Five years experience with Raltegravir in a large HIV centre

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Background

- Raltegravir (RAL) is the first integrase strand transfer inhibitor (INSTI) active against HIV in clinical use as a component of antiretroviral therapy (ART)
- It was licensed by European Medicines Agency in December 2007
- Real life ART experience is informative and complements trial data
- We aimed to evaluate our use of RAL in naive and experienced patients, including those with hepatitis and mycobacterial co-infections and off-license use

Methods

- Pharmacy data and the departmental HIV database were used to identify all patients who had taken at least one dose of RAL, up to 30 November 2012, outside of clinical trials
- A standardised reporting form was used to extract data from clinical and laboratory records

Results

Demographics of patient group

- 215 individuals with HIV-1 infection provided 502 patient-years of RAL experience, with characteristics shown in table:

Gender	Male	Female	Trans-gender	Total
Number (%)	166 (77%)	48 (22%)	1 (0.5%)	215 (100%)
Median age (IQR)	45 (38, 51)	38 (33, 43)	-	43 (37, 49)
Caucasian n (%)	144 (87%)	10 (21%)	-	155 (72%)
African/Caribbean n (%)	19 (11%)	35 (79%)	-	54 (25%)
Other ethnicity	3 (2%)	3 (6%)	-	6 (3%)

- Median duration of RAL use 2.6 years (interquartile range [IQR] 0.8, 3.5)

Previous antiretroviral therapy (ART)

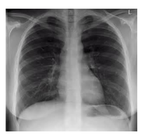
- 189 (88%) ART-experienced, with median CD4 323 cells/uL (IQR 132, 569)
- 26 (12%) ART-naive, with median CD4 54 cells/uL (IQR 23, 258)

- Of 51 patients not on ART at the time of starting RAL, median HIV viral load (VL) was 66650 copies/mL (range 565, 8647191)

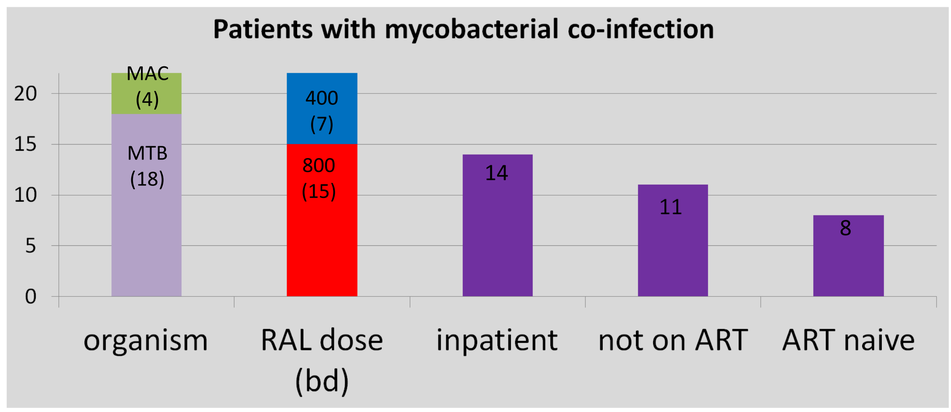
Pregnancy

- 6 women took RAL during pregnancy
- 5/6 added RAL to existing regimen (treatment intensification), at median 32 weeks gestation. One switch from protease inhibitor for tolerability
- All VL <40 at delivery, all infants HIV negative, no foetal abnormalities

Mycobacterial co-infection



- 22 individuals: 9/22 (41%) male; 17/22 (77%) African/Caribbean
- Median VL in 11/22 not on ART on starting RAL: 109833 copies/mL
- 3 with K103N at baseline and 1 with G190S
- Median CD4 count in all 22: 83 cells/uL



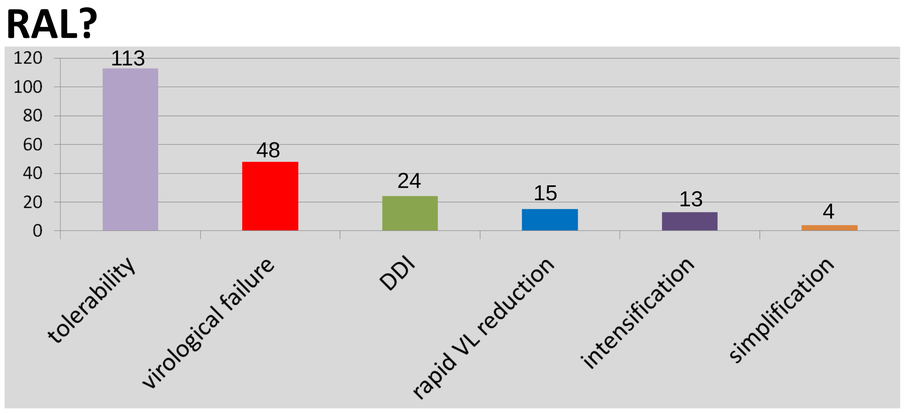
- One stopped RAL due to side effects (peripheral neuropathy)

Why switch/add RAL?

