Session 3 | Subtypes, Gender, and Ethnicity: Do They Impact HIV Care

Clinical Case Presentation

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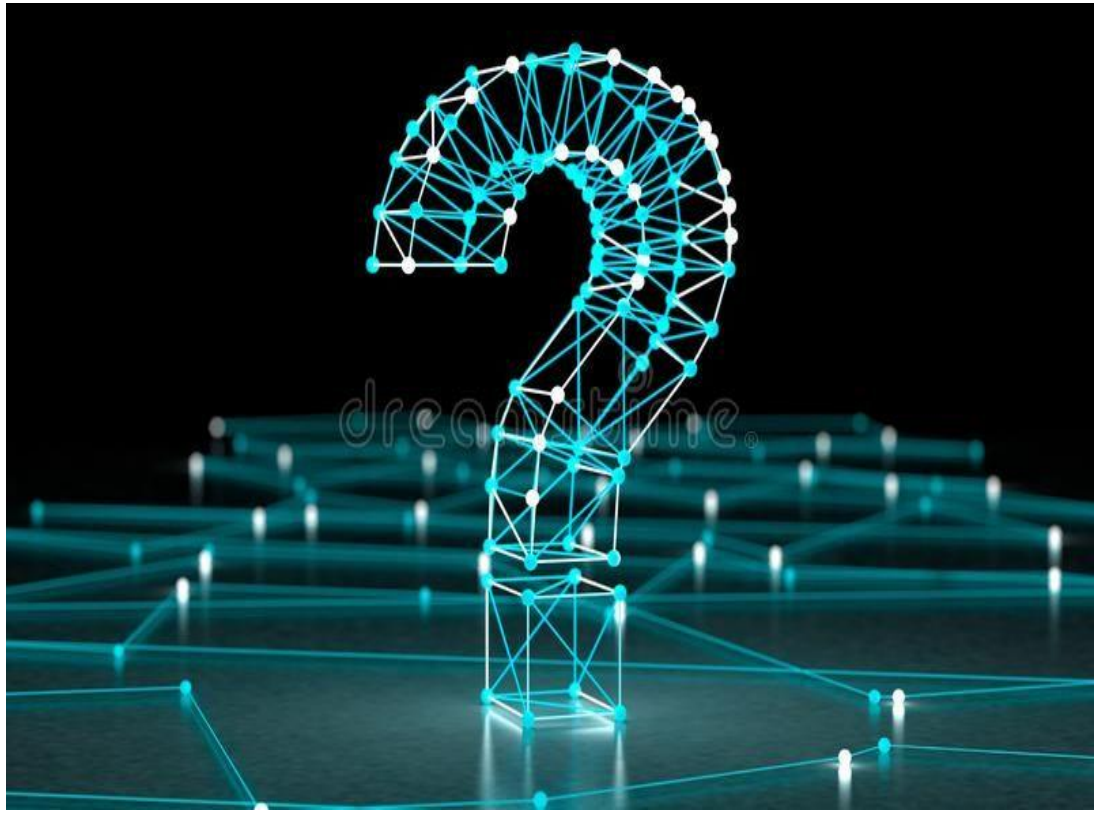
Treat or not treat

- 56 year old
- CD4 127 cells/µl
- Viral load 93,187



Antiretrovirals: 2020

NRTIs
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir disoproxil fumarate
- Tenofovir alafenamide
- Zidovudine

NNRTIs
- Delavirdine*
- Efavirenz
- Etravirine
- Nevirapine
- Nevirapine XR
- Rilpivirine
- Doravirine

Protease inhibitors
- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Saquinavir
- Tipranavir

Integrase inhibitors
- Bictegravir
- Dolutegravir
- Elvitegravir
- Raltegravir

Fusion/Entry/ Attachment inhibitors
- Enfuvirtide
- Maraviroc
- Fostemsevir

Monoclonal Antibodies
- Ibalizumab

PK boosters
- Cobicistat
- Ritonavir

Single-pill regimens
- Atripla
- Biktarvy
- Eviplera
- Genvoya
- Juluca
- Delstrigo
- Odefsey
- Stribild
- Symtuza
- Triumeq
- Dovato

NRTI, nucleoside reverse transcriptase inhibitor;
NNRTI, non-nucleoside reverse transcriptase inhibitor; PK, pharmacokinetic.
*Not available in the EU.

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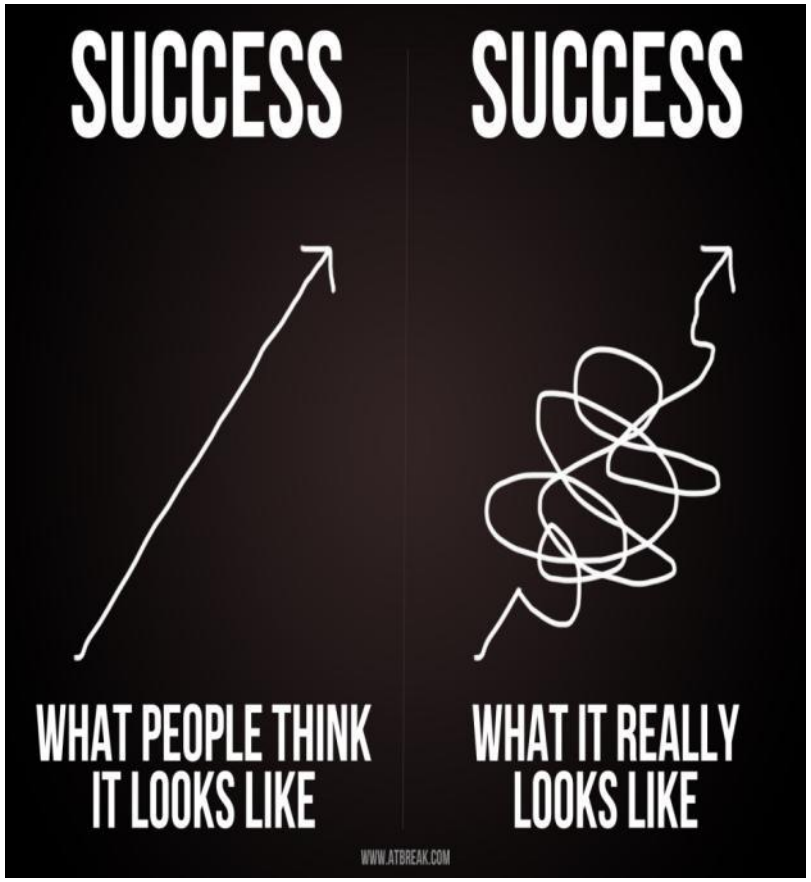
What are we trying to achieve?

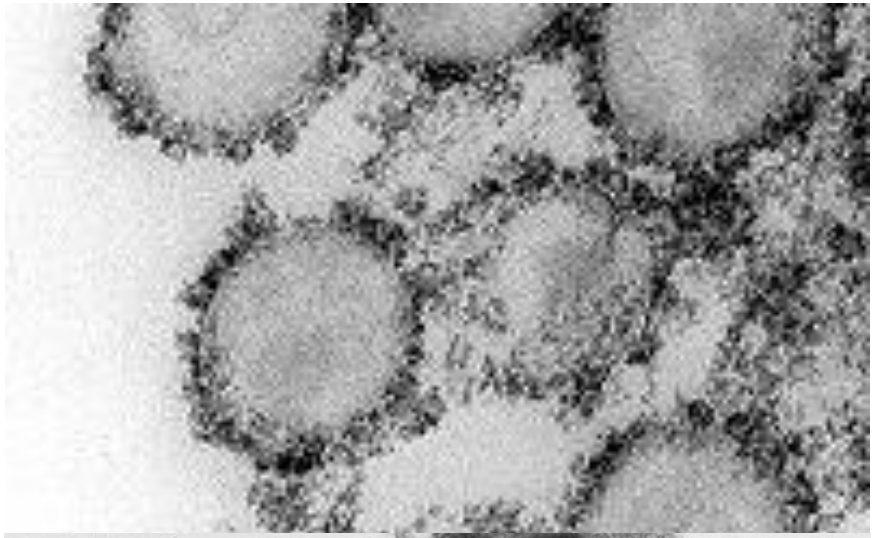
- Undetectable viral load?
- Normal CD4 count?
- Reduced (nil) transmission?
- Quantity of life?
- Quality of life?

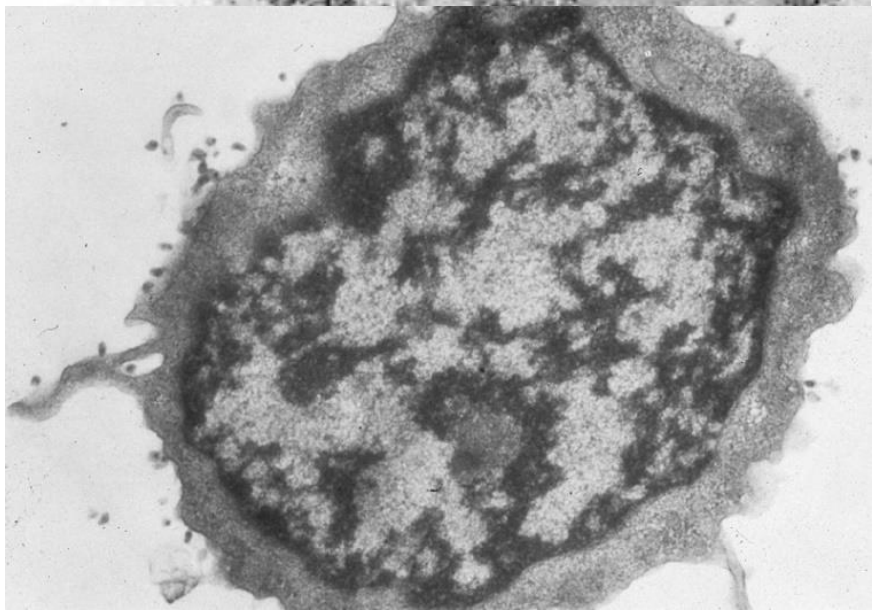


Drug Factors

- Efficacy
- Toxicity
- Adherence
- Drug Interactions
- Barrier to resistance
- Cost

