/65 HIV VL<40, HBV VL<10

Case 3 A 23-year-old-woman, fruit vendor

HIV infection with pregnancy

- Diagnosed from ANC 62(P2)
  - Anti-HIV+, CD4 371(27%)
  - HBsAg-,Anti-HCV-,TPHA-, VDRL-NR
  - CXR normal
- **4/62 TDF/FTC+LPV/r** คลื่นไส้อาเจียน
  - 10/62 CD4 740(28%), HIV VL 10,744
- **1/63 TDF/FTC+ATV+RTV**
  - DRM:none บุตรไม่ติดเชื้อ ทำหมันแล้ว
  - Loss to f/u, move to BKK
- **1/12/64 First visit at ANC clinic (G3P2 GA 12wk)**
  - HBsAg-,TPHA-, CBC normal
  - สามีเป็นคนที่สาม ผลเลือดHIVปกติ*2
  - **Start TAF/FTC/DTG 1*1 PO 17.00**
- 22/12/64 Vitamin B6,FERLI-6 1*1 PO 8.00
- 3/2/65 GA 15^{+5}wk
  - CD4 548(29%),HIV VL <200
- 11/5/65 GA 37wk, HIV VL 91,390 (EDC 9/6/65)
  - ยืนยันกินยาตรงเวลาทุกวัน มีกินช้า 1-3 ชั่วโมงนานๆครั้ง

- **What is your management?**
- **Which regimens will you choose for this patient?**
  1. **Continue + adherence counseling**
  2. **TLD+ AZT+ DTG**
  3. **TLD+ DRV 800 OD+ RTV**
  4. **TLD+ DRV 600 bid+ RTV**
  5. **AZT/3TC+ DRV 600 bid+ RTV**
  6. **AZT/3TC+DRV 600 bid+ RTV+ DTG bid**
- **When will you repeat HIV VL?**
- **Route of delivery: cesarian section?**
- **High-risk new born?**

