CLINICAL CASE

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Demographics

- Woman
- 27 years old
- Born in Romania
- Now stays at her brother’s place
- Only speaks Romanian

HIV history

- HIV-1 infection by 3 years of age, during vaccination (“many children from her village became infected”)
- Diagnosed with HIV at 6 years of age, after recurrent respiratory infections
- Does not remember ART history precisely, but remembers that:
  - No ART until year 2000, when she was 10–11 years old
  - Exposure to AZT, 3TC, IDV and LPV/r
  - Does not recall exposure to NNRTIs
  - Treated with AZT/3TC + LPV/r during the last 3 years
  - Started ABC/3TC + LPV/r 4 months ago due to vomiting

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; IDV, indinavir
LPV, lopinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; r, ritonavir

Current problem

- Overall good evolution since ART initiation. Usual weight 57 kg

- However, since 2009 her health begins to worsen:
  - Recurrent herpes zoster and oral candidiasis
  - Progressive asthenia, anorexia and weight loss (current weight 48 kg)
  - Productive cough
  - No shortness of breath

- In December 2010, her brother is told in their hometown that she has bad prognosis and exhaustion of ART options. He decides to bring her to our HIV Clinic

Physical exam & tests

- **First visit to our clinic in February 2011**
- **Physical examination:**
  - Weight 48 kg
  - Blood pressure 110/75, heart rate 63 x min, O2 sat (FiO2 21%): 99%
  - Multiple cervical enlarged lymph nodes
  - Thick inspiratory rales in both lung bases
  - Enlarged liver and spleen

- **Complementary exams**
  - Hb 9.1 (Htc 27%), platelets 60,000/uL
  - X-ray: bilateral alveolar infiltrates
  - **HIV-1 RNA 330,000 c/mL, CD4+ 54 cells/mm (4%)**
  - HLA-B*57:01 negative

Hb, haemoglobin; HLA, human leukocyte antigen

Diagnosis & Treatment

- Despite initial suspicion of tuberculosis, all tests (sputum, bone marrow aspirate, bronchoscopy, gastroscopy, colonoscopy and blood and urine cultures) are negative for *M tuberculosis*
- HAV positive, HBV in the past (HBsAg: Negative, IgG HBcAc: Positive), HCV negative
- Diagnosed with ***Haemophilus influenzae*** **pneumonia** (presence in sputum) and also treated against ***Pneumocystis jirovecii*** (amoxicilin/clavulanate + CMX DS)
- She also had **pancytopenia with a reactive bone marrow** in a myelogram without evidence of microorganisms, a normal gastroscopy (09/02/11) and no evidence of disease. The pancytopenia gradually recovered with ART

HAV, hepatitis A virus; HBcAc, hepatitis B core antibodies; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus

Genotype 1

- Genotype **February 2011** (VL 330,000 c/mL, CD4+ 58 cells/mm^3):

- RT: T215D
  - **High-level resistance: none**
  - **Intermediate resistance: AZT, d4T**
  - **Low-level resistance: ABC, ddI, TDF**
  - **Susceptible: 3TC, FTC, all NNRTIs**

- PR: L10V, V11I, L33F, M36I, V82A, I84V
  - **High-level resistance: FPV/r, IDV/r, NFV**
  - **Intermediate resistance: ATV/r, LPV/r, SQV/r**
  - **Low-level resistance: DRV/r, TPV/r**

- Integrase: not performed
- Tropism: no amplification

ATV, atazanavir; d4T, stavudine; ddI, didanosine; DRV, darunavir; FPV, fosamprenavir; FTC, emtricitabine
NFV, nelfinavir; RT, reverse transcriptase; SQV, saquinavir; TDF, tenofovir ;TPV, tipranavir; VL, viral load

