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CLINICAL SCENARIOS OF PHARMACOLOGICAL MANAGEMENT

Dr Margherita Bracchi

Chelsea and Westminster Hospital

Clarisse

- 31-year-old female, white British
- Dx with HIV in 2017: CD4+ 161, VL 407’959 cp/mL
- ***Baseline viral resistance****:* low level NNRTI resistance (E138G)
- ***Initial ART regimen:*** TDF/FTC + Dolutegravir

- Oesphageal candidiasis, *Pneumocyctis jirovecii* pneumonia and pulmonary *Mycobacterium avium-intracellulare* complex infection

Previous MAI treatment: Ethambutol + Azithromycin dual therapy
(developed itchy rash and fever with Rifabutin)

Treatment interrupted **at 7 months**

Hx of poor adherence

Lost to follow-up

Three years later

- VL 341’000, CD4+ 80 (13%)
- ***Viral resistance test:*** No additional resistance mutation

Re-starts ART in clinic: ABC/3TC/DTG (Triumeq) due to compliance and swallowing difficulties

Few months later

May 2020 - weight loss & diarrhoea, fever, shortness of breath on exertion , and malnourished (BMI 13.7)

- Pancytopaenic **Hb 39 g/L**
- CT scan - disseminated lymphadenopathy and hepatosplenomegaly

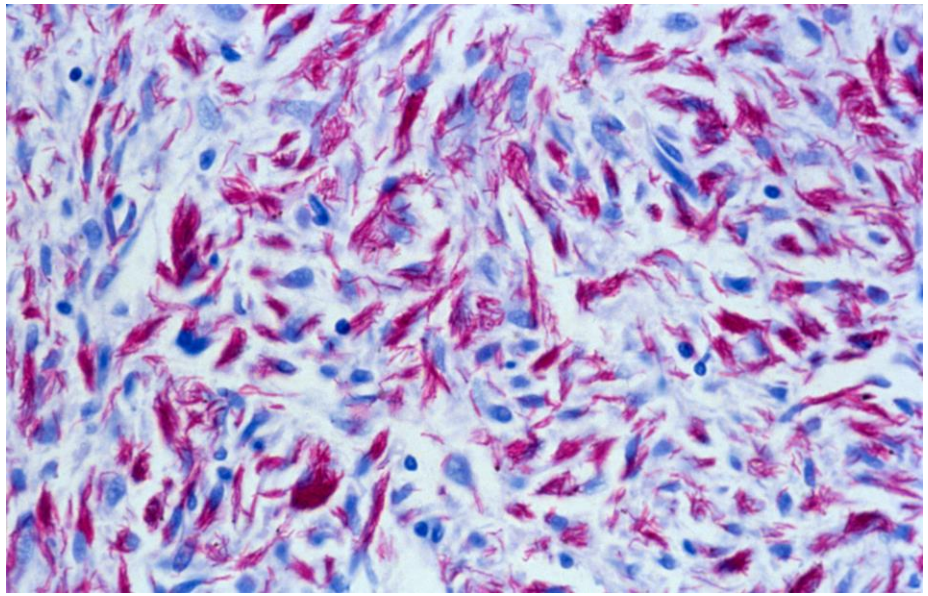
- Transfused two units of blood + inguinal lymphnode excisional biopsy

VL 191’000, CD4+ 75 (11%)
VRT: new NRTI resistance (**K70E and M184V**), INSTI wild type.
ART: bictegravir/TAF/FTC

10 days later ***@*** outpatient follow-up: febrile, anaemic, SOB+, fatigue +++ . Diarrhoea had resolved.

READMITTED

Lymph node biopsy:



AFB +++

TB PCR on tissue – neg for *M tuberculosis*

What would you do next?

A. Wait for the tissue culture and sensitivities

B. Start *M avium* treatment (Rif, Ethambutol, macrolide)

C. Start TB treatment (RHZE) **+** macrolide … and what about the ARVs?

EFV ?

RAL ?

BIC?

E138G, M184V, K70E

*RHZE rifampicin, isoniazid, pyrazinamide & ethambutol

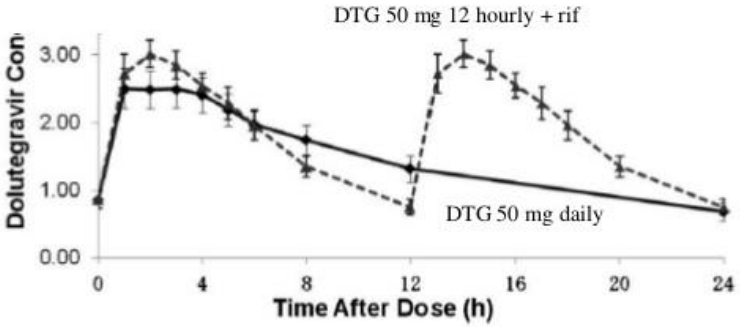
- Starts rifampicin, isoniazid, ethambutol and pyrazinamide (RHZE) + azithromycin.
- **Biktarvy switched to TDF/FTC + Dolutegravir 50 mg bd**

- Coadministration of BIC with Rifampicin: ↓ 75% of BIC AUC;
- Rifabutin: 38% ↓ of BIC AUC and **56%** ↓ of Cmin

Do Not Coadminister

Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF)