PREGNANCY AND PHARMACOKINETIC

Increase gastric emptying time
Decrease intestinal motility

Increase total body water
Decrease albumin

Increase CYP450 metabolism
from progesterone

Increase renal blood flow

Absorption ↓

Distribution

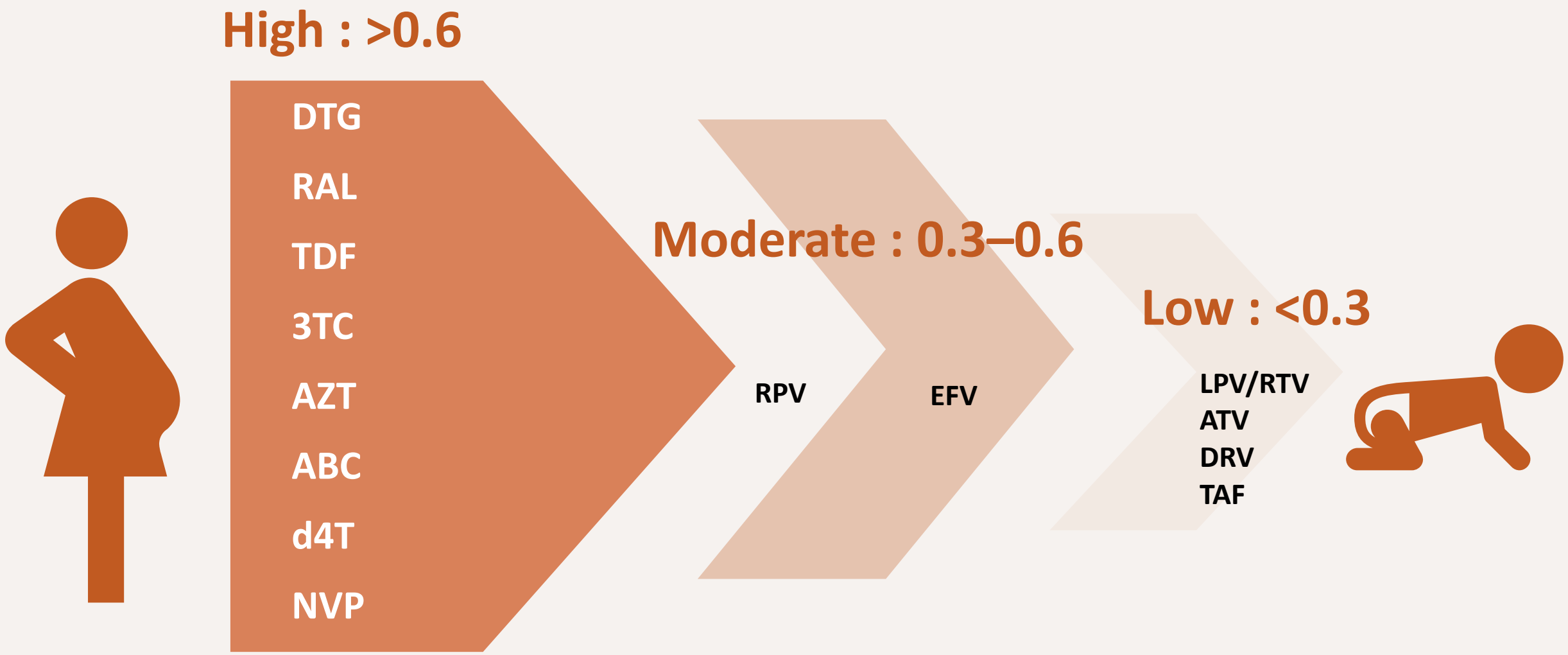
Metabolism

Elimination ↑

In second and third trimester, concentration of some drugs cannot be achieved

PLACENTAL TRANSFER

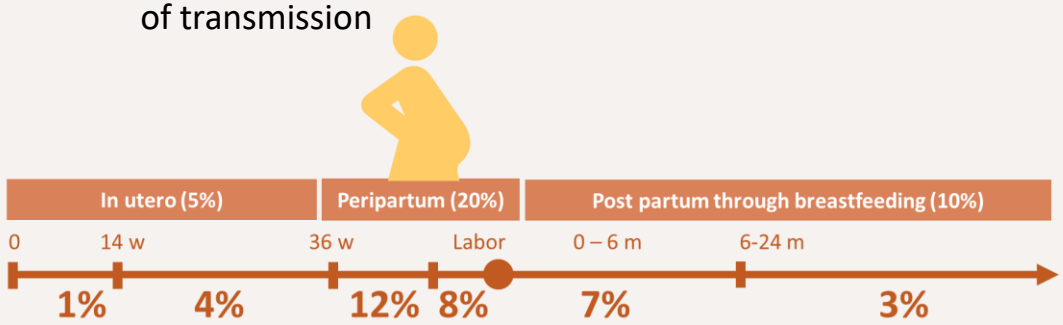
by mean or median cord blood/maternal delivery plasma drug ratio:



ART in late pregnancy: benefits and consideration

Benefits to Achieving and Maintaining Viral Suppression

- **Prevent MTCT in Utero, Labor and Delivery**
  - ART initiation in 3rd vs 1st,2nd trimester increases risk of MTCT 7-fold and infant mortality within the first yr 2-fold
  - Higher maternal viral loads associated with increased risk of transmission



- Optimize maternal health
- Prevent transmission to partner

What to consider?

Pregnancy-related

- Teratogenic
- Experience and data with use in pregnancy
- Pharmacokinetic changes: **DRV/RTV**, RPV
- Potential adverse events: LPV/RTV, EFV

Individual-related

- Drug interactions:
  - Supplements:CaCO3,FeSO4 (DTG ↓)
  - PPIs, H2A(RPV,ATV↓)
  - Methergine in postpartum bleeding (PIs↑), etc.
- ART resistance and experience
- Comorbidities: CKD, depression, etc
- Adherence: taken with a meal
- Convenience: once-daily, STR

De Cock KM,et al. JAMA. 2000 Mar 1;283(9)

Same day ART initiation in first diagnosed HIV in pregnant woman

Prefer TFX+XTC+DTG

GA < 20 wk

HIV RNA at GA 32 wk

- HIV RNA ≤ 50 → Continue same regimen
- HIV RNA > 50-1,000 → Counseling + Advise adherence
- HIV RNA > 1,000
  - DTG based → Counseling+ Advise adherence
  - Non-DTG based → TXF+XTC+DTG or add DTG as 4th drug (RAL)

GA ≥ 20 wk

HIV RNA at GA 32-36 wk and on ART > 12 wk

- HIV RNA ≤ 50 → Continue same regimen
- HIV RNA > 50-1,000 → Counseling + Advise adherence
- HIV RNA > 1,000
  - DTG based → Counseling+ Advise adherence
  - Non-DTG based → TXF+XTC+DTG or add DTG as 4th drug (RAL)

HIV RNA 4 weeks later after adhering well to ART
or at 36 weeks gestation if no HIV RNA result

At GA 32-36 wk, HIV RNA> 1,000, prefer cesarian section

At delivery, add AZT 600 mg STAT if HIV RNA at 32–36 weeks gestation not < 50 copies/mL + AZT/3TC+NVP (Newborn)

Thailand national guidelines on HIV/AIDS diagnosis, treatment and prevention 2021.