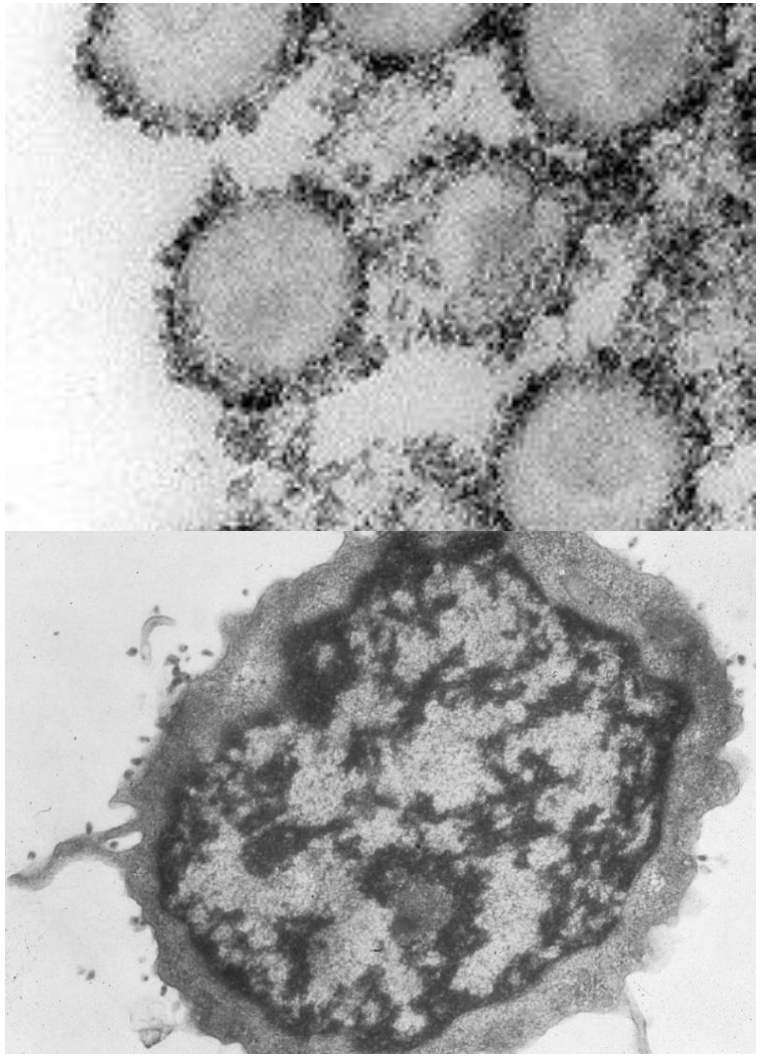
Disease factors?





Disease factors

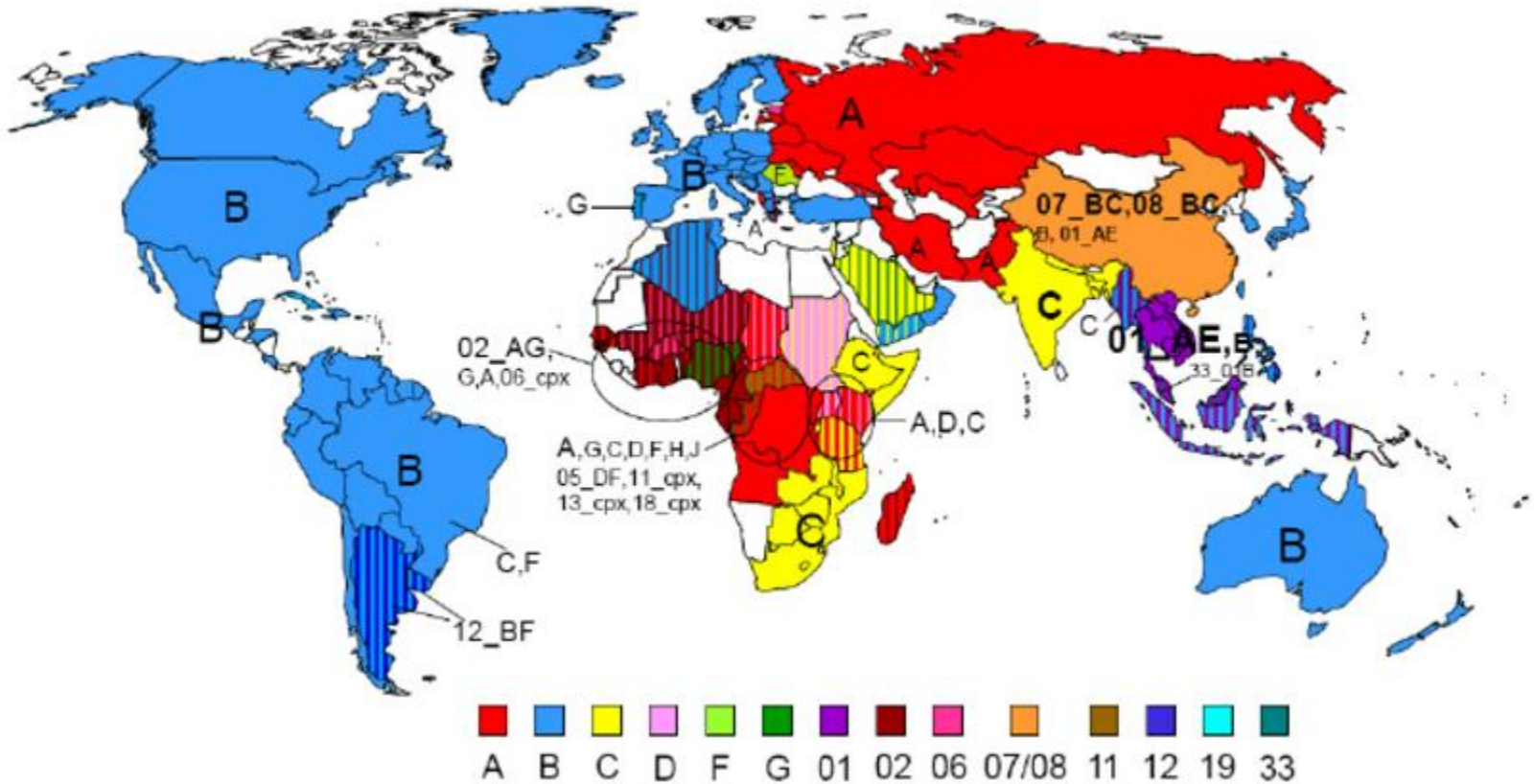
- Viral load
- CD4 count
- HIV resistance
- HIV tropism
- Clade?



Patient Factors

Patient Factors

- Comorbidities
- Co-infections
- Other medications (and interactions)
- HLA status and other genomics
- What the patient wants
- Sex?


A
B
G
B
B
07_BC,08_BC
B, 01_AE
C
C
01_AE,B
33_01B
02_AG,
G,A,06_cpx
C
A,D,C
A,G,C,D,F,H,J
05_DF,11_cpx,
13_cpx,18_cpx
B
C
C,F
12_BF
B
A B C D F G 01 02 06 07/08 11 12 19 33

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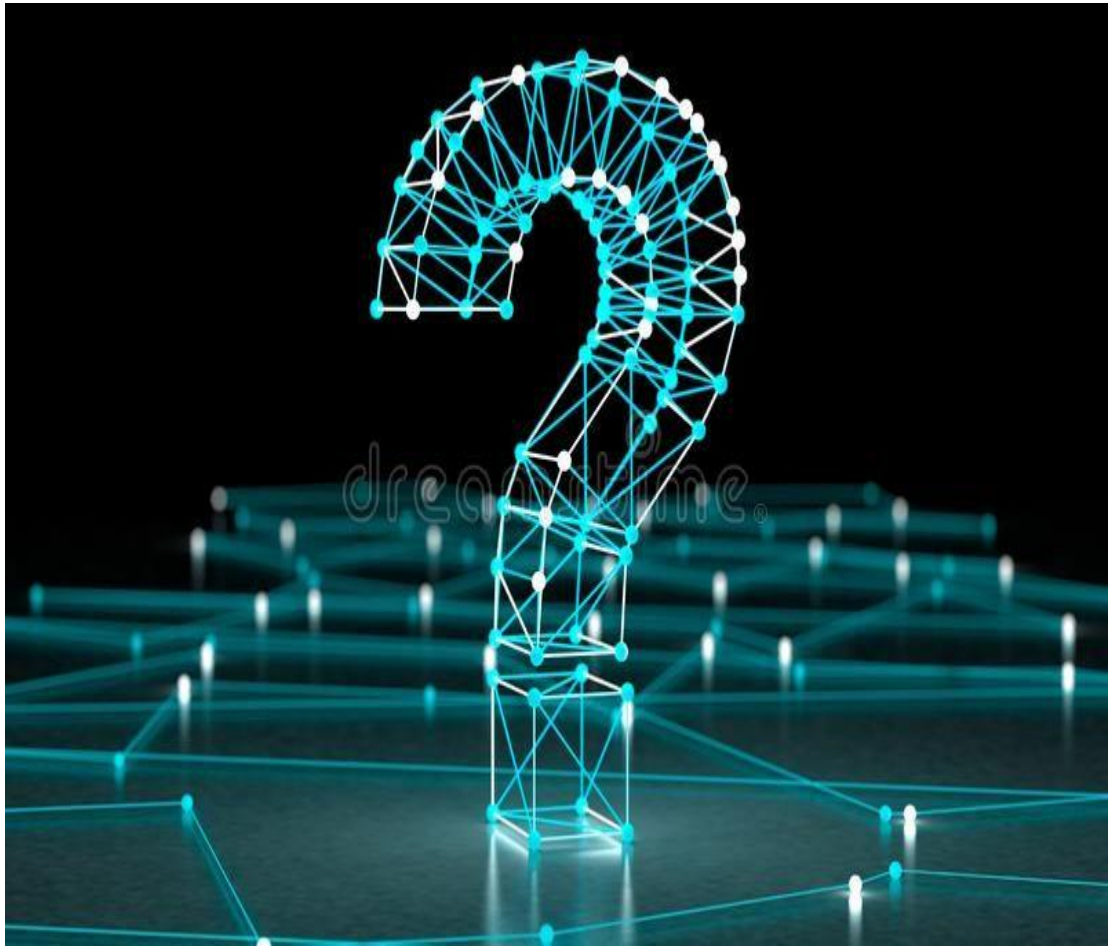