Dolutegravir & rifampicin



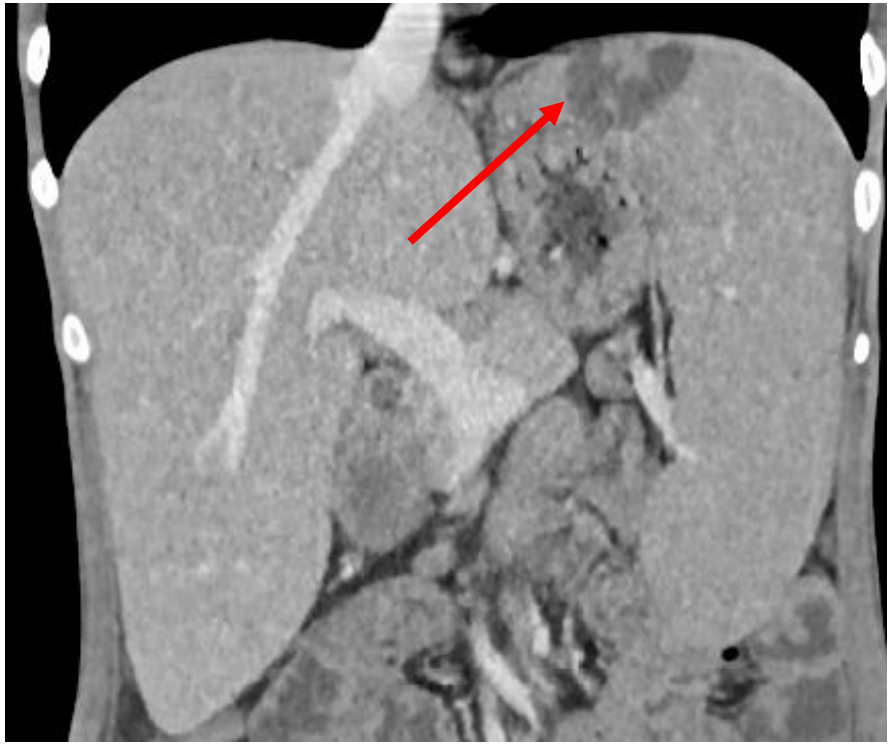
AUC_{0-24} DTG 50 mg/d 32.1
DTG 50 mg 12 hly + rif 42.6

Lymph node tissue cultures & mycobacterial blood cultures: *M. avium* (S to clarithromycin)-> rx adjusted to rifampicin, ethambutol and azithromycin

3 weeks later: abdominal distension + left upper quadrant pain & poor oral intake; **new onset of diarrhoea**

- CT Abdomen: progression of hepatosplenomegaly, wedge infarction of the spleen

- Bloods: severe pancytopaenia, low proteins & hypoalbuminaemia clotting derangement;