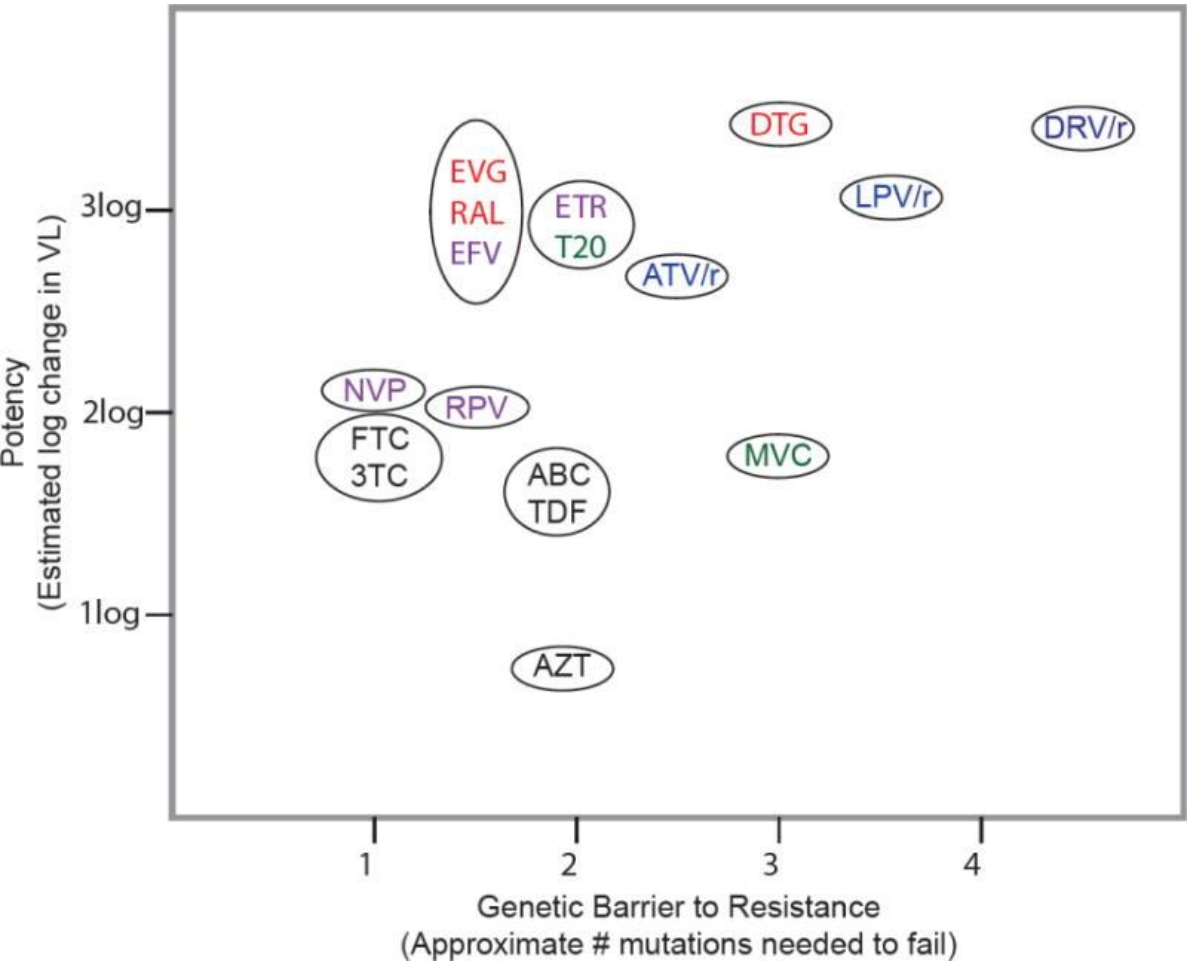
No role of single dose NVP anymore

Drug interaction: dolutegravir(DTG)

ART	Effect	Recommendations
Rifampicin	DTG AUC ↓ 54%, Cmin ↓ 72%	Use DTG 50 mg twice daily (instead of DTG 50 mg once daily)
Metformin	Metformin AUC ↑ 79%, Cmax ↑66% Inhibition of metformin renal excretion by organic cation transporter 2	Start metformin at lowest dose and titrated based on glycemic control. Monitor for adverse effect of metformin. Maximum metformin should not exceed 1,000 mg/day
Al, Mg, +/- Ca-containing antacid	DTG AUC ↓ 74% simultaneously	Administer **DTG at least 2 hours before or at least 6 hours after**
Polyvalent Cation Supplements Mg, Al, Fe, Ca, Zn, including multivitamins with minerals	DTG AUC ↓ 39% if administered simultaneously with **CaCO3** under fasting conditions DTG AUC ↓ 54% if administered simultaneously with **Fe** under fasting conditions ↔ DTG when administered with Ca or Fe supplement simultaneously with food	**With Supplements That Contain Ca or Fe:** Administer DTG and supplements that contain Ca or Fe together with food, or administer DTG at least 2 hours before or at least 6 hours after supplement Do not coadminister DTG under fasting conditions simultaneously with, or 2 hours after, supplements that contain Ca or Fe

DHHS ART Guidelines. September 2022.

ARV potency versus genetic barrier to resistance



- **IMPORTANT: identify and address the underlying reason for VF**

- Comorbidities
- Unstable housing
- Psychosocial factors
- Missed clinic appointments
- Interruption, or intermittent access ART
- Incomplete adherence
- Cost and affordability
- Adverse drug effects
- High pill burden
- Dosing frequency

- Adverse events
- Suboptimal PKs
- Suboptimal potency
- Low barrier to resistance
- Prior exposure to suboptimal regimens
- Food requirements
- Drug–drug interactions
- Prescription errors

Clutter DS, et al. Infect Genet Evol. 2016

Case 3 A 23-year-old-woman, fruit vendor

HIV infection with pregnancy

- Diagnosed from ANC 62(P2)
  - Anti-HIV+, CD4 371(27%)
  - HBsAg-,Anti-HCV-,TPHA-, VDRL-NR
  - CXR normal
- **4/62 TDF/FTC+LPV/r** คลื่นไส้อาเจียน
  - 10/62 CD4 740(28%), HIV VL 10,744
- **1/63 TDF/FTC+ATV+RTV**
  - DRM:none บุตรไม่ติดเชื้อ ทำหมันแล้ว
  - Loss to f/u, move to BKK
- **1/12/64 First visit at ANC clinic (G3P2 GA 12wk)**
  - HBsAg-,TPHA-, CBC normal
  - สามีเป็นคนที่สาม ผลเลือดHIVปกติ*2
  - **Start TAF/FTC/DTG 1*1 PO 17.00**
- 22/12/64 Vitamin B6,FERLI-6 1*1 PO 8.00
- 3/2/65 GA 15^{+5}wk
  - CD4 548(29%),HIV VL <200
- 11/5/65 GA 37wk, HIV VL 91,390 (EDC 9/6/65)
  - ยืนยันกินยาตรงเวลาทุกวัน มีกินช้า 1-3 ชั่วโมงนานๆครั้ง
  - **TAF/FTC/DTG+AZT+RPV**
- 20/5/65 GA 38wk, HIV VL 902 (DRM: none)
- 2/6/65 GA 39wk, HIV VL 92
  - Elective C/S with bilateral salpingectomy (Failed TS)
  - Male 3070g, APGAR 8,9

Genotypic resistance assay (5/65)	
TAF/FTC/DTG, HIV VL 902	
NRTIs	-
NNRTIs	-
PIs	-
INSTIs	-

Which regimens will you choose for this patient?

Case 3 A 23-year-old-woman, fruit vendor

HIV infection with pregnancy

- Diagnosed from ANC 62(P2)
  - Anti-HIV+, CD4 371(27%)
  - HBsAg-,Anti-HCV-,TPHA-, VDRL-NR
  - CXR normal
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  - DRM:none บุตรไม่ติดเชื้อ ทำหมันแล้ว
  - Loss to f/u, move to BKK
- **1/12/64** First visit at ANC clinic (G3P2 GA 12wk)
  - HBsAg-,TPHA-, CBC normal
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  - **TAF/FTC/DTG+AZT+RPV**
- 20/5/65 GA 38wk, HIV VL 902 (DRM: none)
- 2/6/65 GA 39wk, HIV VL 92
  - Elective C/S with bilateral salpingectomy (Failed TS)
  - Male 3070g, APGAR 8,9 on AZT+3TC+NVP
  - **Negative for HIV PCR at 0,2,4m**
- 16/9/65 Postpartum 3m, good adherence
  - ทิ้งยาไว้ในรถยนต์ตอนไปเยี่ยมบ้านสามีที่สุพรรณบุรี
  - ออกไปกินยาในรถ จอดรถกลางแดด 1-17/4/65
- 4/10/65 Postpartum 4m, good adherence
  - CD4 572(19%), HIV VL 53,390 (11/65)
  - ขอดูกล่องยา พบว่าชื้นมาก มีมดขึ้น ผู้ป่วยเก็บซ่อนในตู้เสื้อผ้ากลัวแม่สามีทำความสะอาดบ้านแล้วสงสัย

Which regimens will you choose for this patient?

