Caso Clínico

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Conflito de Interesses

- Sem conflito de interesses a declarar

Sexo masculino, nascido em fevereiro de 1972, primeira consulta em abril de 2016.

Hipertensão arterial grave com evolução de dez anos, em uso irregular de antihipertensivos. PA 140x100 (primeira consulta). Não fuma. Não usa drogas recreativas. Sedentário. Risco cardiovascular alto (32% em 10 anos).

Obeso (110Kg), relatando emagrecimento progressivo de quase 30 kg nos três meses anteriores, quando procurou assistência médica e diagnosticaram Diabetes Mellitus e Infecção pelo HIV.

Janeiro/16: testes anti-HIV (reagentes); HbsAg não reagente; AntiHbs + (vacina) e Pesquisa de Anticorpos para hepatite C não reagente; VDRL não reagente; LDL 116; Trig 212; Glicose 117; Hemoglobina Glicada 7,2; Microalbuminúria 18; Clearance 100; CD4=344 (não realizou carga viral).

Usando Metformina 2g/dia, Insulina NPH e Regular, Clortalidona, Atenolol e Atorvastatina 20mg/dia.
Orientado sobre importância da reeducação alimentar e de exercícios; rever conduta terapêutica com cardiologista e endocrinologista.

Prescritos (abril/16) Darunavir/Ritonavir/Raltegravir (solicitada autorização ao Departamento Nacional)

Qual teria sido sua conduta?
Em relação às interações medicamentosas, o que precisa ser avaliado?
Que ajustes precisam ser feitos?

Interações Medicamentosas com antihipertensivos

		ATV/r	DRV/r	EFV	RPV	DTG	RAL	ABC	FTC	3TC	TDF	EVG/c/ FTC/TAF	EVG/c/ FTC/TDF
Antihypertensive agents	Amlodipine												
	Atenolol												
	Bisoprolol												
	Enalapril												
	Felodipine												
	Indapamide												
	Lisinopril												
	Losartan												
	Nifedipine												
	Olmesartan												
	Perindopril												
	Valsartan												

No clinically significant interaction expected

Potential interaction, no dose adjustment required

Potential interaction, may require dose adjustment or monitoring

Interações Medicamentosas com Hipolipemiantes e Hipoglicemiantes

		ATV/r	DRV/r	EFV	RPV	DTG	RAL	ABC	FTC	3TC	TDF	EVG/c/ FTC/TAF	EVG/c/ FTC/TDF
Lipid-lowering agents	Atorvastatin												
	Fluvastatin												
	Lovastatin												
	Pravastatin												
	Rosuvastatin												
	Simvastatin												
Antidiabetic agents	Glibenclamide (Glyburide)												
	Linagliptin												
	Metformin												
	Nateglinide												
	Saxagliptin												
	Sitagliptin												

No clinically significant interaction expected

Potential interaction, no dose adjustment required

Potential interaction, may require dose adjustment or monitoring

Do not co-administer

Resultados de Exames

Junho/2016

- CV= 273 (2,43log) => primeira carga realizada após 2 meses de ARV
- CD4=760 (24%)
- Creatinina 1,10