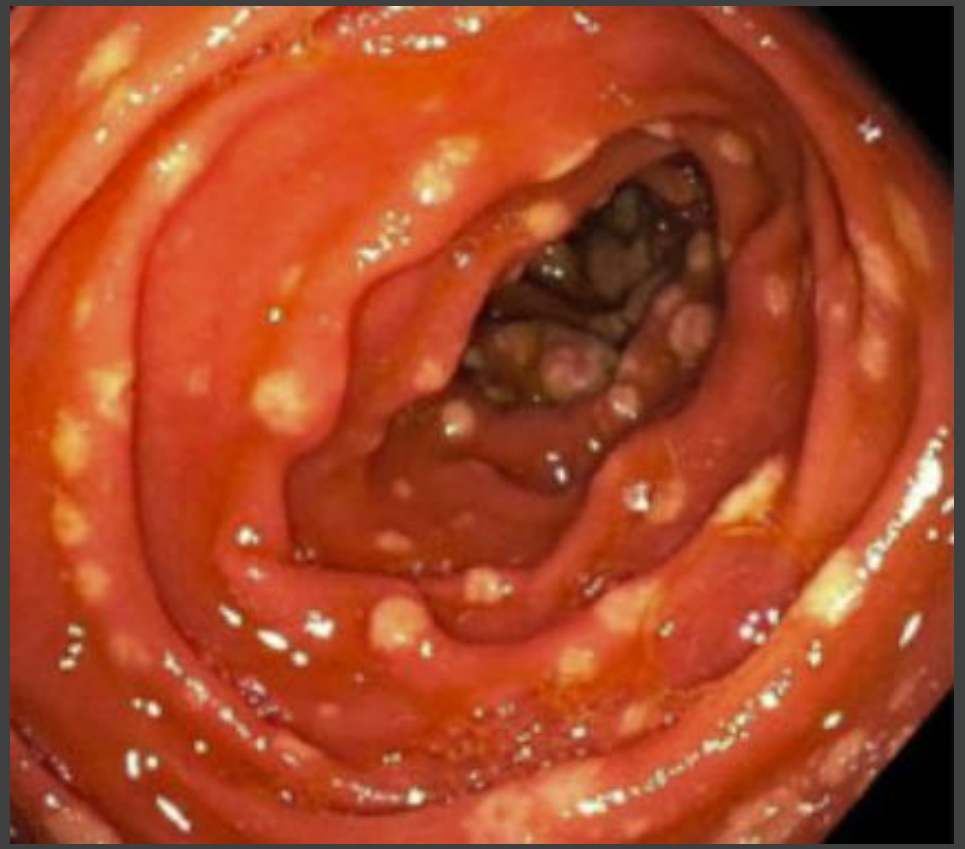


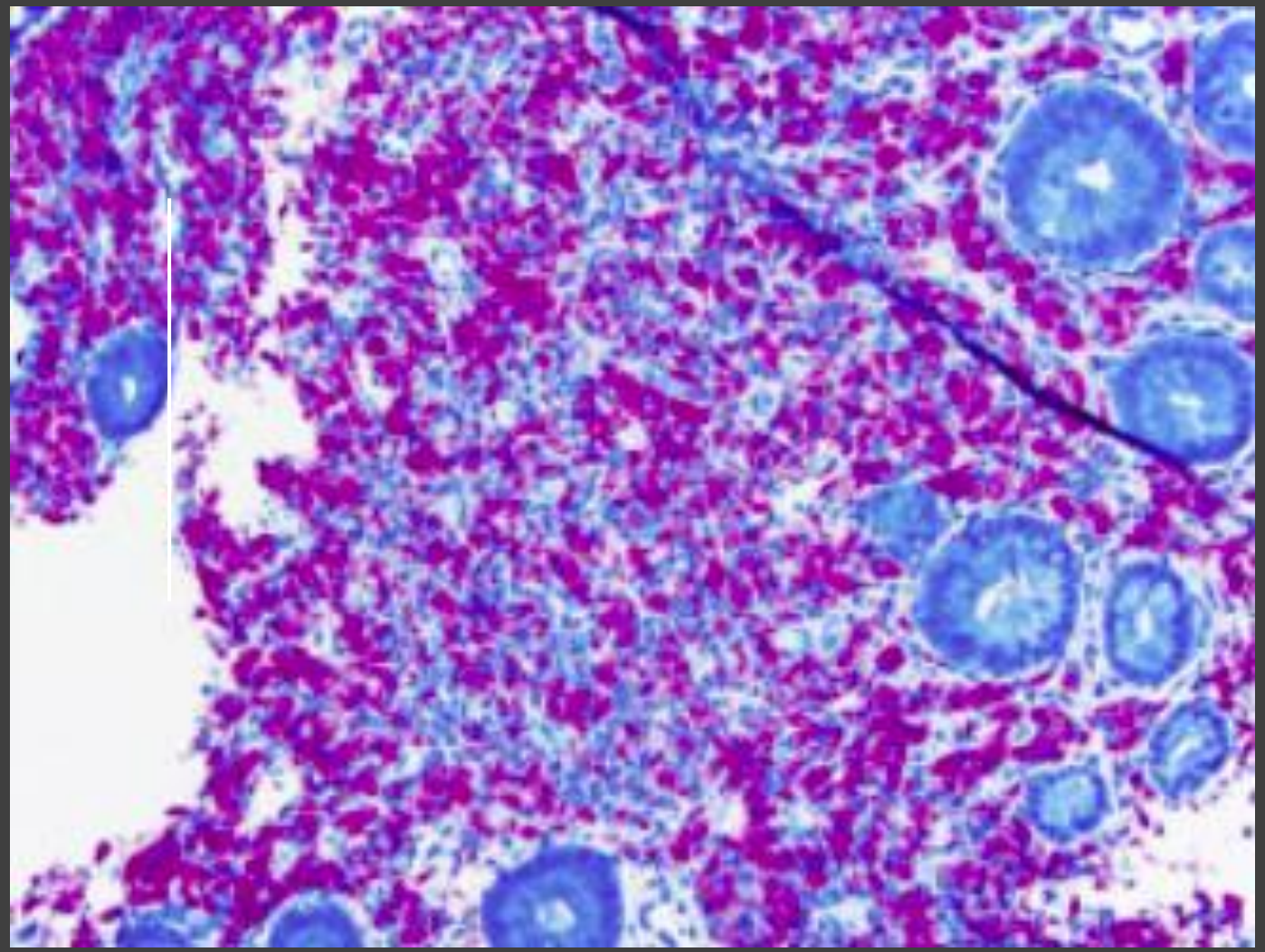
CD4+ 158 (from 80) and HIV-1 VL 1130 cp/ml (from 341’000 cp/ml)

What is happening?

A. Suboptimal treatment ?
B. Immune-reconstitution inflammatory syndrome?

Prednisolone
Amikacin
Bone Marrow – infiltrated by MAI
Screen for other OIs (CMV PCRs, Stools OCP, mycro/cryptosporidium)

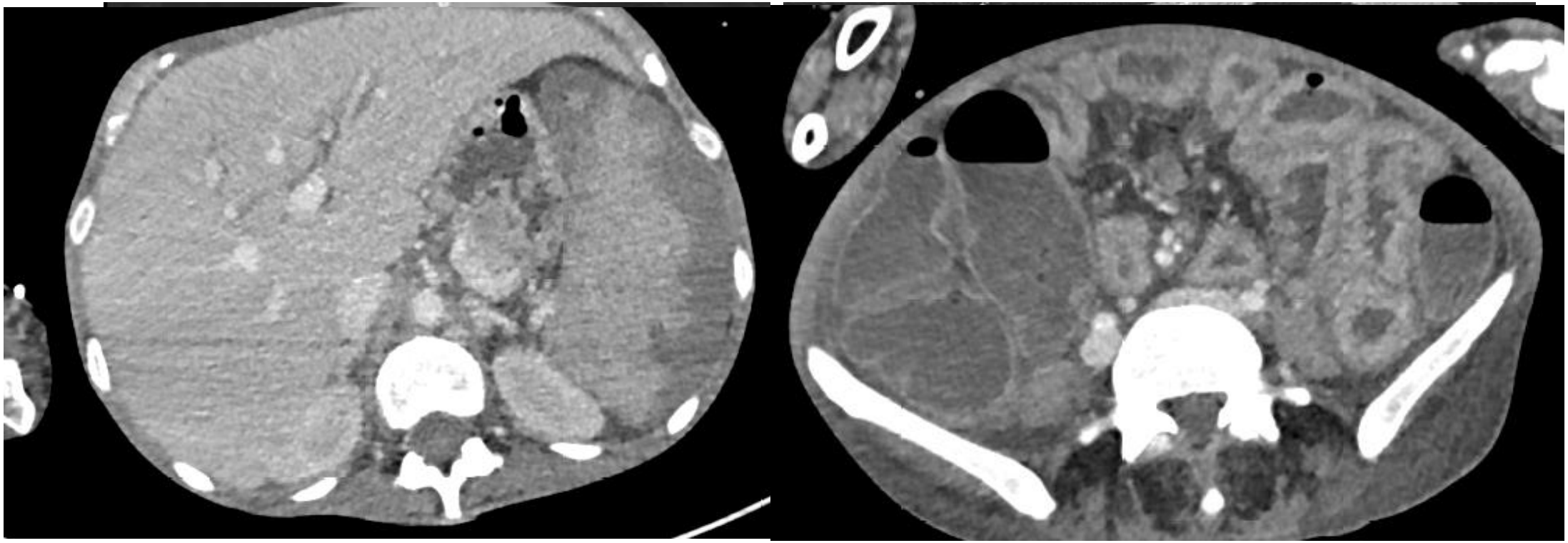




Gastroscopy: erosive gastritis and duodenitis, (multiple mucosal nodules)