Case 3 A 23-year-old-woman, fruit vendor

HIV infection with pregnancy

- Diagnosed from ANC 62(P2)
  - Anti-HIV+, CD4 371(27%)
  - HBsAg-,Anti-HCV-,TPHA-, VDRL-NR
  - CXR normal
- **4/62 TDF/FTC+LPV/r** คลื่นไส้อาเจียน
  - 10/62 CD4 740(28%), HIV VL 10,744
- **1/63 TDF/FTC+ATV+RTV**
  - DRM:none บุตรไม่ติดเชื้อ ทำหมันแล้ว
  - Loss to f/u, move to BKK
- **1/12/64** First visit at ANC clinic (G3P2 GA 12wk)
  - HBsAg-,TPHA-, CBC normal
  - สามีเป็นคนที่สาม ผลเลือดHIVปกติ*2
  - **Start TAF/FTC/DTG 1*1 PO 17.00**
- 22/12/64 Vitamin B6,FERLI-6 1*1 PO 8.00
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  - ยืนยันกินยาตรงเวลาทุกวัน มีกินช้า 1-3 ชั่วโมงนานๆครั้ง
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  - CD4 572(19%), HIV VL 53,390
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- **1/11/65 TLD+DRV+RTV**

Case 4 A 39-year-old-woman

HIV infection with TB with multiclass ARV resistance

- Diagnosed from ANC 42(P2)
  - Anti-HIV+, CD4 371(27%)
  - HBsAg-,Anti-HCV-,TPHA-, VDRL-NR
  - CXR normal
- **GPOvirZ 250 4-5y, loss 1y** ย้ายงานไปชลบุรี
- **AZT/3TC+LPV/r 4y, loss f/u** ขาดยา
- **17/4-5/5/59 TDF/FTC/EFV** ผื่นขึ้นทั้งตัวจนต้องหยุดยา
- **11/6-5/61 TDF/FTC+LPV/r** สิทธิ์ปกส.ขาด 4 เดือน
- **9-10/61 TDF/FTC+LPV/r** ขาดยา
- **10/61 revisit with PCP pneumonia,** ปกส.รพ.เดิม
  - Prolonged fever, generalizedLN, cough, BW 43->39kg
  - CXR: bilateral reticulonodular infiltration
  - Sputum AFB*3 neg, **PCR TB+** (LPA no resistance)
  - **10/61 CD4 129(12%), HIV VL 562,463** (ไม่ทราบDR)
  - **AZT/3TC+LPV/r**
- 11/61 Dx disseminated TB
  - **HRZE(11/61)-> HZE(12/61)->HZEL(7/62)->HR(9/62)**
- 12/61 High grade fever, LN progression, abdominal pain
  - CT WA: hepatomegaly, periaortic, mesenteric LN
  - s/p LN Bx*3 (12/61,1/62,5/62,8/62)
    - Patho: necrotizing granulomatous LN
    - negative for AFB,PCR-C/S TB, fungal C/S
- **3/62 CD4 48(12%), HIV VL 235,424**
- Dx Disseminated TB with IRIS
  - Add prednisolone
  - BW 42-> 50kg (4/62)
  - DRM(4/62):

Genotypic resistance assay (4/62)	
AZT/3TC+LPV/r, HIV VL 235,424	
RT TAMs **RT NRTIs**	**D67N, K70R, T215F, K219E** **A62V, D67N, K70R, F77L, M184V,T215F, K219E**
NNRTIs	**-**
PIs major **PIs accessory**	**I54V, V82A** **L10F, V32T**
INSTIs	**-**

Which regimens will you choose for this patient?

กลุ่มอาการอักเสบจากภาวะฟื้นตัวของระบบภูมิคุ้มกัน (immune reconstitution inflammatory syndrome: IRIS)

- เกิดจากการฟื้นตัวอย่างรวดเร็วของระบบภูมิคุ้มกันต่อเชื้อวัณโรคส่งผลให้เกิดการตอบสนองของการอักเสบที่รุนแรงต่อเชื้อก่อโรคหรือแอนติเจนที่ยังหลงเหลืออยู่ทั้งที่ยังมีชีวิตและเป็นซากที่ตายแล้ว
- มักเกิดหลังเริ่มยาต้านเอชไอวีใน 3 เดือนแรก
- ยังไม่มีการทดสอบทางห้องปฏิบัติการที่ใช้ในการวินิจฉัยได้โดยตรง ต้องตัดสาเหตุอื่นๆออก ได้แก่
  - วัณโรคดื้อยา, การไม่กินยาวัณโรคของผู้ป่วย,ระดับยารักษาในร่างกายไม่เพียงพอเนื่องจากปฏิกริยาระหว่างยา หรือ
  - การติดเชื้อฉวยโอกาสใหม่หรือภาวะความเจ็บป่วยใหม่ หรือ
  - ความล้มเหลวของยาต้านเอชไอวี

Unmasking IRIS	ภาวะที่เกิดจากเชื้อวัณโรคที่ซ่อนอยู่ แสดงอาการหลังเริ่มยาต้านเอชไอวีไม่นาน
Paradoxical IRIS	ภาวะที่มีอาการทรุดลงของวัณโรคหลังเริ่มยาต้านเอชไอวี