KATHOLIEKE UNIVERSITEIT LEUVEN

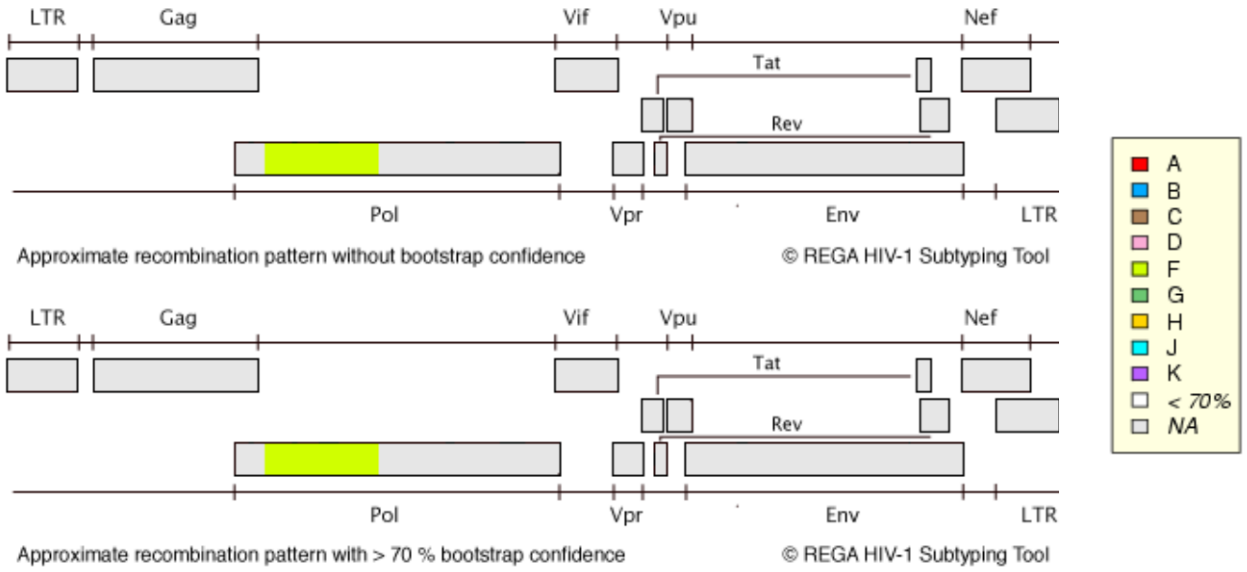
REGA HIV Subtyping Tool

HIV BIOINFORMATICS BIOAFRICA

Sequence Assignment

Sequence name : LP, length: 924 bps

Assignment: HIV-1 Subtype F (F1), Bootstrap: 100.0%



Motivation: *Subtype assigned based on sequence > 800 bps clustering with a pure subtype with bootstrap > 70% without recombination in the bootscan.*

Developed in cooperation with the Evolutionary group at University of Oxford, UK., the HIV-1 Pathogenesis and Immunotherapeutics Program at University of Pretoria, South Africa, and the REGA Institute at the Katholieke Universiteit Leuven, Belgium. Funded by the Flanders Bilateral Cooperation Program and the Wellcome Trust (grant #061238).. Suggestions or problems on the program please contact: Dr Tulio de Oliveira

Virology questions

- Shouldn’t there be an M184V?
- How should we interpret the T215D?
- What can we tell about her ART adherence?
- Do we care at all about the subtype?
- Would you perform any other diagnostic tests?

What would you do?

- **In February 2011,** what ART would you have started?
  - **A:** TDF/FTC + DRV/r
  - **B:** TDF/FTC + DRV/r + RAL
  - **C:** TDF/FTC + ETR + RAL
  - **D:** DRV/r + RAL
  - **E:** DRV/r + MVC