189 experienced patients had 217 reasons for starting RAL

Naive patients chose RAL for rapid VL reduction (14/26) or avoiding DDIs (13/26)

DDI = drug-drug interactions

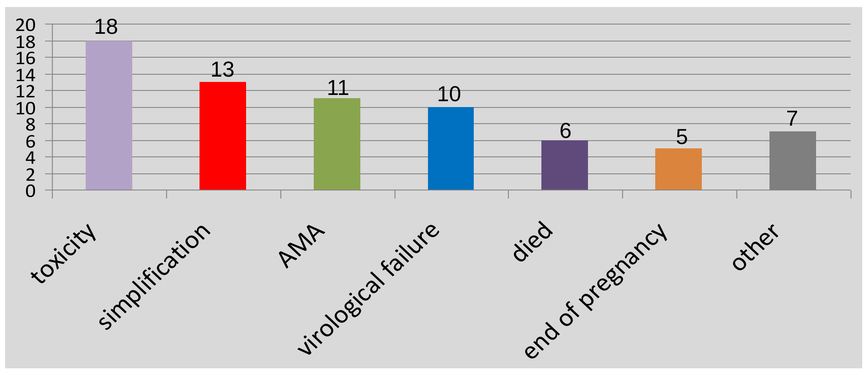


Why stop?

- 71 stopped RAL
  – reasons clear in 70/71

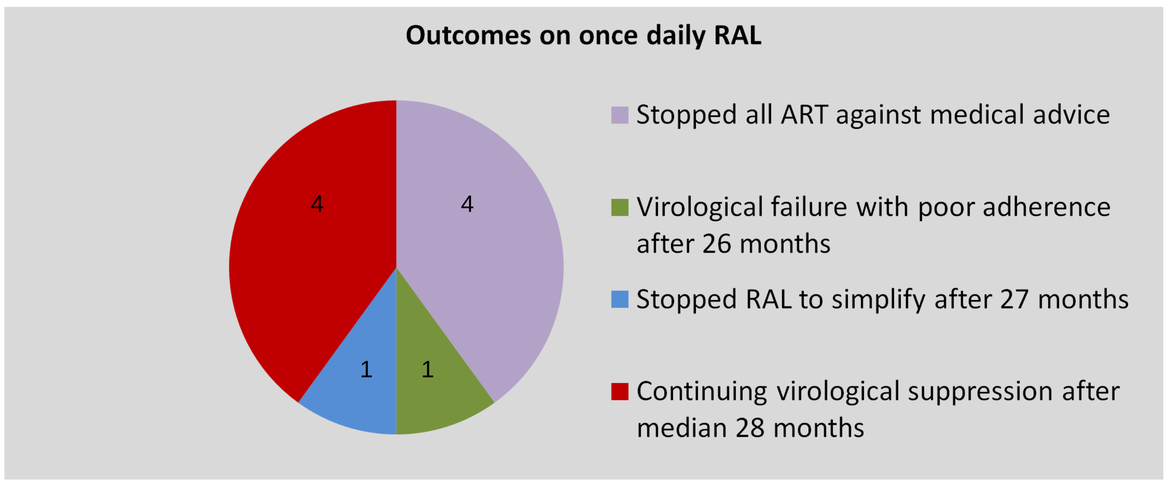
Toxicity: 1 with acute hepatitis due to RAL; 3 with headaches

AMA = patient stopped all/some of ART against medical advice



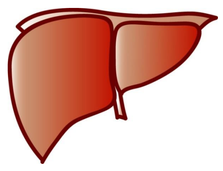
Once daily dosing

- 10 individuals took RAL 800mg od: all were ART experienced
- All had previous PI use and 5/10 switched directly from PI-based regimens
- 3/10 undetectable at switch
- 6/10 had nNRTI resistance mutations (K103N or Y181C or both)
- 7/10 took RAL once daily with a once-daily PI-based regimen



- 4 still virologically suppressed: median time on RAL 28 months (range 7.2 – 29.3 months). 3/4 on once daily protease inhibitors; 1/4 with NRTI backbone

Hepatitis co-infection



- 35 individuals providing 92 patient-years on RAL
- 21 hepatitis B sAg+ and 14 hepatitis C RNA+

21 with hepatitis B infection
19/21 on tenofovir-containing ART

14/21 with raised ALT on RAL, but 5/14 raised at baseline

14 with hepatitis C infection
3 started treatment with interferon and ribavirin while on RAL

- None stopped RAL due to hepatotoxicity

Integrase resistance after virological failure

- 10/215 (5%) stopped RAL due to virological failure:
- 4/10 had successful sequencing
  (6 had low level viraemia precluding sequencing or failed sequencing)
  2/4 showed INSTI resistance after virological failure:

Patient 1: **Q148R**, on background of extensive triple-class resistance

Patient 2: **Y143R**, plus pre-existing M184V, Y115F and major PI mutations

2/4 without INSTI resistance had no pre-existing resistance mutations

Conclusions

- RAL appears safe in clinical practice, with no excess toxicity seen above that reported in clinical trials
- RAL was used safely and effectively in pregnancy and with hepatitis and mycobacterial co-infections
- Once daily dosing is effective where adherence is good
- INSTI resistance on failure occurred in those with pre-existing resistance to other classes

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