- การรักษา ให้ยาต้านการอักเสบ (non-steroidal drugs หรือ systemic corticosteroids) ตามแต่ความรุนแรง
  - ขนาด prednisolone 1 มก./กก./วัน และค่อยลดขนาดยาทุก 2 สัปดาห์ จนหยุดยาได้ภายในระยะเวลา 4-8 สัปดาห์
- ให้การรักษาวัณโรคและยาต้านเอชไอวีต่อเนื่อง โดยไม่ต้องมีการปรับชนิดและขนาดของยา

Case 4 A 39-year-old-woman

HIV infection with TB with multiclass ARV resistance

0-9 susceptible	10-14 Potential low-level	15-29 low-level	30-59 Intermediate	≥60 High-level

Genotypic resistance assay (4/62)	
AZT/3TC+LPV/r, HIV VL 235,424	
RT TAMs	**D67N, K70R, T215F, K219E**
RT NRTIs	**A62V, D67N, K70R, F77L, M184V,T215F, K219E**
NNRTIs	**-**
PIs major	**I54V, V82A**
PIs accessory	**L10F, V32T**
INSTIs	**-**

NRTI
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.
D67N is a non-polymorphic TAM associated with low-level resistance to AZT.
K70R is a TAM that confers intermediate resistance to AZT and contributes to reduced ABC and TDF susceptibility in combination with other TAMs.
F77L usually occurs in combination with the multi-NRTI resistance mutation Q151M. When it occurs alone, its clinical significance is uncertain.
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.
T215Y/F are TAMs that causes intermediate/high-level resistance to AZT and potentially low-level resistance to ABC and TDF.
K219E/Q/N/R are accessory TAMS that usually occur in combination with multiple other TAMs.
PR comments
Major
I54V is a non-polymorphic PI-selected mutation that contributes reduced susceptibility to each of the PIs except DRV.
V82A is a non-polymorphic mutation selected primarily by IDV and LPV. It is associated with reduced susceptibility to LPV and to a lesser extent ATV. It increases DRV susceptibility.
Accessory
L10F is a common non-polymorphic, PI-selected accessory mutation associated with reduced in vitro susceptibility to LPV and DRV.

Rule	ABC	AZT	FTC	3TC	TDF
A62V	5	5	0	0	5
D67N	5	15	0	0	5
D67N + K70R + M184V + K219E	10	0	0	0	0
D67N + K70R + K219E	10	15	10	10	10
D67N + T215F + K219E	5	5	0	0	5
K70R	5	30	0	0	5
F77L	5	10	5	5	5
M184V	15	-10	60	60	-10
T215F	10	60	0	0	10
K219E	5	10	0	0	5
K70R + T215F	0	0	0	0	0
Total	75	140	75	75	40

Rule	ATV/r	DRV/r	LPV/r
I54V	15	0	15
I54V + V82A	10	0	10
V82A	15	0	30
L10F	0	5	5
Total	40	5	60

Nucleoside Reverse Transcriptase Inhibitors

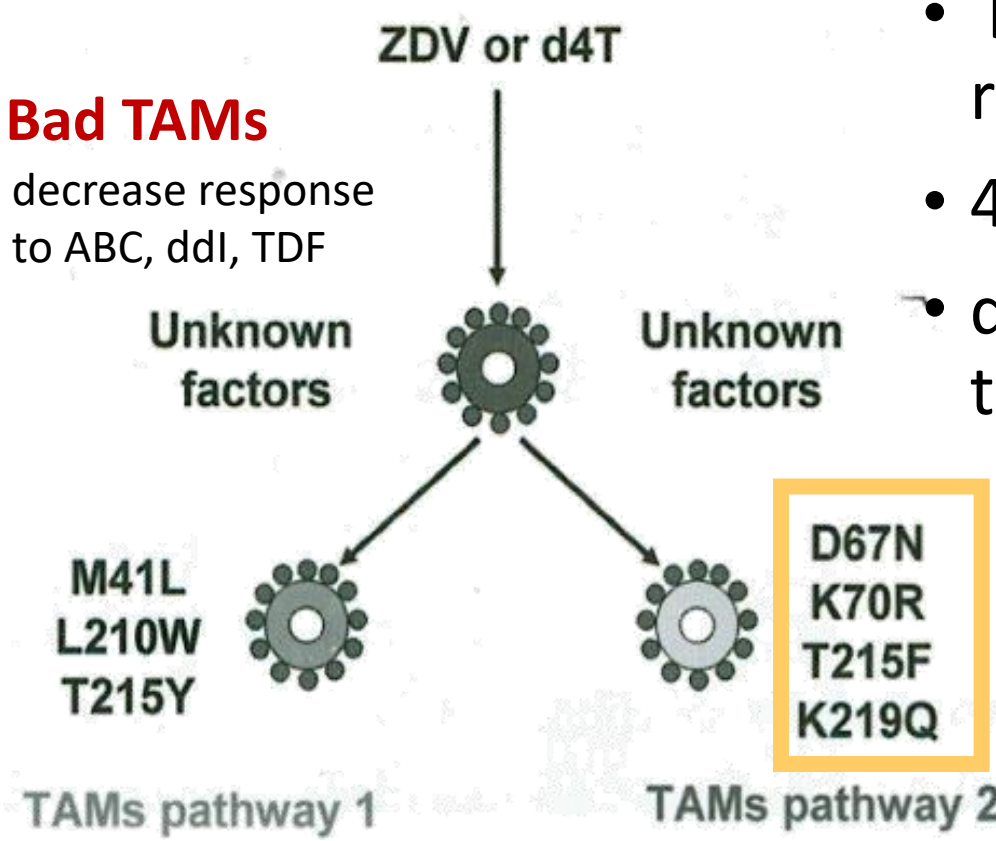
abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	High-Level Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Intermediate Resistance

Protease Inhibitors

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

Which regimens will you choose for this patient?