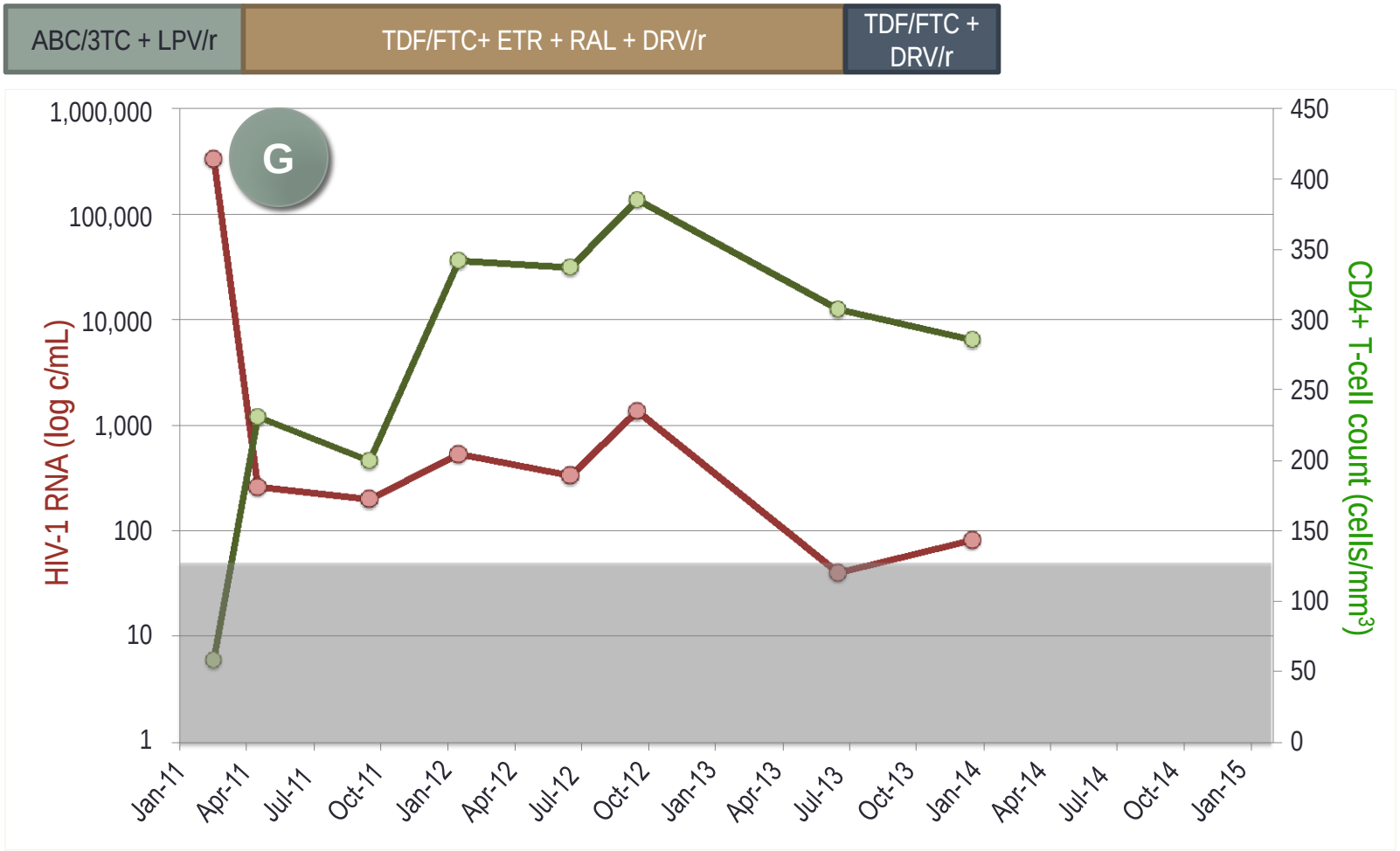
ETR, etravirine; MVC, maraviroc; RAL, raltegravir

ART started

- She's started on **TDF/FTC + ETR + RAL + DRV/r**
- Good initial response, but residual replication at low levels
- … simplified ART to **TDF/FTC + DRV/r BID** 2 years later
  - to facilitate adherence
  - to preserve ETR and RAL susceptibility
- Achieves VL <40 c/mL after simplifying ART
- 6 months later (November 2013) she returns to her hometown
- Her last VL was 82 c/mL (previous <40 c/mL) and CD4+ counts were 285 cells/mm^3 (16%)