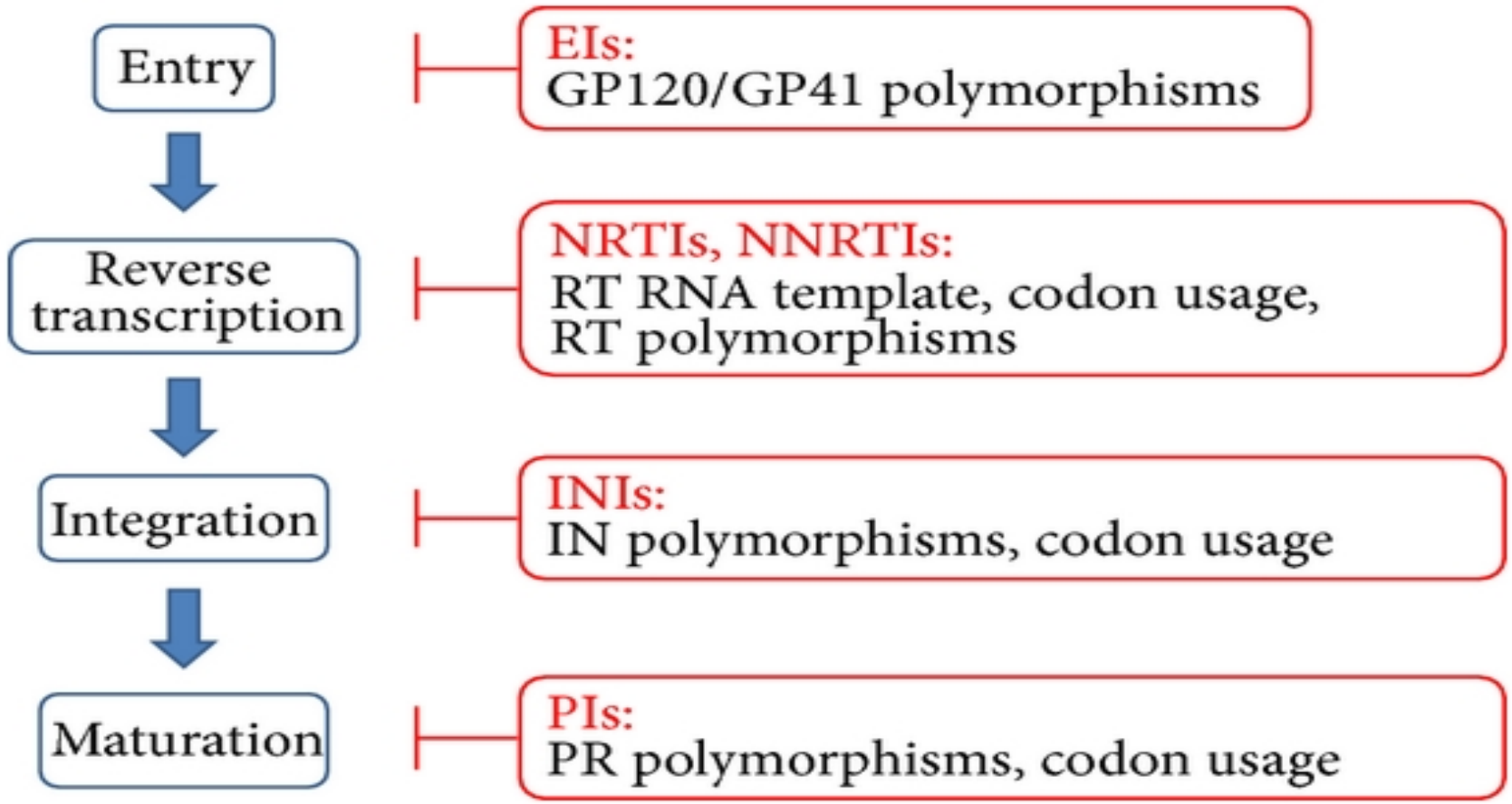

SUCCESS
FAILURE

Table 4. ATLAS and FLAIR Confirmed Virologic Failures: CAB + RPV LA Arm

Study	Sex, Country, HIV-1 Subtype	Previous CAR	Baseline RAMs*		Viral Load at SVF / CVF (c/mL)	SVF Timepoint RAMs		Drug Sensitivity at SVF (Fold Change)‡
			RT	INSTI		RT	INSTI†	
ATLAS	F, Russia, A/A1	3TC, AZT, LPV/r	E138E/ A	None	79,166 / 25,745	E138A	None	**RPV (2.4)** CAB (0.8) DTG (0.9)
	F, France, AG	3TC, AZT, NVP to 3TC, ABC, NVP	V108V/I E138K	None	695 / 258	V108I E138K	None	**RPV (3.7)** CAB (1.2) DTG (1.0)
	M, Russia, A/A1	FTC, RAL, TDF to ABC, EFV, 3TC	None	None	544 / 1841	E138E/K	N155H	**RPV (6.5)** **CAB (2.7)** DTG (1.2)
FLAIR§	F, Russia, A1	–	None	None	373 / 456	E138E/A/K/T	Q148R	**RPV (7.1)** **CAB (5.2)** DTG (1.0)
	M, Russia, A1	–	None	None	287 / 299	K101E	G140R	**RPV (2.6)** **CAB (6.7)** DTG (2.2)
	F, Russia, A1	–	None	None	488 / 440	E138K	Q148R	RPV (1.0) **CAB (9.4)** DTG (1.1)

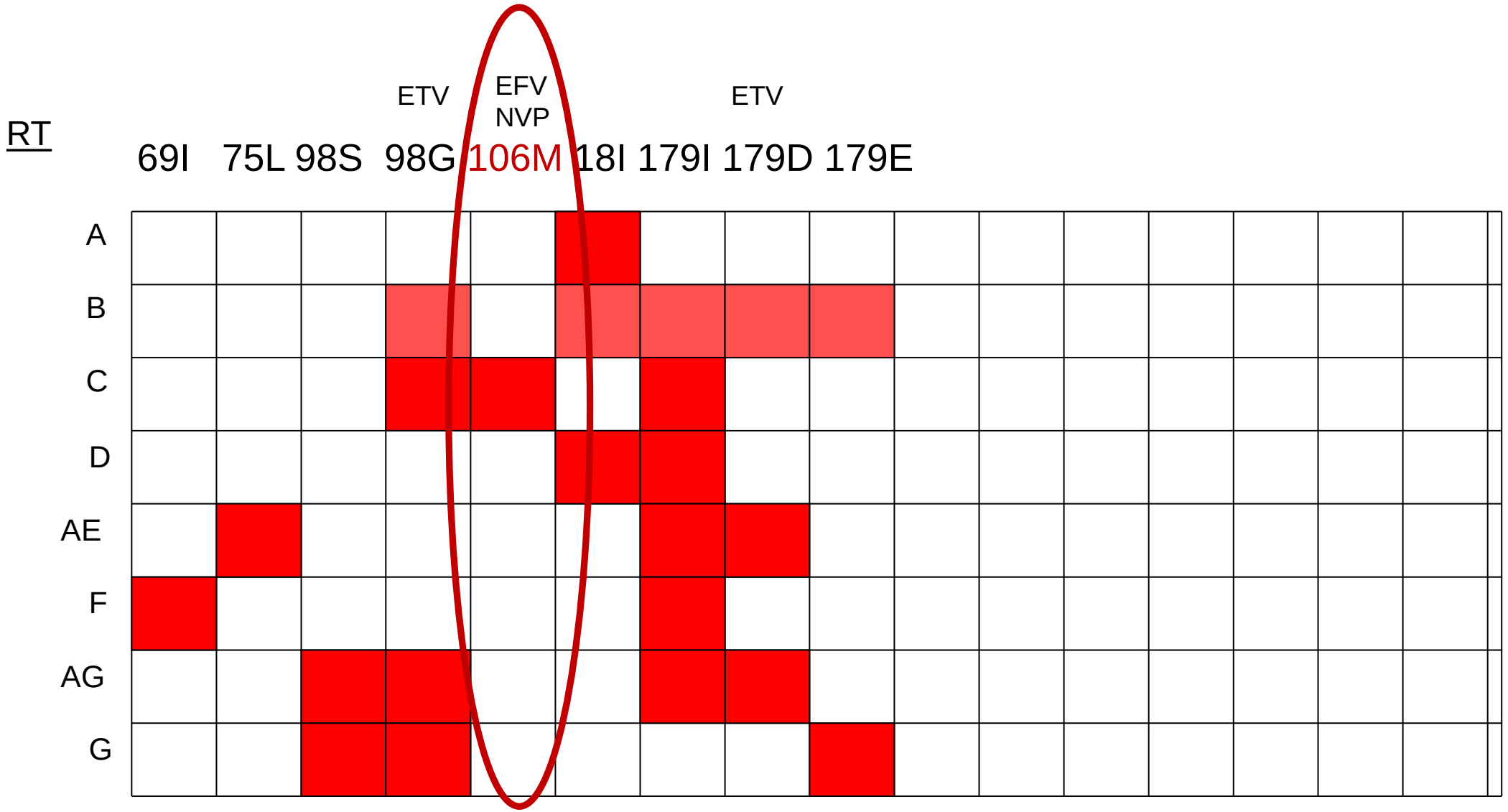
- In the CAR arm, there were seven CVFs. In ATLAS, there were 4 CVFs in the CAR arm, where RT mutations M184I, M184V+G190S, and M230M/I were detected in HIV-1 RNA samples from one participant each, and one had no mutations. In FLAIR, there were 3 CVFs in the CAR arm without treatment-emergent resistance mutations or phenotypic changes.