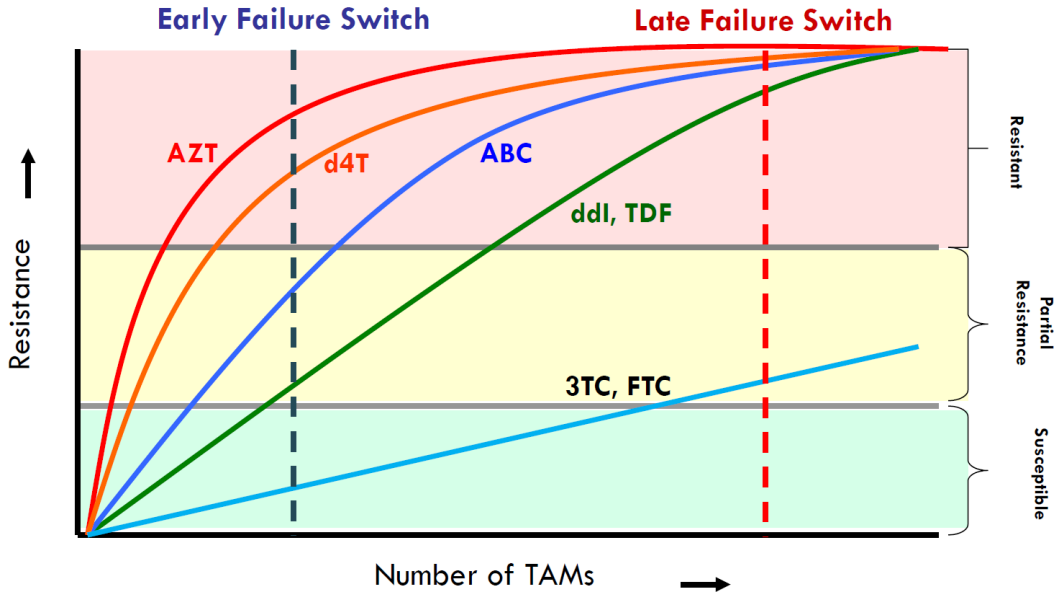
Thymidine Analogue associated Mutations (TAMs) pathways



Higher level AZT resistance
More NRTI cross resistance

Lower level AZT resistance
Less NRTI cross resistance

- Emerge sequentially with AZT, d4T containing regimen after M184V
- 41, 67, 70, 210, 215, 219
- delayed detection of virological failure may lead to accumulation of more TAMs



Case 4 A 39-year-old-woman

HIV infection with TB with multiclass ARV resistance

- Diagnosed from ANC 42(P2)
  - Anti-HIV+, CD4 371(27%)
  - HBsAg-,Anti-HCV-,TPHA-, VDRL-NR
  - CXR normal
- **GPOvirZ 250 4-5y, loss 1y** ย้ายงานไปชลบุรี
- **AZT/3TC+LPV/r 4y, loss f/u** ขาดยา
- **17/4-5/5/59 TDF/FTC/EFV** ผื่นขึ้นทั้งตัวจนต้องหยุดยา
- **11/6-5/61 TDF/FTC+LPV/r** สิทธิ์ปกส.ขาด 4 เดือน
- **9-10/61 TDF/FTC+LPV/r** ขาดยา
- **10/61 revisit with PCP pneumonia,** ปกส.รพ.เดิม
  - Prolonged fever, generalizedLN, cough, BW 43->39kg
  - CXR: bilateral reticulonodular infiltration
  - Sputum AFB*3 neg, **PCR TB+** (LPA no resistance)
  - **10/61 CD4 129(12%), HIV VL 562,463** (ไม่ทราบDR)
  - **AZT/3TC+LPV/r**
- 11/61 Dx disseminated TB
  - **HRZE(11/61)-> HZE(12/61)->HZEL(7/62)->HR(9/62)**
- 12/61 High grade fever, LN progression, abdominal pain
  - CT WA: hepatomegaly, periaortic, mesenteric LN
  - s/p LN Bx*3 (12/61,1/62,5/62,8/62)
    - Patho: necrotizing granulomatous LN
    - negative for AFB,PCR-C/S TB, fungal C/S
- **3/62 CD4 48(12%), HIV VL 235,424**
- Dx Disseminated TB with IRIS
  - Add prednisolone
  - BW 42-> 50kg (4/62)
  - DRM(4/62):NRTIs,PIs resistance
- **8/62 TDF/FTC+RAL(400) bid+ HR (9/62-5/63)**
  - 10/62 CD4 286(19%), HIV VL 58
  - **5/63 CD4 258(14%), HIV VL 10,544**

Genotypic resistance assay (5/63)	
TDF/FTC+ RAL(400) bid+ HR, HIV VL 10,544	
RT NRTIs	ประวัติหาย ไม่สามารถตามได้คะ
PIs major **PIs accessory**	**M46I, I54V, V82A** **L10F**
INSTIs major **INSTIs accessory**	**G140A, Q148R** **D232N**

Which regimens?

Case 4 A 39-year-old-woman

HIV infection with TB with multiclass ARV resistance

- Diagnosed from ANC 42(P2)
  - Anti-HIV+, CD4 371(27%)
  - HBsAg-,Anti-HCV-,TPHA-, VDRL-NR
  - CXR normal
- **GPOvirZ250 4-5y, loss 1y** ย้ายงานไปชลบุรี
- **AZT/3TC+LPV/r 4y, loss f/u**
- **17/4-5/5/59 TDF/FTC/EFV** ผื่นขึ้นทั้งตัวจนต้องหยุดยา
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- **10/61 PCP pneumonia, AZT/3TC+LPV/r** ปกส.
  - Prolonged fever, generalizedLN, cough, BW 43->39kg
  - CXR: bilateral reticulonodular infiltration
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- Dx DisseminatedTB with IRIS
  - Add prednisolone, BW 42-> 50kg(4/62)
  - DRM(4/62) NRTIs,PIs resistance
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Genotypic resistance assay (5/63)	
TDF/FTC+ RAL(400) bid+ HR, HIV VL 10,544	
RT NRTIs	ประวัติหาย ไม่สามารถตามได้คะ
NNRTIs	-
PIs major **PIs accessory**	**M46I, I54V, V82A** **L10F**
INSTIs major **INSTIs accessory**	**G140A, Q148R** **D232N**

Which regimens?