BID, twice daily

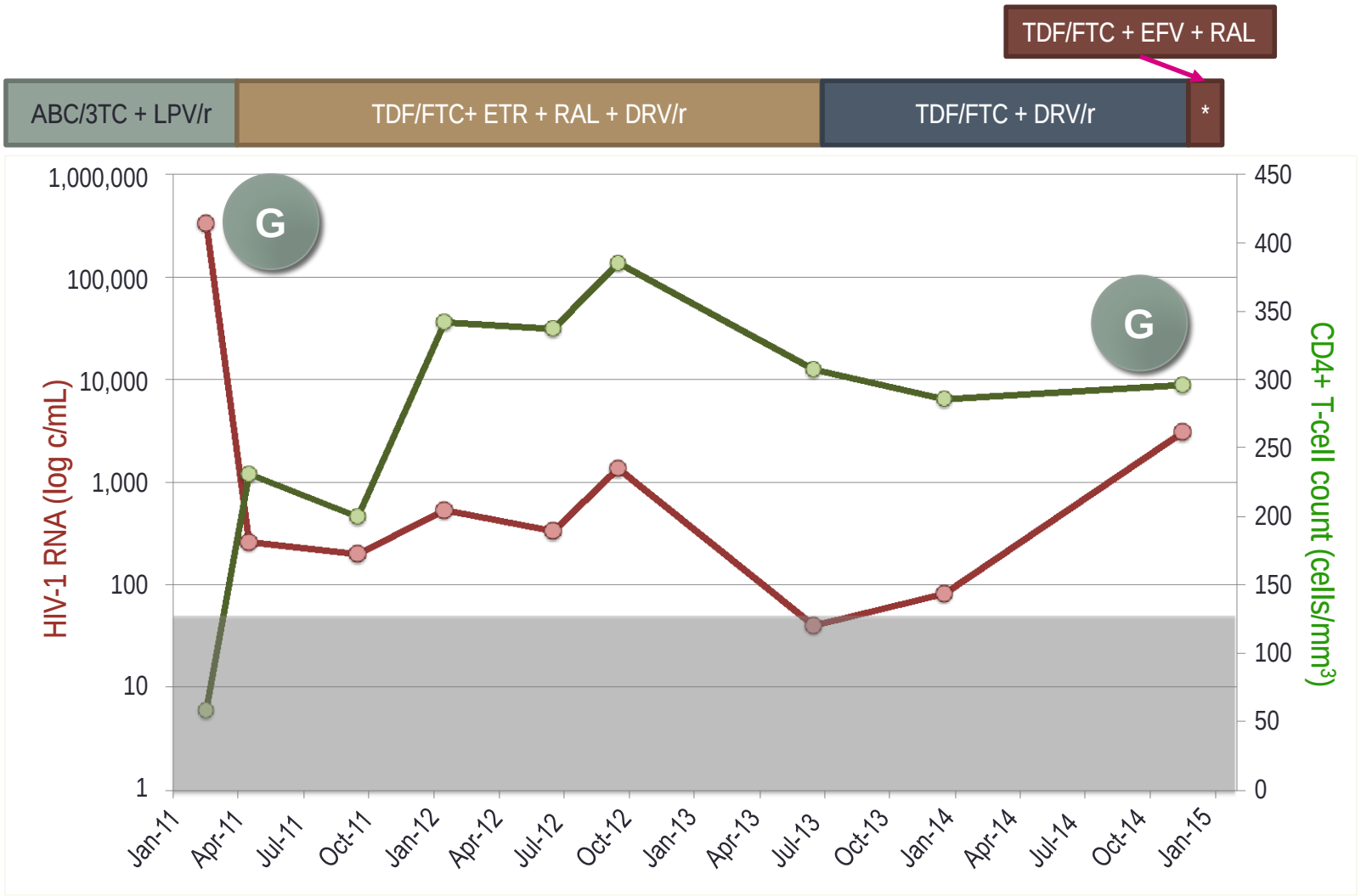
CD4+ & VL EVOLUTION



Returns to the clinic

- Her brother brings her to the clinic in **January 2015**. In **November 2014**, she has been diagnosed with:
  - **Rifampin-resistant pulmonary tuberculosis** (GeneXpert®)
    - Isoniazide + Ethambutol + Pirazinamide + Moxifloxacin
    - Stable, no shortness of breath, able to walk and talk
  - Virologic failure:
    - VL 3.046 c/mL, CD4 296 cells/mm^3
    - In Nov 2014 Genotype
    - Meanwhile started on **TDF/FTC + DRV/r + ETR + RAL**

CD4+ & VL evolution



EFV, efavirenz

Genotype 2 (VL 3.046 c/mL, CD4 296 cells/mm^3) November 2014

- RT: M184V, T215C
  - **High-level resistance: 3TC, FTC**
  - **Intermediate resistance: AZT, ABC, d4T,**
  - **Low-level resistance: ddI**
  - **Susceptible: TDF, all NNRTIs**

- PR:
- **Major**: V32I, M46I, I54L, V82A, I84V
- **Minor**: L10V, V11I, L33F; **Other**: M36I
  - **High-level resistance: DRV/r, FPV/r, IDV/r, NFV, ATV/r, LPV/r, SQV/r**
  - **Intermediate resistance: TPV/r**
  - **Low-level resistance: none**
  - **Susceptible: none**