Histopathology: Lamina propria expanded and replaced by numerous foamy macrophages, filled by numerous AFB (ZN and PAS stains)

Early July 2020 - Gram negative sepsis (*Serratia marcescens*) -> ITU

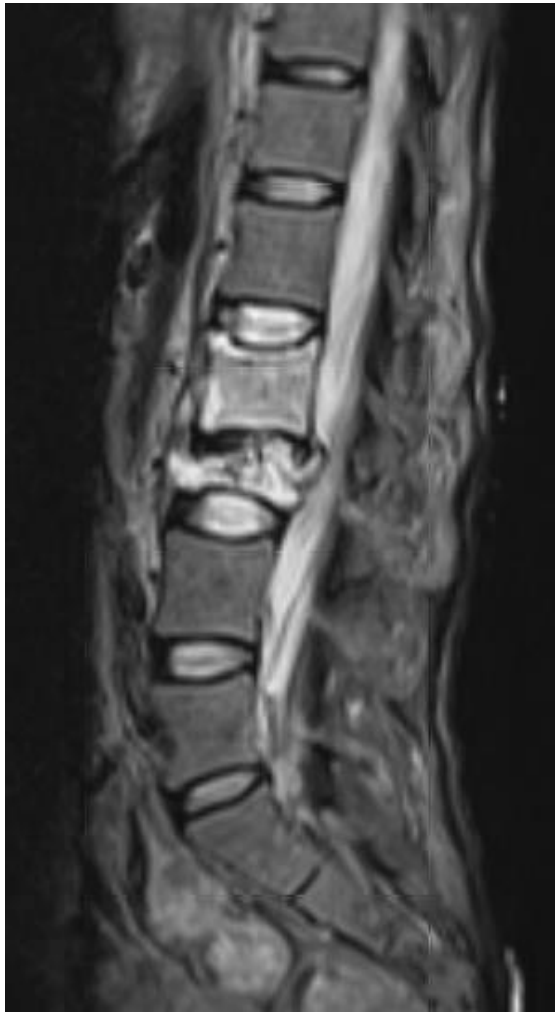


CT CAP – New innumerable bilateral lung nodules, some cavitating, progressive splenic infarct (1/3 of spleen) small bowel thick walled and mildly dilated, suggestive of hyoperfusion syndrome/shock syndrome.

Persistent profuse diarrhoea and high volume NG aspirates
starts **Total Parenteral Nutrition**
(BMI 13.3 Kg/m^2)

- **Three-week ITU stay:** two further episodes of sepsis (*Candida glabrata* and *Vancomycin Resistant Enterococcus* blood stream infections*)*

- Ongoing positive blood cultures for *Candida glabrata* and new onset of back pain -> **Vertebral osteomyelitis** (biopsy + for *M avium* & *Candida glabrata)*



Konishi et al. AIDS Research and Therapy (2021) 18:90
https://doi.org/10.1186/s12981-021-00417-0

AIDS Research and Therapy

CASE REPORT Open Access

Protein-losing enteropathy caused by disseminated *Mycobacterium avium* complex infection in a patient receiving antiretroviral therapy: an autopsy case report

Keiji Konishi[1*], Hidenori Nakagawa[1], Akio Nakahira[2], Takahiro Okuno[3], Takeshi Inoue[3] and Michinori Shirano[1]

Abstract

Background: Disseminated *Mycobacterium avium* complex infection is an important indicator of acquired immunodeficiency syndrome (AIDS) in patients with advanced human immunodeficiency virus (HIV) infection. Effective antiretroviral therapy has dramatically reduced the incidence of and mortality due to HIV infection, although drug resistance and poor medication adherence continue to increase the risk of disseminated *M. avium* complex infection. However, gastrointestinal lesions in cases of disseminated *M. avium* complex infection resulting in protein-losing enteropathy have been rarely discussed. Therefore, we present a case of protein-losing enteropathy caused by disseminated *M. avium* complex infection in a patient undergoing antiretroviral therapy.

Case presentation: A 29-year-old man was diagnosed with AIDS 4 years ago and was admitted for a 10-month history of refractory diarrhea and fever. Despite receiving antiretroviral therapy, the viral load remained elevated due to poor medication adherence. The patient was diagnosed with disseminated *M. avium* complex infection and started on antimycobacterial drugs 2 years before admission. However, the infection remained uncontrolled. The previous hospitalization 1 year before admission was due to hypoalbuminemia and refractory diarrhea. Upper gastrointestinal endoscopy revealed a diagnosis of protein-losing enteropathy caused by intestinal lymphangiectasia, and treatment with intravenous antimycobacterial drugs did not resolve his intestinal lymphangiectasia. The patient inevitably died of sepsis.

Conclusions: Clinical remission is difficult to achieve in patients with AIDS and protein-losing enteropathy caused by disseminated *M. avium* complex infection due to limited options of parenteral antiretroviral drugs. This report highlights the importance of identifying alternative treatments (such as an injectable formulation) for patients who do not respond to antiretroviral therapy due to protein-losing enteropathy with disseminated *M. avium* complex infection.