Case 4 A 39-year-old-woman

HIV infection with TB with multiclass ARV resistance

0-9 susceptible	10-14 Potential low-level	15-29 low-level	30-59 Intermediate	≥60 High-level

Genotypic resistance assay (4/62)	
AZT/3TC+LPV/r, HIV VL 235,424	
RT TAMs RT NRTIs	D67N, K70R, T215F, K219E A62V, D67N, K70R, F77L, M184V,T215F, K219E
NNRTIs	-
PIs major PIs accessory	I54V, V82A L10F, V32T
INSTIs	-

Rule	ABC	AZT	FTC	3TC	TDF
A62V	5	5	0	0	5
D67N	5	15	0	0	5
D67N + K70R + M184V + K219E	10	0	0	0	0
D67N + K70R + K219E	10	15	10	10	10
D67N + T215F + K219E	5	5	0	0	5
K70R	5	30	0	0	5
F77L	5	10	5	5	5
M184V	15	-10	60	60	-10
T215F	10	60	0	0	10
K219E	5	10	0	0	5
K70R + T215F	0	0	0	0	0
Total	75	140	75	75	40

Genotypic resistance assay (5/63)	
TDF/FTC+ RAL(400) bid+ HR, HIV VL 10,544	
PIs major PIs accessory	M46I, I54V, V82A L10F
INSTIs major INSTIs accessory	G140A, Q148R D232N

Rule	ATV/r	DRV/r	LPV/r
M46I	10	0	10
M46I + V82A	10	0	10
I54V	15	0	15
I54V + V82A	10	0	10
V82A	15	0	30
L10F	0	5	5
Total	60	5	80

Rule	BIC	CAB	DTG	EVG	RAL
G140A	10	10	10	30	30
G140A + Q148R	10	20	10	0	0
Q148R	25	40	25	60	60
D232N	0	0	0	10	10
Total	45	70	45	100	100

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Intermediate Resistance
cabotegravir (CAB)	High-Level Resistance
dolutegravir (DTG)	Intermediate Resistance
elvitegravir (EVG)	High-Level Resistance
raltegravir (RAL)	High-Level Resistance

Protease Inhibitors

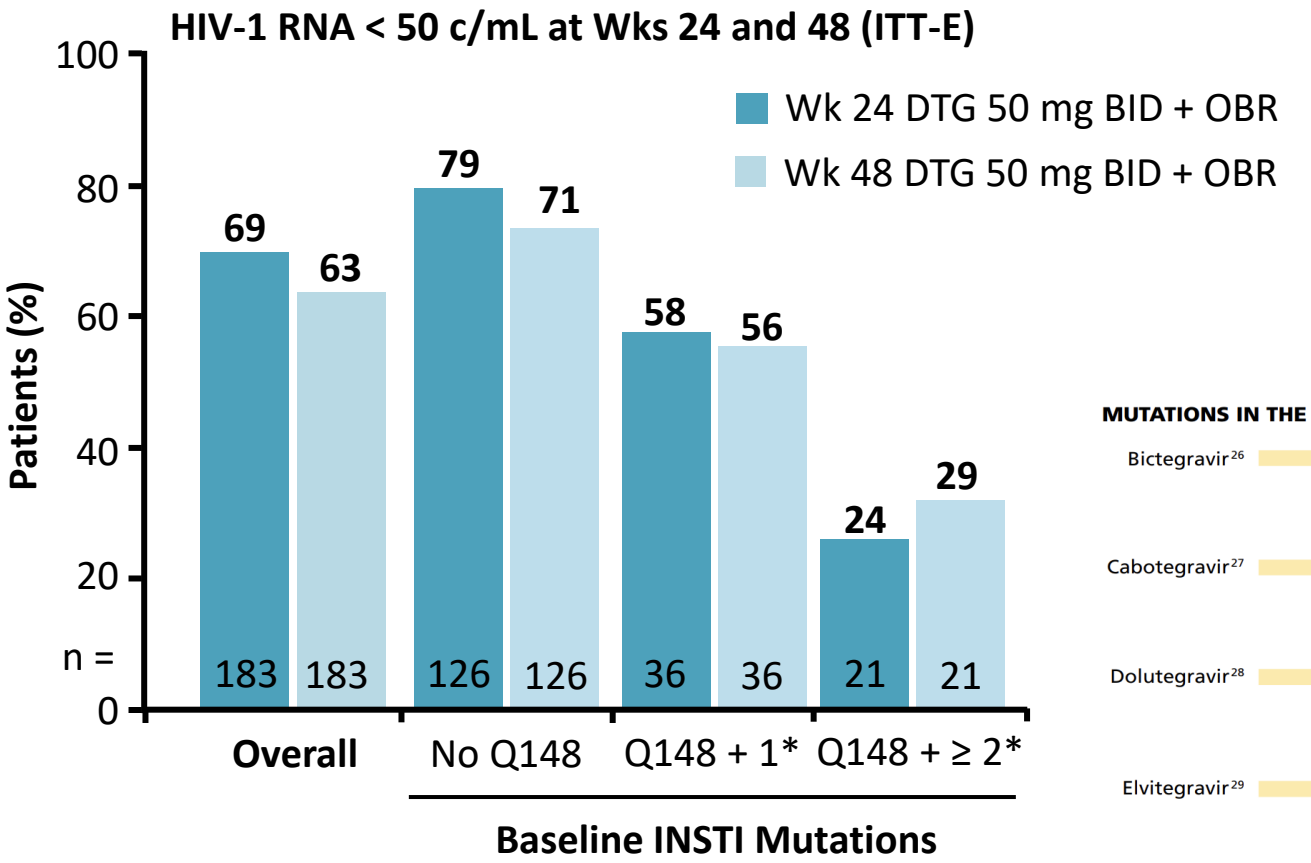
atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	Susceptible
lopinavir/r (LPV/r)	High-Level Resistance