*Baseline RAMs were determined using DNA for ATLAS and RNA for FLAIR. †L74I was present at baseline in 5/6 subjects and is not considered an INSTI RAM by IAS-US guidelines and has no impact on CAB activity. ‡Monogram biological cutoffs are: RPV=2.0, CAB=2.5, and the Monogram clinical cutoff for DTG=4.0. §One additional participant in FLAIR had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test and upon re-initiation of oral therapy, had suspected VF that was confirmed;


Entry
Reverse transcription
Integration
Maturation
EIs:
GP120/GP41 polymorphisms
NRTIs, NNRTIs:
RT RNA template, codon usage,
RT polymorphisms
INIs:
IN polymorphisms, codon usage
PIs:
PR polymorphisms, codon usage

Drug class	Subtype	Polymorphisms or mutations or positions associated with drug resistance	Drug(s) related	Comments
Reverse transcriptase				
NRTI	C	K65R	d4T, ddI, ABC, TDF	Preferential selection
	C	K70E	d4T, ddI, AZT	High prevalence in subtype C endemic area
	B	D67N	d4T, AZT	Preferential selection
NNRTI	G	A98S	NNRTIs	Common polymorphism
	B, C, F, CRF02_AG	K103N	EFV, DLV, NPV	Lower frequency in subtype C compared to B, F, and AG subtype
	B, C	V106M	EFV, NVP	Lower genetic barrier in subtype C in comparison with subtype B
	C	E138K	ETR	Preferential selection under drug pressure in subtype C
	C	G190A	NNRTIs	High frequency in subtype C
	A, B	Y181C	ETR	Preferential selection under drug pressure on A and B subtypes
	C	Y181C, Y188L	EFV, DLV, NPV	Higher frequency in subtype C
	C	N348I	ETR	Higher frequency in subtype C at etravirine failure

Some Mutations May Be Clade Dependant

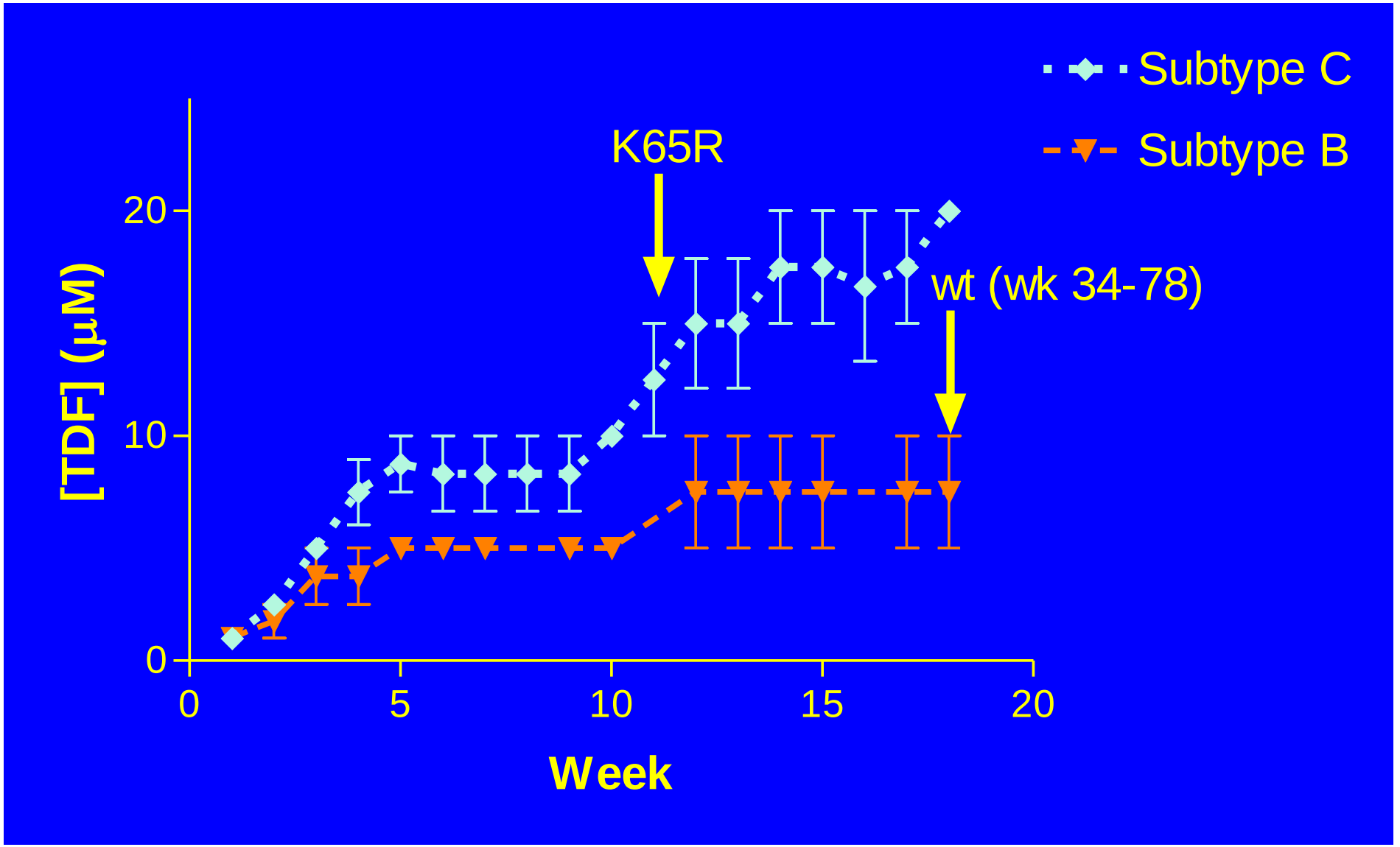


Note: AE = CRF01_AE; AG = CRF02_AG

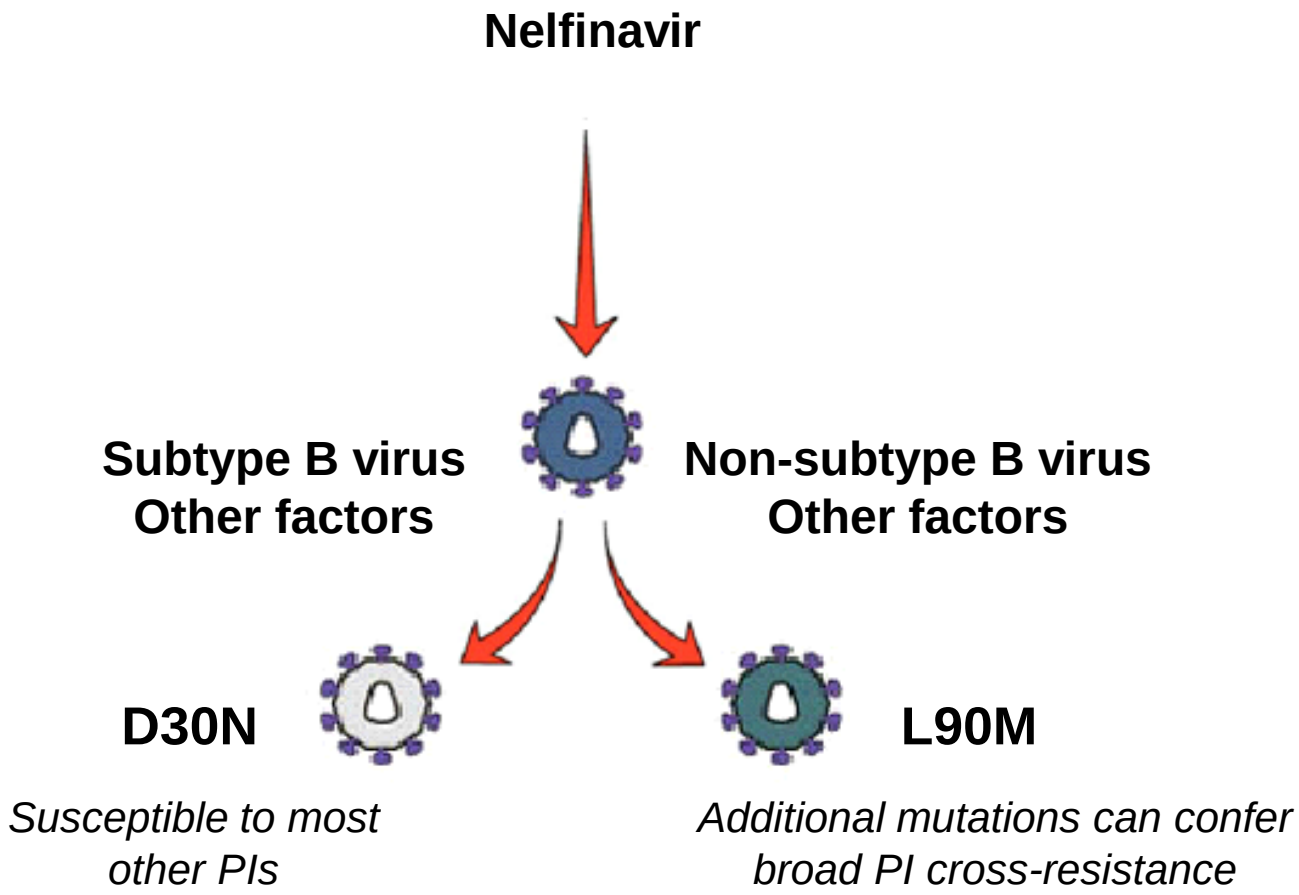
Silent Mutation at Codon 106 Responsible for the V106M Mutation in Clade C RT with NNRTIs