Keywords: Disseminated *Mycobacterium avium* complex infection, Protein-losing enteropathy, Antiretroviral therapy, Acquired immunodeficiency syndrome

J Antimicrob Chemother 2018; **73**: 546–548
doi:10.1093/jac/dkx385
Advance Access publication 25 October 2017

Undetectable antimicrobial plasma concentrations in an HIV-positive patient with protein-losing enteropathy and chylothorax during *Mycobacterium genavense* and *Leishmania* abdominal infections

I. Motta[1]*†, M. Trunfio[1†], A. Calcagno[1], V. Pirriatore[1], S. Scabini[1], A. Palazzo[1], S. Audagnotto[1], G. Fatiguso[1], V. Liberini[2], M. Bellò[2], A. D'Avolio[1], G. Di Perri[1] and S. Bonora[1]

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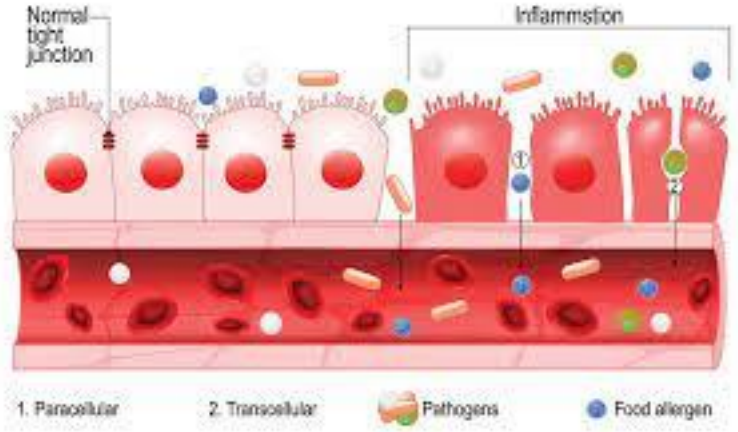
L 3 weeks prior)

tput diarrhoea ?

Inflammation, further immunosuppression, gut microbial translocation



Reduced ARVs absorption due to duodenal disease (*M avium* infiltration) and **PROTEIN LOSING ENTEROPATHY**

Craven MD, J Intern Med. 2019 Mar;33(2):383-402; Konishi et al. AIDS Research and Therapy (2021) 18:90; Motta et al. J Antimicrob Chemother 2018; 73: 546–548

What next?

A. Leave on current regimen until resistance test is back
B. Send TDM/repeat sample to confirm VF
C. Switch to boosted protease inhibitor + TDF/FTC and switch to rifabutin (…but previous allergy, DDIs and ?malabsorption)
D. Add IV AZT, T20 sc and continue DTG + TDF/FTC …

<u>Added T20 + IV AZT (2 mg/Kg q4hrs) + EFV 600 mg</u>,
continued DTG 50 mg bd + TDF/FTC
Sent out request for IBALIZUMAB
Switched Rifampicin, Ethambutol and Azithromycin IV
continued Amikacin (IV)

Concomitant medications

- Meropenem (*Serratia* in Blood cultures and Urine cultures)
- Daptomycin (*Vancomycin Resistant Enterococcus* in Blood cultures and Urine cultures)
- Anidulafungin (*Candida glabrata* in Blood cultures and vertebral biopsy)
- Inhaled Pentamidine
- Treatment dose LMWH (Deep Vein Thrombosis)
- Naso-gastric feeding (intermittently tolerated) and Total Parenteral Nutrition

Viral Resistance Test
RT 184V, K70E, E138G
PR nil

Drug resistance interpretation: IN — HIVDB 9.0 (2021-02-22)

IN Major Resistance Mutations:	**R263K**
IN Accessory Resistance Mutations:	None
Other Mutations:	None

Integrase Strand Transfer Inhibitors	
bictegravir (BIC)	Intermediate Resistance
cabotegravir (CAB)	Intermediate Resistance
dolutegravir (DTG)	Intermediate Resistance
elvitegravir (EVG)	Intermediate Resistance
raltegravir (RAL)	Low-Level Resistance

IN comments

IN Major

- **R263K** is selected in vitro by EVG, DTG, and BIC, and in patients receiving DTG. It reduces DTG and BIC susceptibility about 2-fold and EVG susceptibility somewhat more.

Dosage Considerations

- This virus is predicted to have intermediate-level reduced susceptibility to **CAB**. The use of the combination of **CAB**/RPV should be considered to be contraindicated.
- There is evidence for intermediate **DTG** resistance. If **DTG** is used, it should be administered twice daily.

Therapeutic Drug Monitoring

Test Results

Dolutegravir	*Sample Date & Time*	*Time post-dose*	*Dosing Regimen*	*Concentration (ng/ml)*
	24 July 2020 7:00	11H 37MIN	Twice Daily Equal	58
Comments	The dolutegravir concentration is low and is below the target. The estimated cut off for dolutegravir has yet to be defined. Based on in vitro protein-adjusted IC90, the estimated minimum trough concentration required for HIV-1 is 64 ng/ml.			

Suggested therapeutic targets established in vitro (DTG): inhibitory concentration at 90% (IC90) for wild type virus:

64 ng/mL

Kobayashi M et al. Antimicrob Agents Chemother. 2011; 55:813–821.
Elliot E et al. Curr Opin Infect Dis 2017; 30: 58-73.