- IN: **Major**: none; **Accessory**: none
  - **Susceptible: RAL, EVG, DTG**

- Subtype: F
- Tropism: no amplification

DTG, dolutegravir; EVG, elvitegravir

PI mutation scores

G1

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
V82A	15	0	15	30	30	30	15	0
I84V	60	15	60	60	30	60	60	30
L10V	0	0	0	0	0	0	0	0
V11I	0	5	5	0	0	0	0	0
L33F	5	5	10	0	5	5	0	10
V82A+L33F	-	-	10	-	-	-	-	-
Total:	**80**	**25**	**100**	**90**	**65**	**95**	**75**	**40**

G2

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
V32I	15	15	30	15	15	15	0	5
M46I	10	0	10	10	10	20	5	5
I54L	15	20	60	10	15	20	15	-10
V82A	15	0	15	30	30	30	15	0
I84V	60	15	60	60	30	60	60	30
L10V	0	0	0	0	0	0	0	0
V11I	0	5	5	0	0	0	0	0
L33F	5	5	10	0	5	5	0	10
V82A+V32I	-	-	10	-	-	-	-	-
V82A+I54L	10	-	-	10	10	10	10	-
V32I+I54L	-	10	-	-	10	-	-	-
V82A+M46I	10	-	10	10	5	10	-	-
V82A+L33F	-	-	10	-	-	-	-	-
Total:	**140**	**70**	**220**	**145**	**130**	**170**	**105**	**40**

PI, protease inhibitor

What salvage ART?

- What **SALVAGE ART** would you construct?
  - **A:** DTG + ETR + TDF + T-20
  - **B:** RAL + ETR + TDF + T-20
  - **C:** DTG + DRV/r + TDF/FTC
  - **D:** RAL + ETR + DRV/r + TDF/FTC
  - **E:** DTG + ETR + DRV/r + TDF/FTC + AZT

Would your choice be different if the integrase genotype showed:

- N155H ?
- Q148R + G140S?

T-20, enfuvirtide

Treatment decision

- Starts **DTG 50 mg BID + ETR 200 mg BID + TDF/FTC 1c/QD + AZT 300 mg BID + DRV/r 600/100 BID**

- Isoniazide + Ethambutol + Pirazinamide + Moxifloxacin continued until completing 12 months

QD, once daily

Rationale

DTG BID + ETR BID + TDF/FTC QD + AZT BID + DRV/r BID

- Could be her last opportunity to construct a fully active regimen; she's severely ill
- Apparently fully susceptible to **ETR** and **RAL**, but has selected high-level resistance to DRV/r during residual replication while on ETR & RAL: **Could have selected ETR & RAL-resistant minority variants**
- Likely susceptible to **DTG**, even in the presence of RAL/EVG resistance
- Limited or no **DRV/r** susceptibility, but:
  - Need a PI/r to counteract ETR / DTG interaction
  - Could expect some residual activity based on DUET studies[1]
- Full susceptibility to **TDF.** Adding co-formulated **FTC** does not increase pill burden and contributes to maintain M184V → TDF & AZT hypersusceptibility
- Partial susceptibility to **AZT** → beware toxicity (nausea/anaemia)!