HIV-1 RT	Subtype B	Subtype C
Wild type codon at position 106	V(GTA)	V(GTG)
In clade C, V106M arises	two codon changes	M(ATG)
In clade B, V106A occurs	A(GCA)	two codon changes

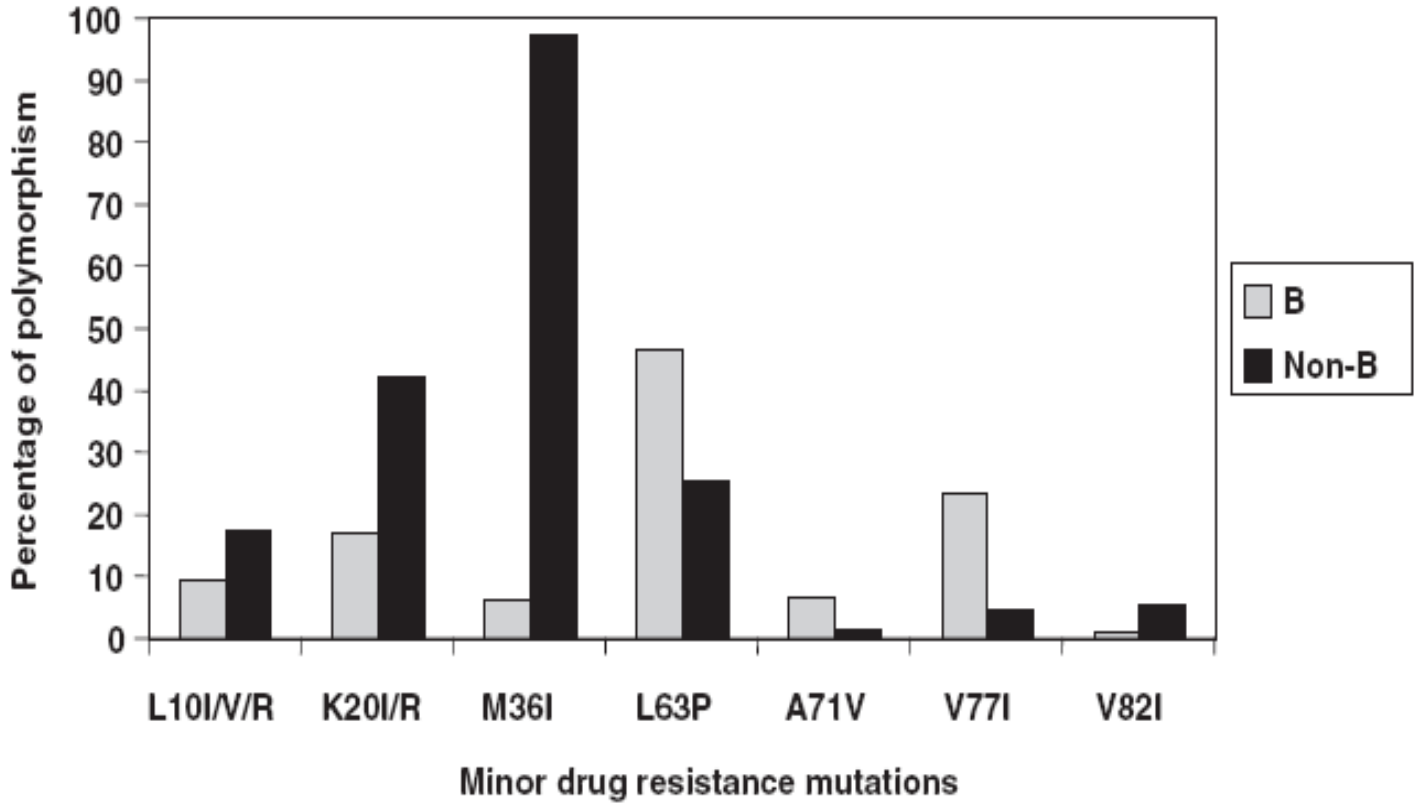
Rapid Selection of K65R Resistance in Subtype C Isolates



Dichotomous Pathways to Resistance



HIV Subtype/Clade Effects Drug Resistance



Differences in amino acid substitutions in the protease gene for subtypes B and non-B were compiled from several published HIV-1 strains: 108 subtypes B and 348 non-B subtypes (87A, 74C, 31D, 8F1, 13F2, 11G, 10J, 4O, 26CRF02_AE and 84CRF02_AG).

Nkengasong, AIDS Rev, 2004

Treat or not treat

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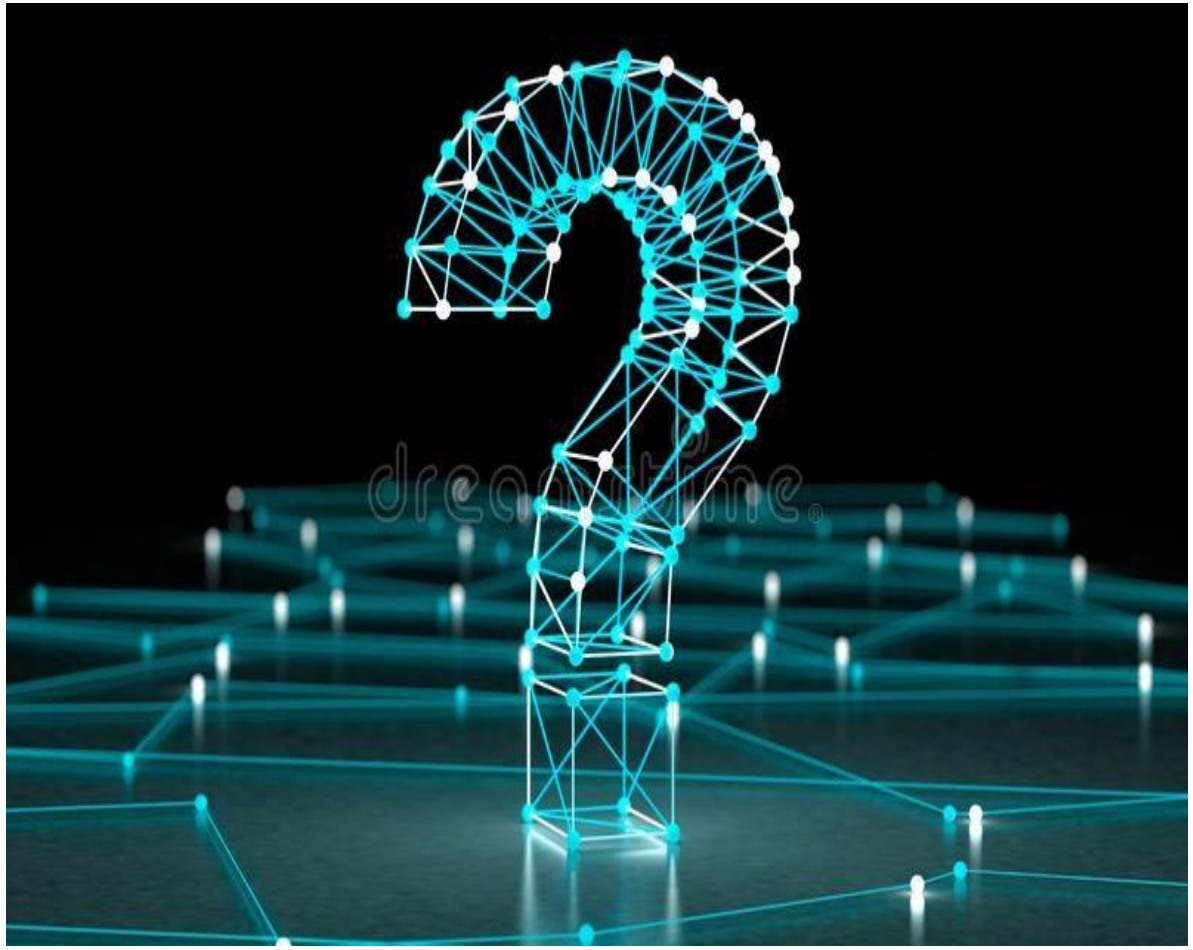
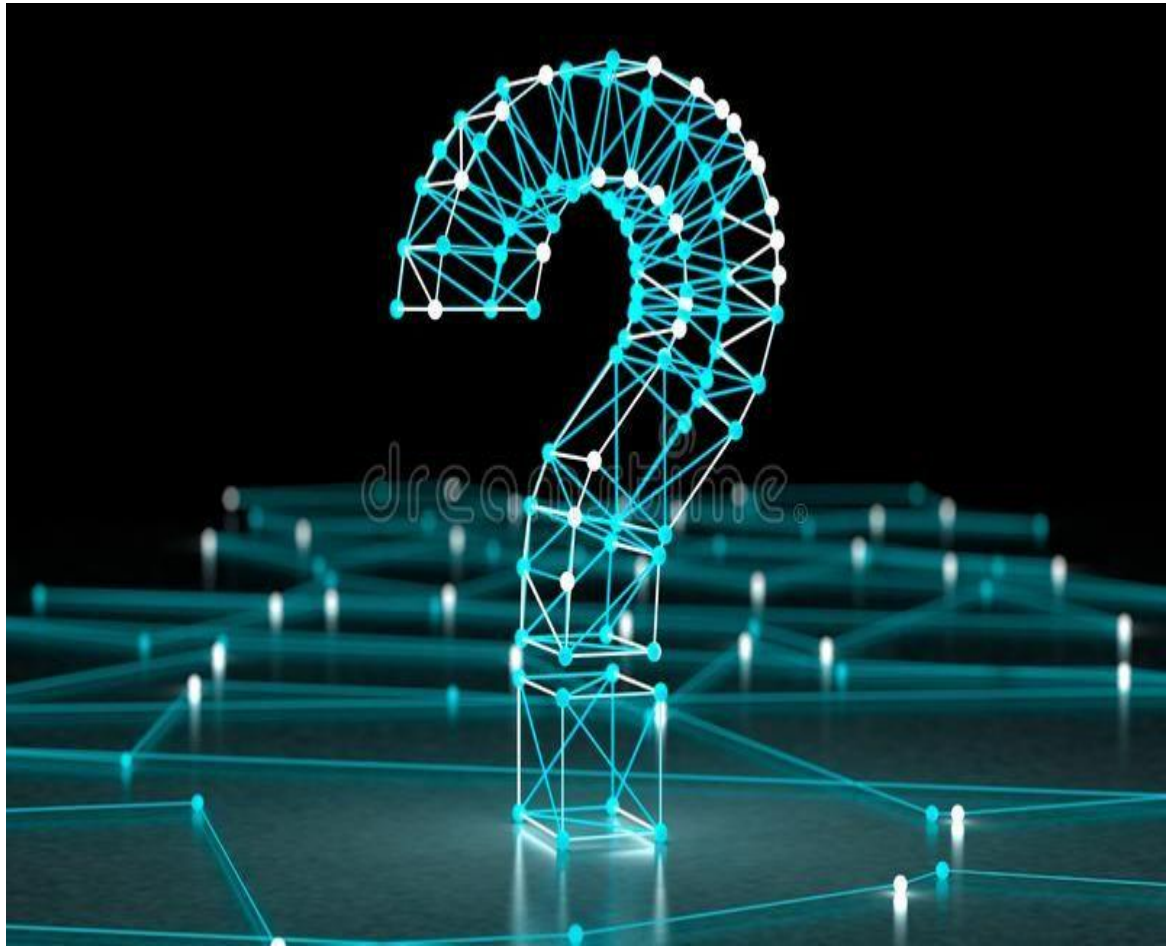
- CD4 127 cells/µl
- Viral load 93,187
- Subtype C
- Concerns over non adherence