Summary of Steady-State Plasma DTG PK Parameters When DTG is Given at a Dose of 50 mg Once Daily Alone (Period 1), of 50 mg Twice Daily Alone (Period 2), or of 50 mg Twice Daily Together With Steady-State RIF (Period 3)

Pharmacokinetic Parameter	Period 1: 50 mg of DTG Once Daily	Period 2: 50 mg of DTG Twice Daily	Period 3: 50 mg DTG Twice Daily Plus RIF	GMR (90% CI) (Period 3 vs. Period 1)	GMR (90% CI) (Period 3 vs. Period 2)
$AUC_{0-\tau}$ (μg·h/mL)	32.1 (44)	46.3 (55)	21.3 (31)	ND	0.46 (0.38 to 0.55)
AUC_{0-24} (μg·h/mL)*	32.1 (44)	92.7 (55)	42.6 (31)	1.33 (1.15 to 1.53)	ND
C_{τ} (μg/mL)	0.55 (91)	2.41 (77)	0.67 (55)	1.22 (1.01 to 1.48)	0.28 (0.23 to 0.34)
C_{max} (μg/mL)	2.65 (32)	5.55 (49)	3.13 (25)	1.18 (1.03 to 1.37)	0.57 (0.49 to 0.65)
CL/F (L/h)	1.56 (44)	1.08 (55)	2.35 (31)	1.51 (1.30 to 1.75)	2.17 (1.87 to 2.53)
$t_{1/2}$ (h)	10.7 (40)	9.5 (48)	4.2 (23)	0.40 (0.34 to 0.46)	0.45 (0.38 to 0.52)

PK values are provided as geometric means with coefficient of variance (% CV).
AUC_{0-24} were calculated by doubling the AUC_{0-12} estimates.
*For twice daily dosing, AUC_{0-24} was calculated by doubling the AUC_{0-12} estimates.
ND, not determined.

JAIDS JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES

Safety, Tolerability, and Pharmacokinetics of the HIV Integrase Inhibitor Dolutegravir Given Twice Daily With Rifampin or Once Daily With Rifabutin: Results of a Phase 1 Study Among Healthy Subjects

Dooley, Kelly et al JAIDS Journal of Acquired Immune Deficiency Syndromes62(1):21-27, January 1, 2013.

Test Results

Dolutegravir	*Sample Date & Time*	*Time post-dose*	*Dosing Regimen*	*Concentration (ng/ml)*
	24 July 2020 10:00	2H 15MIN	Twice Daily Equal	319.00
Comments	There are insufficient data for this dosing regimen to predict a trough concentration. Please repeat TDM with a sample collected at trough. The estimated cut off for dolutegravir has yet to be defined. Based on the in vitro protein-adjusted IC90, the estimated minimum trough concentration required for wild type HIV-1 is 64 ng/ml			

Cmax : ~3670 ng/mL* (2 hrs post 50 mg qd dosing)

Kobayashi M et al. Antimicrob Agents Chemother. 2011; 55:813–821.
**Elliot E et al. Curr Opin Infect Dis 2017; 30: 58-73.*

Next steps- bridging to bPI

- DTG 50 mg TDS + TDF/FTC + EFV 600 mg + AZT IV
- T20 (switched to IV)
- Rifampicin stopped and Rifabutin started

Further TDMs

Physician Information

CCL Account No	DD1050	Requesting Physician	Bracchi
Clinic/Hospital Name	Chelsea And Westminster		

Test Results

Dolutegravir	*Sample Date & Time*	*Time post-dose*	*Dosing Regimen*	*Concentration (ng/ml)*
	04 August 2020 7:00	7H 20MIN	8 Hourly	2337.00
Comments	No interpretive comment available for 8 hourly dosing regimen.			

Efavirenz	*Sample Date & Time*	*Time post-dose*	*Dosing Regimen*	*Concentration (ng/ml)*
	04 August 2020 7:00	10H 00MIN	Once Daily	1526.00
Comments	Based on a population mean half-life of 36 h, the projected trough efavirenz concentration is estimated at ~ 1165 ng/ml and is within the target range. Trough concentrations greater than 1000 ng/ml have been reported to be associated with a good virological response, whereas concentrations greater than 4000 ng/ml have been reported to be associated with an increased incidence of CNS effects. Please note, projected trough concentrations calculated using a population mean half-life may be affected by ethnicity and concurrent medications.			

Emtricitabine	*Sample Date & Time*	*Time post-dose*	*Dosing Regimen*	*Concentration (ng/ml)*
	04 August 2020 7:00	11H 50MIN	Once Daily	146.00
Comments	Since emtricitabine (FTC) undergoes intracellular phosphorylation to the active triphosphate, plasma concentrations are difficult to directly relate to efficacy and toxicity. The clinical cut off for emtricitabine has yet to be defined. Based on data derived from a study in healthy volunteers with a dose of 200 mg daily, mean (CV) steady-state Cmax and Cmin values of emtricitabine in plasma are 1800ng/ml (39%) and 90 ng/ml (78%), respectively. Steady-state trough plasma concentrations reached levels approximately 4-fold above the in vitro IC90 values for anti-HIV activity (20 ng/ml).			

After 10 days…

- DRV 600 mg bd + RIT 100 mg bd
- DTG 50 mg tds +Truvada
- EFV stopped
- Rifabutin reduced to 150 mg od

Repeat VL 1100 cp (from 66’000 cp)

Further TDMs

Test Results

Darunavir	Sample Date & Time	Time post-dose	Dosing Regimen	Concentration (ng/ml)
	13 August 2020 11:30	4H 0MIN	Twice Daily Equal	11508
Comments	It is difficult to accurately predict darunavir trough concentrations. Based on population data for darunavir/ritonavir (600/100 mg twice daily) in HIV infected adults (non-pregnant, in the absence of known interacting drugs), the observed concentration lies above the 90th percentile. In this study patients with drug concentrations above the 90th percentile had trough concentrations above the estimated minimum trough concentration required for WT HIV-1 (55 ng/ml). In addition, the trough concentrations were above the estimated minimum trough concentration for protease inhibitor resistant HIV-1 (550 ng/ml) For highly experienced patients a greater concentration may be required, with a suggested target of 1800 ng/ml.			