1. Katlama C, et al. AIDS 2009;23:2298–300

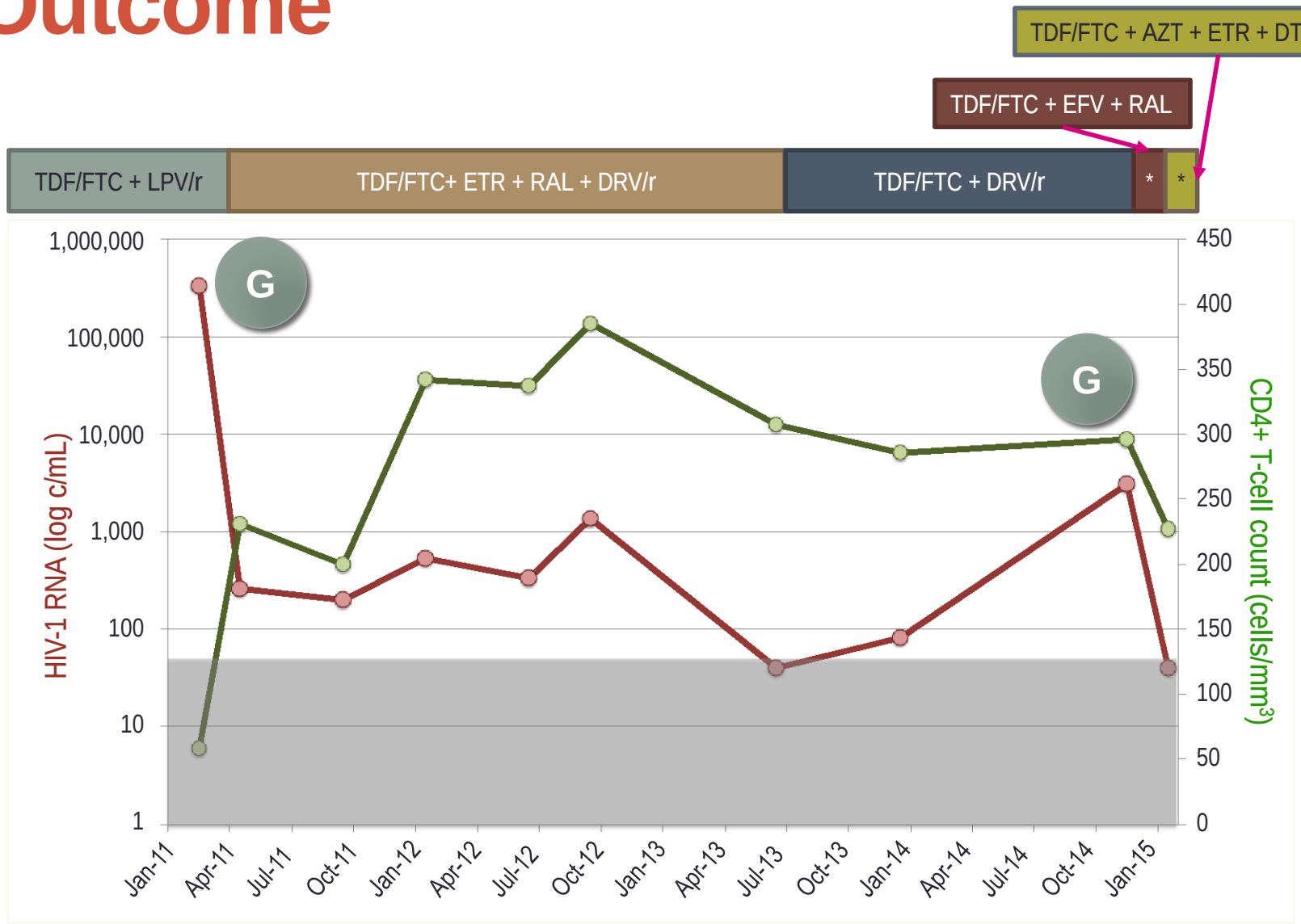
ETR reduces DTG levels unless given with a PI/r

	DTG+ETR	DTG+ETR + DRV/r	DTG+ETR + LPV/r
DTG C_{max}	↓ 52%	↓ 12%	↑ 7%
DTG AUC	↓ 71%	↓ 25%	↑ 11%
DTG C_{trough}	↓ 88%	↓ 37%	↑ 28%

DTG should not be used with ETR without co-administration of ATV/r, DRV/r, or LPV/r

DTG 50 mg QD; ETR 200 mg BID, DRV/r 600/100 mg BID; LPV/r 400/100 mg BID
AUC, area under curve; C_{max}, maximum dose concentration

Outcome


TDF/FTC + AZT + ETR + DTG + DRV/r
TDF/FTC + EFV + RAL
TDF/FTC + LPV/r
TDF/FTC+ ETR + RAL + DRV/r
TDF/FTC + DRV/r
*
*
G
G
1,000,000
100,000
10,000
1,000
100
10
1
HIV-1 RNA (log c/mL)
450
400
350
300
250
200
150
100
50
0
CD4+ T-cell count (cells/mm3)
Jan-11
Apr-11
Jul-11
Oct-11
Jan-12
Apr-12
Jul-12
Oct-12
Jan-13
Apr-13
Jul-13
Oct-13
Jan-14
Apr-14
Jul-14
Oct-14
Jan-15

How would you continue in the long run?

- Any chance of simplifying ART?
- Role of T-20
- Drug levels? Which ones?
- Phenotypic testing?
- Cost issues?