Treat or not treat

- 56 year old
- CD4 127 cells/µl
- Viral load 93,187
- Subtype C
- Female



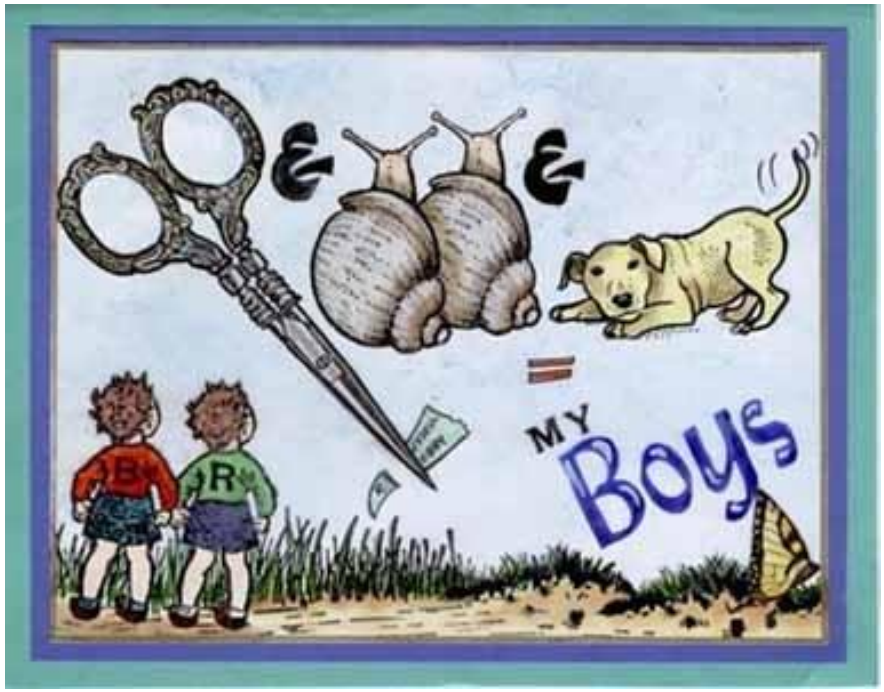

DOES
THE
SEX
MATTER
voot originals
14th DEC

What are women made of?

- Biological factors that impact on HIV and its therapy ?
  - Body composition
  - Female specific organs
  - Immune responses
  - Surrogate markers.

What are men made of?

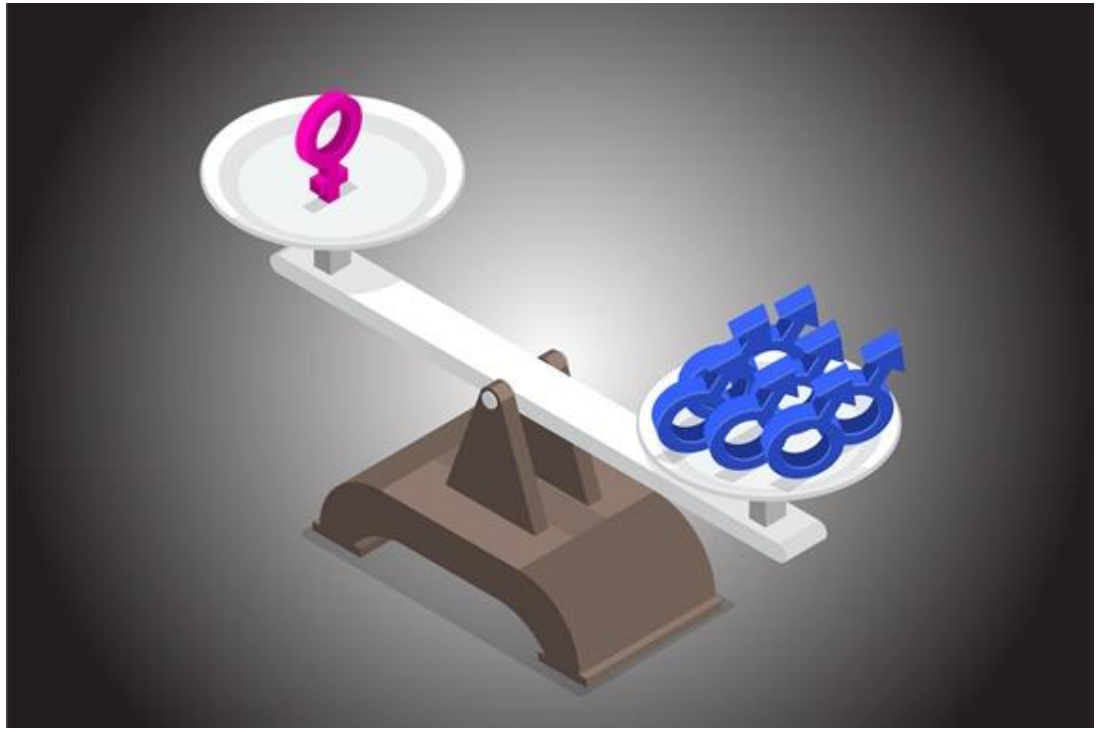
- Biological factors that impact on HIV and its therapy ?
  - Body composition
  - Male specific organs
  - Immune responses
  - Surrogate markers.



Women and drug metabolism

- At the “body level”
  - Weight
  - Fat distribution
- Perhaps at a molecular level [1,2]
  - Sex variation in cytochromes
- What about transport mechanisms? [1,3]
  - *p*-glycoprotein expression may be lower in women.

- Do we need specific studies for females?
- Do we need specific studies for males?



Is there an optimal ARV for women?

- Most pivotal trials of ARV largely in MSM
- Typically the proportion of women < 20%
- Even if sub-analysis by gender reported, underpowered to detect differences
- Most studies show no differences in efficacy although there may be differences in toxicity
- Most guidelines only comment on pregnancy as the only gender consideration

And we aren't doing any better: Latest Pharmaceutical RCT for Naïve Patients

Study- Naive	(%) women
Gilead- Biktarvy studies	10%
Viiv- Gemini- Dovato (DTG)	14%
Drive forward /ahead Doravirine	15%
Jannsen-Emerald-Symtuza	12%
Viiv- Atlas-cabotegravir/rilpivirine	25%

Latest Pharmaceutical Switch Studies

Study	% women
Dolutegravir to Biktarvy	13% (separate study of 400 women)
CAR to Juluca	22%
Atlas- CAR to cabotegravir/rilpivirine	25%
Emerald- CAR to Symtuza	18%
DRIVE SHIFT-CAR to doravirine	15%
TANGO- CAR to Dovato	8%