Cmax

VL 150 cp

Dolutegravir	Sample Date & Time	Time post-dose	Dosing Regimen	Concentration (ng/ml)
	13 August 2020 11:30	4H 0MIN	Other	2533
Comments	In the absence of the exact dosing details, it is not possible to comment fully on this result. The estimated cut off for dolutegravir has yet to be defined. Based on the in vitro protein-adjusted IC90, the estimated minimum trou			

Ritonavir	Sample Date & Ti			
	13 August 2020 11			
Comments	In this instance ritonavir required has not been d			

Test Results

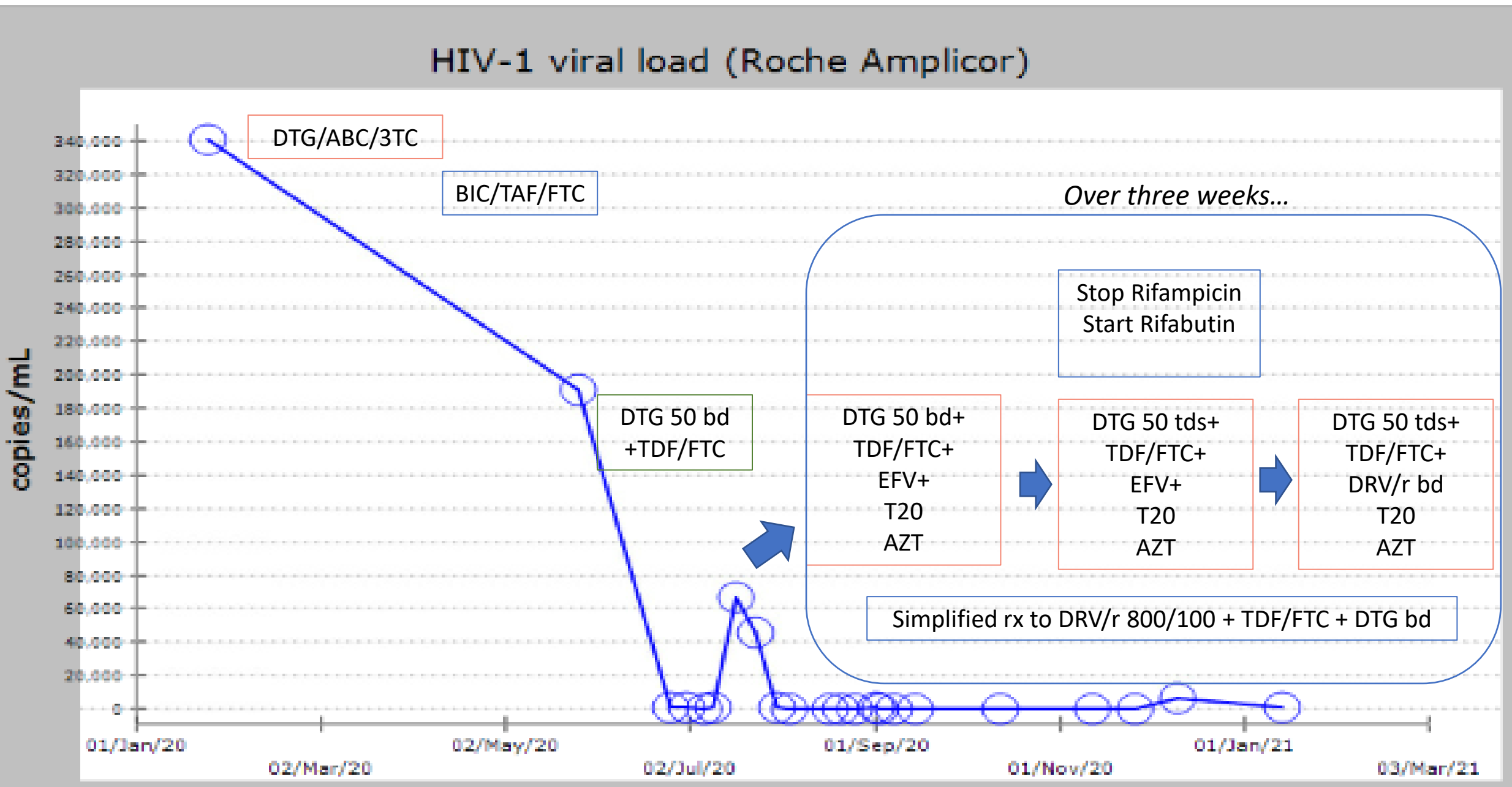
Darunavir	Sample Date & Time	Time post-dose	Dosing Regimen	Concentration (ng/ml)
	13 August 2020 07:02	10H 10MIN	Twice Daily Equal	11722
Comments	The darunavir trough concentration is 213.1x the target. The clinical cut off for darunavir has yet to be defined. Based on the in vitro protein-binding-corrected IC50, the estimated minimum trough concentration required for WT HIV-1 is 55 ng/ml and for protease inhibitor resistant HIV-1 is 550 ng/ml. For highly experienced patients a greater concentration may be required, with a suggested target of 1800 ng/ml.			

Cmin

Dolutegravir	Sample Date & Time	Time post-dose	Dosing Regimen	Concentration (ng/ml)
	13 August 2020 07:02	7H 10MIN	Other	2206
Comments	In the absence of the exact dosing details, it is not possible to comment fully on this result. The estimated cut off for dolutegravir has yet to be defined. Based on the in vitro protein-adjusted IC90, the			

	13 August 2020 07:02	10H 10MIN	Twice Daily Equal	476
Comments	In this instance ritonavir is being used as a pharmacokinetic enhancer and the minimum plasma concentration required has not been defined.			