Nucleoside Reverse Transcriptase Inhibitors

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

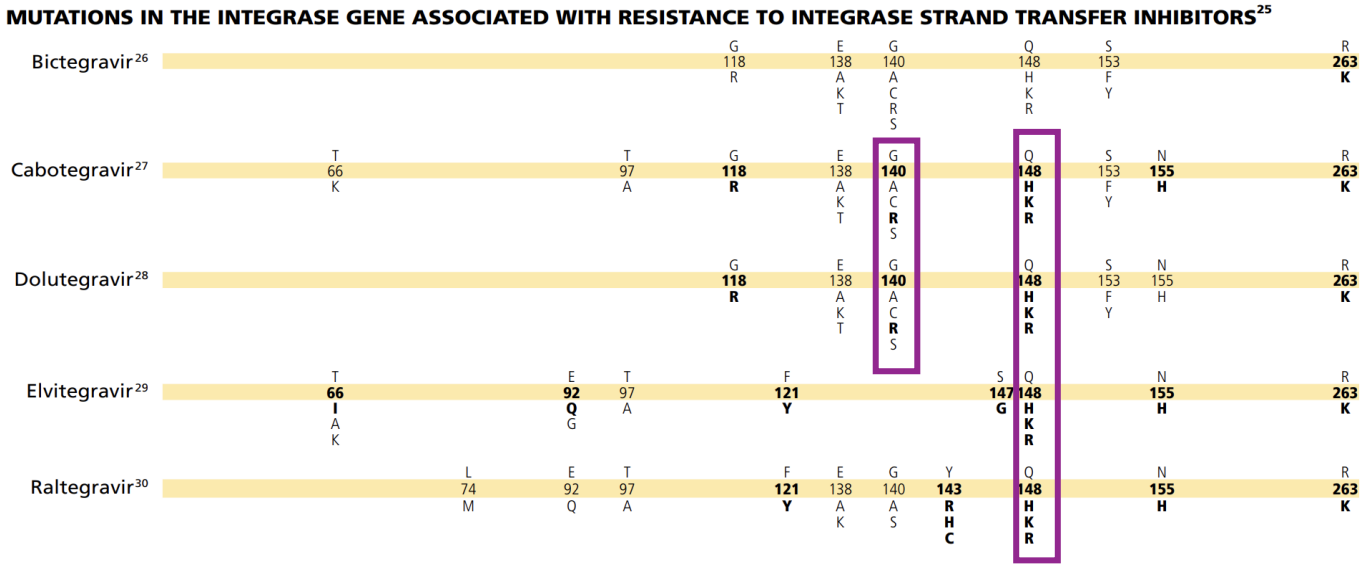
Which regimens?

VIKING-3: DTG BID in Previously Treated With RAL and EVG Resistance



*Key secondary mutations were G140A/C/S, L74I and E138A/K/T.

- 4 of 33 patients with N155H mutation at baseline had protocol-defined VF
- In INSTI-Experienced Patients
  - DTG (50) twice daily



Castagna. J Infect Dis. 2014;210:354. Vavro. EUDRW 2014. Abstr O_10.

Options for Active Drugs in Multiclass Resistance

- Drugs in existing drug classes that **may** have residual activity
  - **Boosted PI:**
    - For most patients with PI resistance, PI of choice is boosted DRV
      - No DRV-associated mutations: DRV 800 mg once daily
      - Any DRV-associated mutations: **DRV 600 mg twice daily**
  - **DTG 50 mg bid** in INSTIs experienced
  - Consider **NRTIs**

V	V L	I	I	I	T L	I	L
11	32 33	47	50	5 4	74 76	84	89
I	I F	V	V	M L	P V	V	V

- Drugs with a **novel mechanism of action** and no cross-resistance
  - Enfuvirtide SC BID
  - Fostemsavir oral BID
  - Ibalizumab IV Q2W
  - Lenacapavir SC Q6M
- All indicated with other ARVs for heavily treatment–experienced adults with MDR HIV and current ART failure

Adapted from DHHS ART Guidelines. September 2022.

Rifampicin and ART drug-drug interactions

Rifampicin should be included in regimens for patients with HIV and active TB, unless resistance or toxicity

Antiretroviral therapy	Recommendation	Drug interaction with rifampin
Efavirenz (EFV)	**No dose adjustment**	• EFV AUC ↓ 26%
Dolutegravir (DTG)	**50 mg twice daily**	• **Rifampin with DTG 50 mg Twice Daily Compared to DTG 50 mg Twice Daily Alone:** DTG AUC ↓ 54% and C_{min} ↓ 72% • **Rifampin with DTG 50 mg Twice Daily Compared to DTG 50 mg Once Daily Alone:** DTG AUC ↑ 33% and C_{min} ↑ 22%
Raltegravir (RAL)	**800 mg twice daily**	• **RAL 400 mg:** RAL AUC ↓ 40% and C_{min} ↓ 61% • **Rifampin with RAL 800 mg Twice Daily Compared to RAL 400 mg Twice Daily Alone:** RAL AUC ↑ 27% and C_{min} ↓ 53%
Rilpivirine (RPV) **Protease inhibitors (PIs)** **Bictegravir (BIC)** **Elvetegravir/Cobi**	**Contraindicated**	• RPV AUC ↓ 80% • ↓ PI concentration by >75% • BIC AUC ↓ 75% • Significant ↓ EVG and COBI expected

Adapted from DHHS 2020

Take home points

- Needs an **individualized** approach
- Always review **all** history with **all prior DRMs(Cumulative)**
- Perform DRMs before discontinuing regimens
  - No resistance profile detected in low drug level ≠ No resistance
- Identify and address reason for VF: most important
- Careful consideration of **drug–drug interactions** for complex cases
- Consult with guidelines and/or online tools/ expert opinions