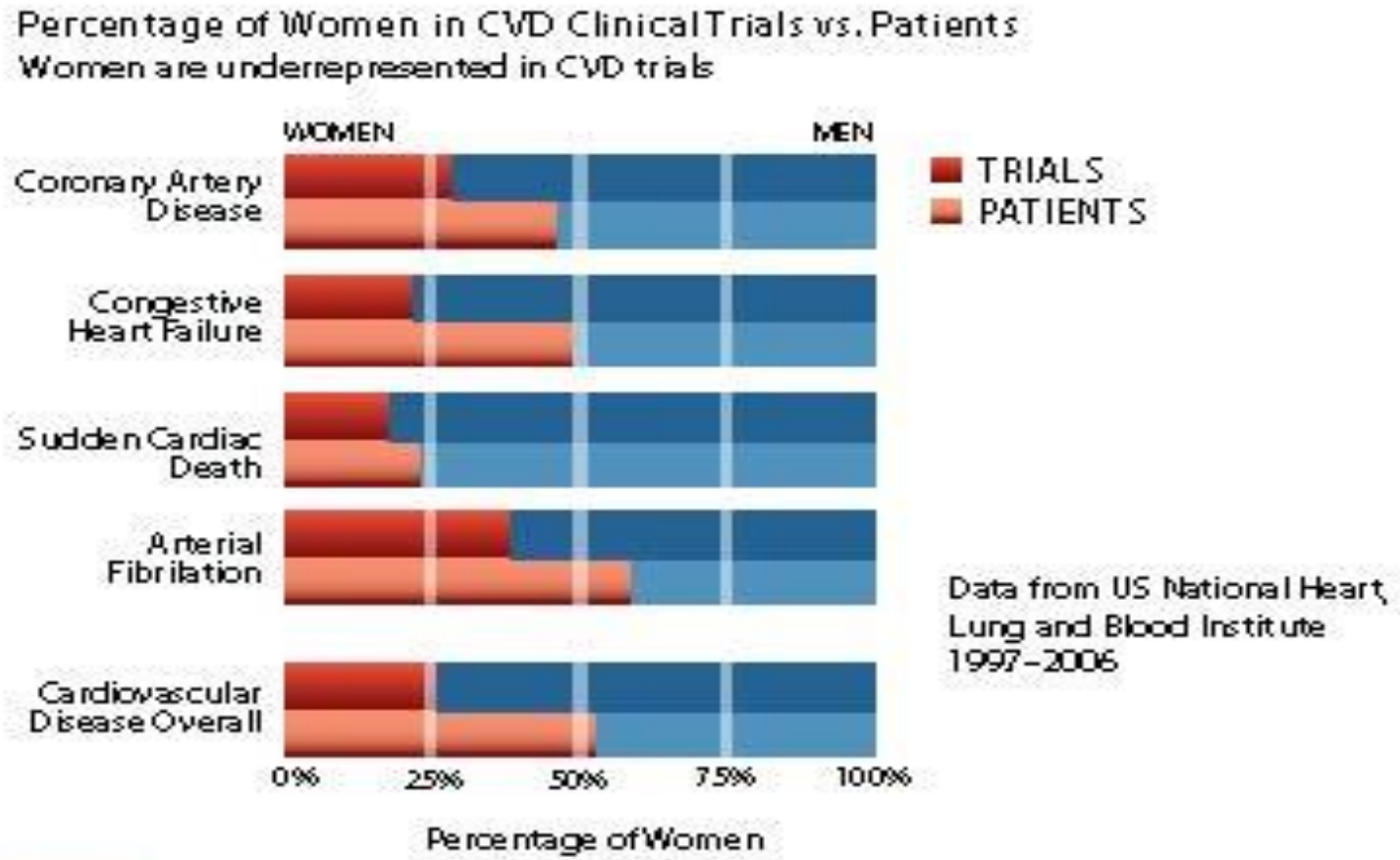

Percentage of Women in CVD Clinical Trials vs. Patients
Women are underrepresented in CVD trials
WOMEN
MEN
Coronary Artery Disease
Congestive Heart Failure
Sudden Cardiac Death
Arterial Fibrilation
Cardiovascular Disease Overall
TRIALS
PATIENTS
Data from US National Heart, Lung and Blood Institute 1997–2006
0%
25%
50%
75%
100%
Percentage of Women

Figure 1.

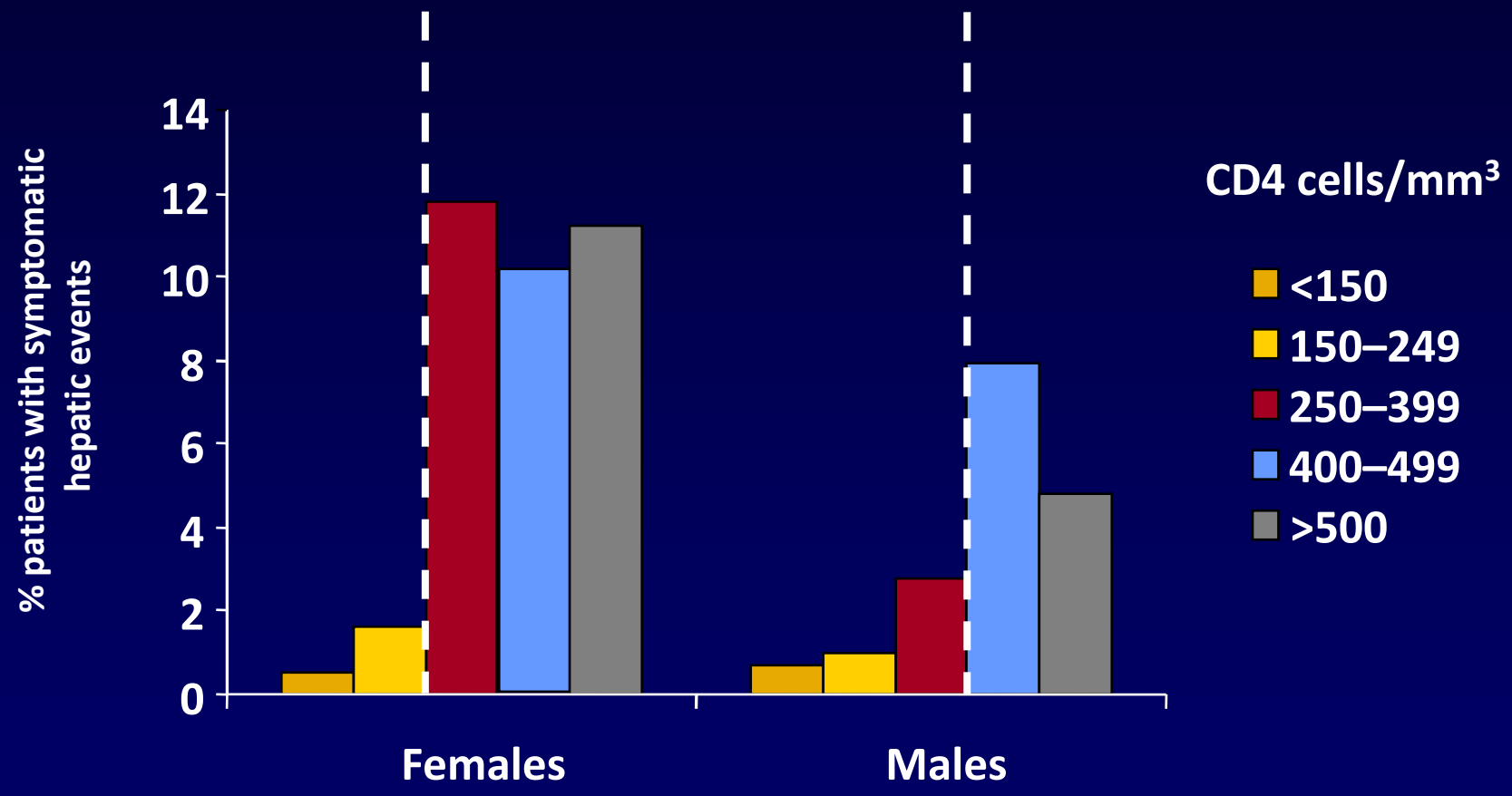
Barriers to enrollment of women

- Proportion of women in a clinical trial site
- Need for “multiple” methods of contraception
- Uncertain pregnancy intentions
- Accommodation for other demands- childcare, partner, etc- more women leave trials for “ other reasons”
- Not have a natural support group to encourage clinical trials
- “TRUST”

Are they important?

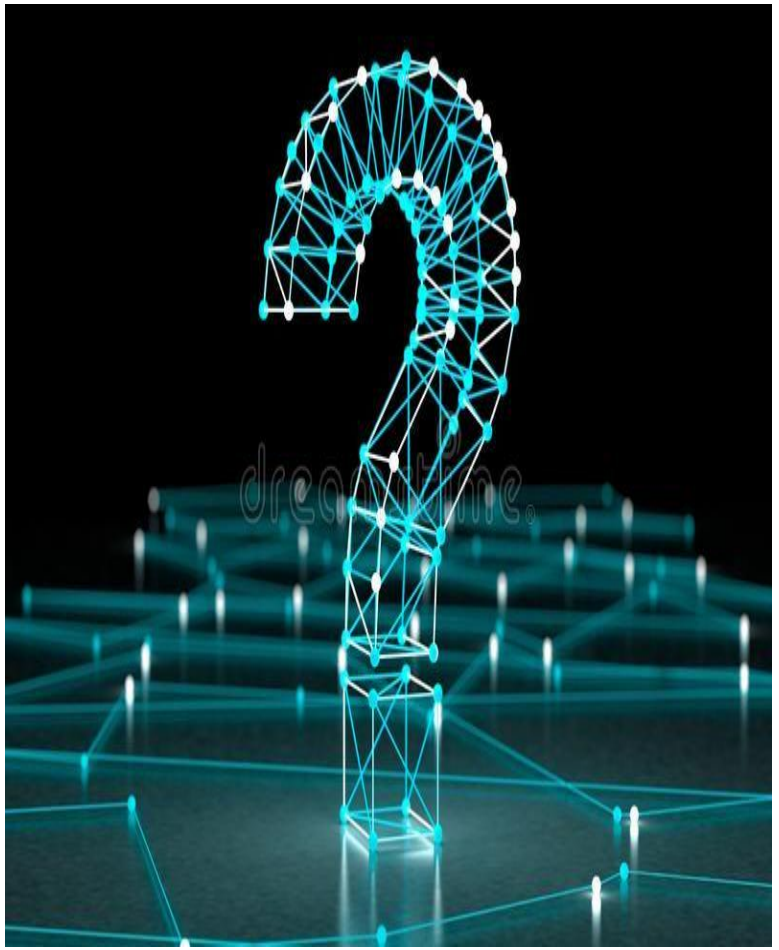
- Most studies show that viral efficacy is similar
- Over the years we have learned that there may be differences in toxicity
  - Rash and hepatitis with nevirapine
  - Lactic acidosis with DDI/d4T
  - Patterns of lipodystrophy
  - Different rates of diarrhea, nausea with the protease inhibitor
- And women may have different thresholds for tolerability of different adverse events

Basis for NVP warning: CD4 cut-offs



Stern JO *et al*. *XIV Inter AIDS Conf* Barcelona, 2002.