Switched to DRV/r 800/100 + DTG 50 bd + TDF/FTC

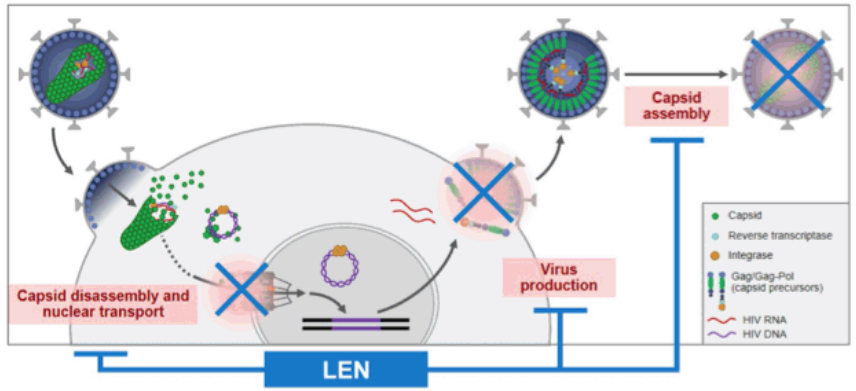

HIV-1 viral load (Roche Amplicor)
copies/mL
340,000
320,000
300,000
280,000
260,000
240,000
220,000
200,000
180,000
160,000
140,000
120,000
100,000
80,000
60,000
40,000
20,000
0
01/Jan/20
02/Mar/20
02/May/20
02/Jul/20
01/Sep/20
01/Nov/20
01/Jan/21
03/Mar/21
DTG/ABC/3TC
BIC/TAF/FTC
DTG 50 bd
+TDF/FTC
Over three weeks…
Stop Rifampicin
Start Rifabutin
DTG 50 bd+
TDF/FTC+
EFV+
T20
AZT
DTG 50 tds+
TDF/FTC+
EFV+
T20
AZT
DTG 50 tds+
TDF/FTC+
DRV/r bd
T20
AZT
Simplified rx to DRV/r 800/100 + TDF/FTC + DTG bd

What options now & future ?

LEN DDI Clinical Recommendations

- CYP3A P-gp + LEN
  - Increased LEN [illegible] after coadministration with strong CYP3A/P-gp inhibitors is not clinically relevant; supports coadministration without dose modification
- UGT1A1 + LEN
  - In the absence of additional data, coadministration of LEN and strong UGT1A1 inhibitors is not recommended
- [illegible] inducers of CYP/P-gp/UGT should be avoided
- Gastric acid + LEN
  - LEN can be coadministered with gastric acid reducers
- LEN + CYP3A
  - Caution is advised if LEN is coadministered with sensitive CYP3A substrates, but not P-gp, BCRP nor OATP substrates

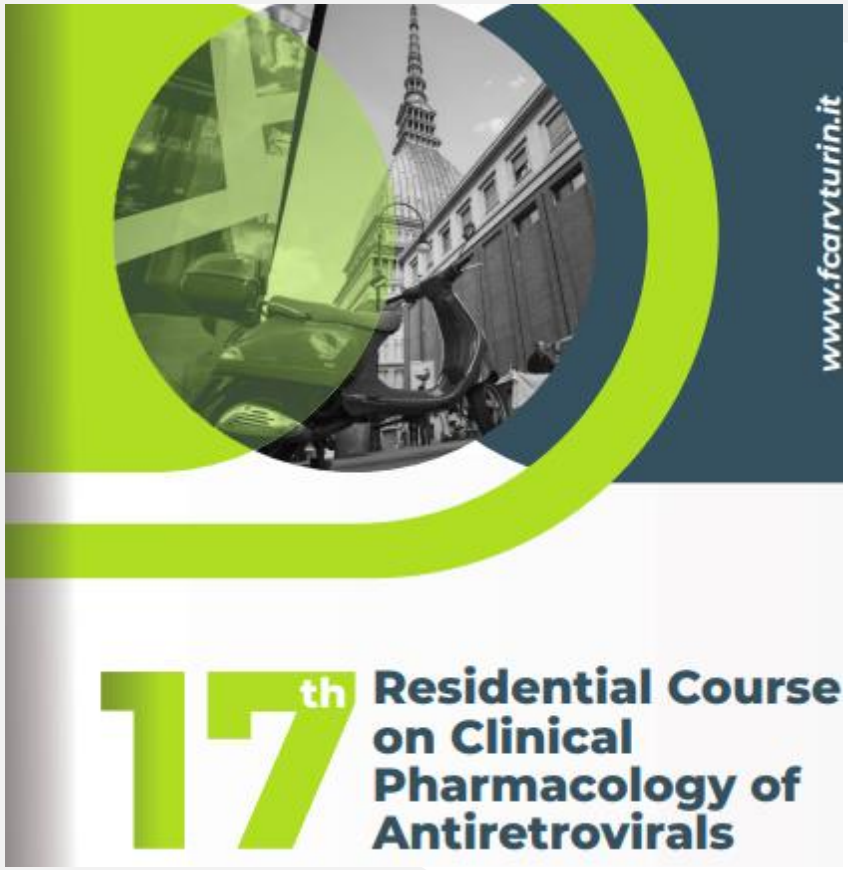
Lenacapavir (LEN): First-in-class HIV Capsid Inhibitor



EC_{50}, half maximal effective concentration.

Conclusions

- GI involvement in **disseminated M avium infection** can lead to malabsorption via invasion of mucosa and onset of **PROTEIN LOSING ENTEROPATHY**
- **Clinical management is often complex** (polypharmacy, DDIs, severity of disease) and requires **enhanced MTD approach**: gastroenterologist, pharmacologists, dieticians, ITU, radiologists, microbiology..
- **ARVs malabsorption is rare & extremely difficult to manage:** Importance of frequent **VL monitoring** and **TDM** to guide choice and dosing of antiretrovirals
- **ARVs with administration routes alternative than oral** (IV, injectables,implants)



THANK YOU

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”Clarisse”
Prof Marta Boffito
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Dr David Asboe
Dr Jessica Longley
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CWH ITU