Treat or not treat



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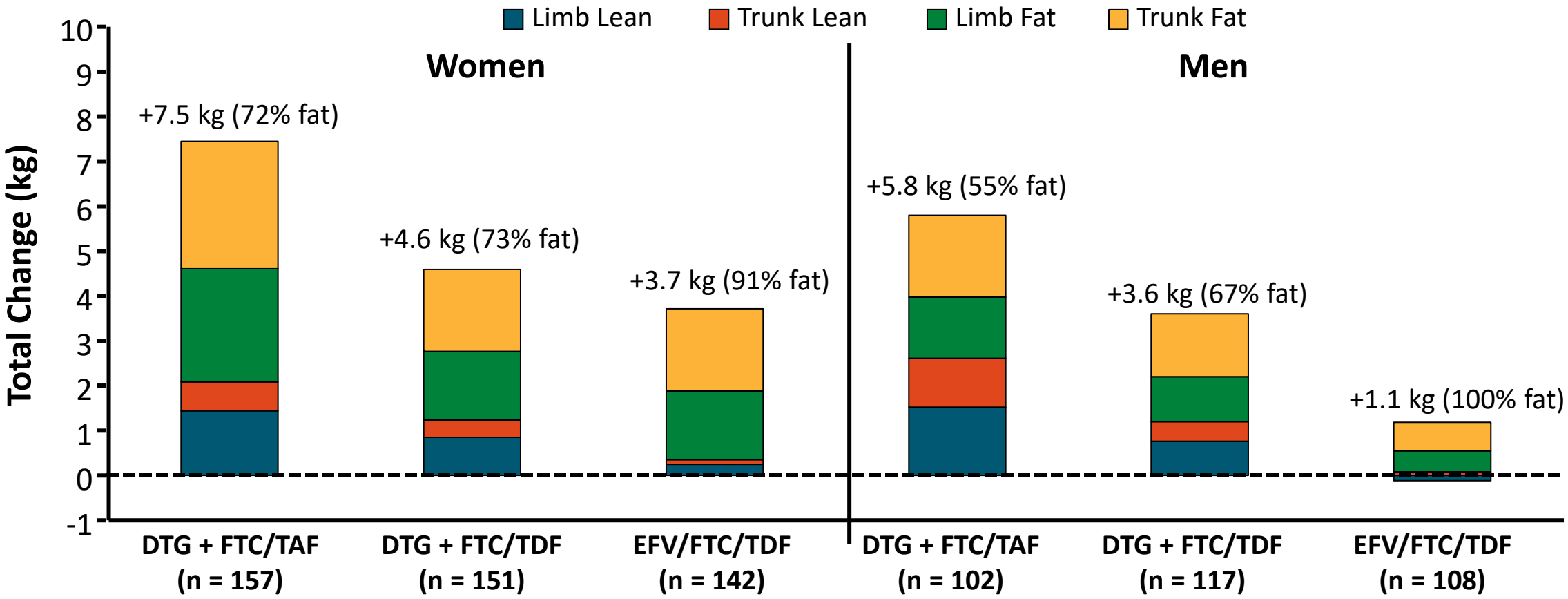
- Subtype C
- Female
- Worried re toxicity particularly weight gain
- Takes hormonal treatment post menopause which “has revolutionized her life”

ADVANCE 96-Wk Analysis: Body Composition Changes to Wk 96

- Mass increases predominantly driven by fat gain and distributed between limbs and trunk across all study arms; women gained significantly more fat mass vs men ($P < .001$)



Sokhela. AIDS 2020. Abstr OAXLB0104. Reproduced with permission.

www.hiv-druginteractions.org

HRT Treatment Selector

Charts reviewed October 2019. Full information available at www.hiv-druginteractions.org

	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC/ F/TAF	DTG	EVG/c/ F/TAF	EVG/c/ F/TDF	RAL	ABC	FTC or 3TC	F/TAF	TDF	ZDV
Estrogens																					
Estradiol	↑ [a]	↓ [b]	↑ [a]	↓ [b]	↓ [b]	↔	↓ [b]	↓ [b]	↓ [b]	↔	↔	↔	↔	↑ [a]	↑ [a]	↔	↔	↔	↔	↔	↔
Progestins (HRT)																					
Drospirenone	↑ [a,c]	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↔	↓ [b]	↓ [b]	↓ [b]	↔	↔	↔	↔	↑ [a]	↑ [a]	↔	↔	↔	↔	↔	↔
Dydrogesterone	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↔	↓ [b]	↓ [b]	↓ [b]	↔	↔	↔	↔	↑ [a]	↑ [a]	↔	↔	↔	↔	↔	↔
Levonorgestrel	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↔	↓ [b]	↓ [b]	↓ [b]	↔	↔	↔	↔	↑ [a]	↑ [a]	↔	↔	↔	↔	↔	↔
Medroxy-progesterone (oral)	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↔	↓ [b]	↓ [b]	↓ [b]	↔	↔	↔	↔	↑ [a]	↑ [a]	↔	↔	↔	↔	↔	↔
Norethisterone (Norethindrone)	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↔	↓ [b]	↓ [b]	↓ [b]	↔	↔	↔	↔	↑ [a]	↑ [a]	↔	↔	↔	↔	↔	↔
Norgestrel	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↑ [a]	↔	↓ [b]	↓ [b]	↓ [b]	↔	↔	↔	↔	↑ [a]	↑ [a]	↔	↔	↔	↔	↔	↔

Colour Legend

- No clinically significant interaction expected.
- These drugs should not be coadministered.
- Potential interaction which may require a dose adjustment or close monitoring.
- Potential interaction predicted to be of weak intensity. No *a priori* dosage adjustment is recommended.

Text Legend

- ↑ Potential increased exposure of the hormone
- ↓ Potential decreased exposure of the hormone
- ↔ No significant effect

Notes

a The clinical significance of increased exposure in terms of overall risk of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women receiving substitution hormones is unknown.

b Monitor for signs of estrogen deficiency.

c Coadministration is contraindicated in the US product label due to the potential for hyperkalaemia. The European product label recommends clinical monitoring for hyperkalaemia.

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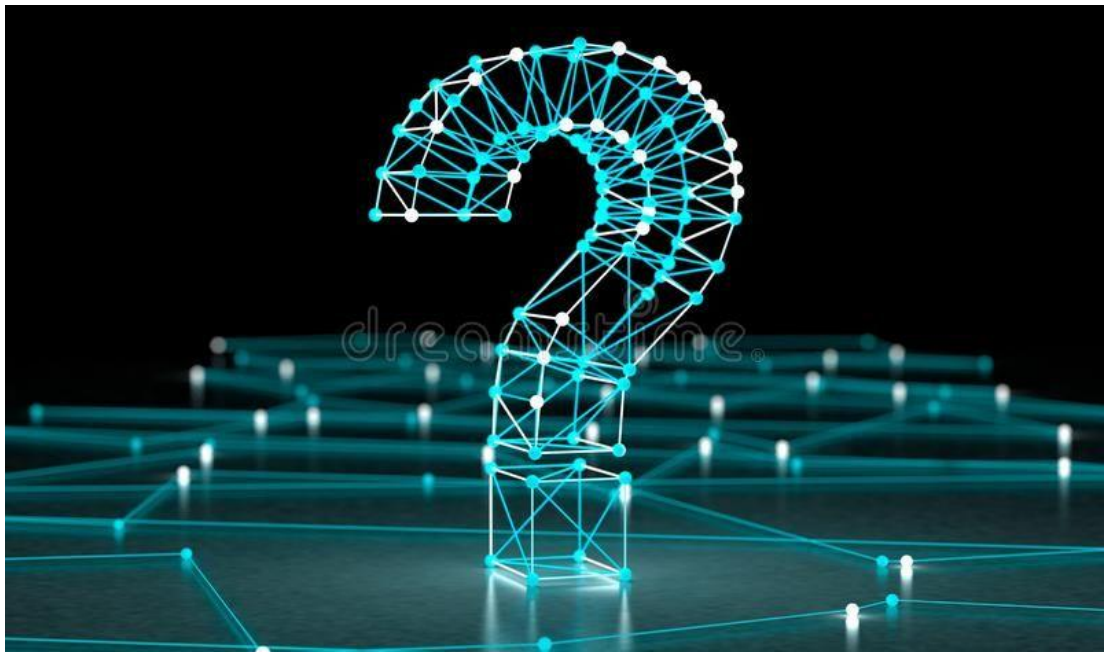
- TENOFVIR
- LAMIVUDINE
- DORAVARINE

BUT……

- Is doravarine as effective as an integrase?
- Bone health
- Renal health
- Other ddis
- New toxicities with new agents
- Could clade effect resistance if fails?



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- Nevirapine XR
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Protease inhibitors
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- Stribild
- Symtuza
- Triumeq
- Dovato

NRTI, nucleoside reverse transcriptase inhibitor;
NNRTI, non-nucleoside reverse transcriptase inhibitor; PK, pharmacokinetic.
*Not available in the EU.

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