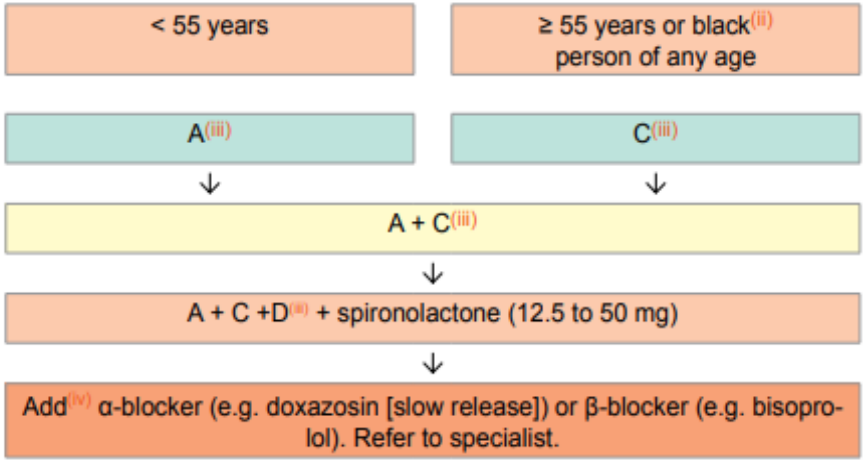
Dezembro/2016

- CV < 40

EACS Guideline 9.0

Hypertension: Drug Sequencing Management

Choosing drugs[i] for persons newly diagnosed with hypertension



Abbreviations + details

A ACE inhibitor (e.g. perindopril, lisinopril or ramipril) or low cost angiotensin receptor blockers (ARB) (e.g. losartan, candesartan)

C Dihydropyridine calcium-channel blocker (e.g. amlodipine). If not tolerated or if deemed at high risk of heart failure, 'D' drugs can be used instead. Where a C drug is preferred but not tolerated, verapamil or diltiazem may be used (note: dose with caution with PIs as these may increase plasma concentrations of these calcium-channel blockers, potentially leading to toxic reactions)

D Thiazide-type diuretic* e.g. indapamide or chlorthalidone

i Some calcium-channel blockers interact marginally with the pharmacokinetics of ARVs, see Drug-drug Interactions between Antihypertensives and ARVs

ii Black persons are those of African or Caribbean descent, and not mixed race, Asian or Chinese persons

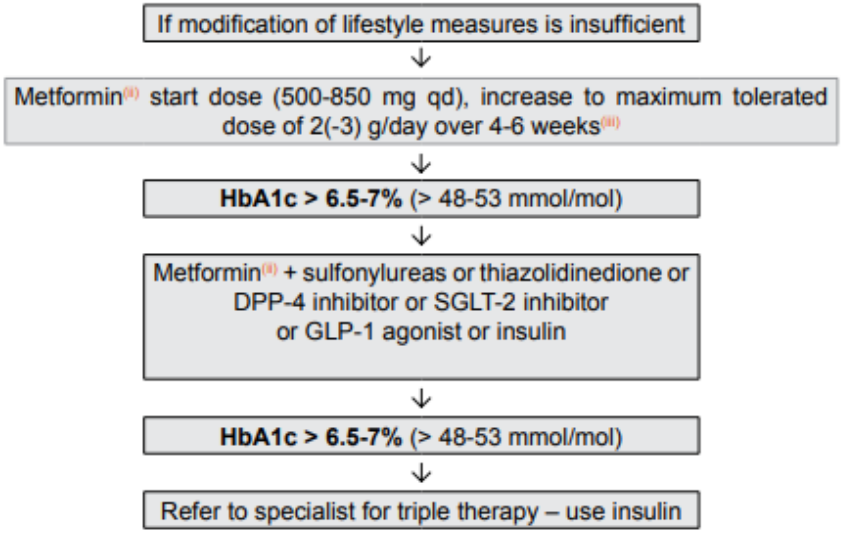
iii Wait 4-6 weeks to assess whether target, see page 40, is achieved; if not, go to next step

iv Requirement of 4-5 drugs to manage hypertension needs specialist training

* This excludes thiazides (e.g. hydrochlorothiazide (HCTZ), bendroflumethiazide etc.)

EACS Guideline 9.0

Type 2 Diabetes[i]: Management



Treatment goals:

Prevention of hyper-/hypoglycaemia, glucose control (HbA1c < 6.5-7% without hypoglycaemia, fasting plasma glucose 4-6 mmol/L (73-110 mg/dL), prevention of long-term complications.

- Normal blood lipids, see page 40, and blood pressure < 130/80 mmHg, see page 41.
- Acetylsalicylic acid (75-150 mg qd) considered in diabetics with elevated underlying CVD risk, see page 40.
- Nephropathy, polyneuropathy and retinopathy screening should be performed as in diabetic persons without HIV
- Consultation with a specialist in diabetology is recommended

i Type 1 diabetes should be treated according to national guidelines.

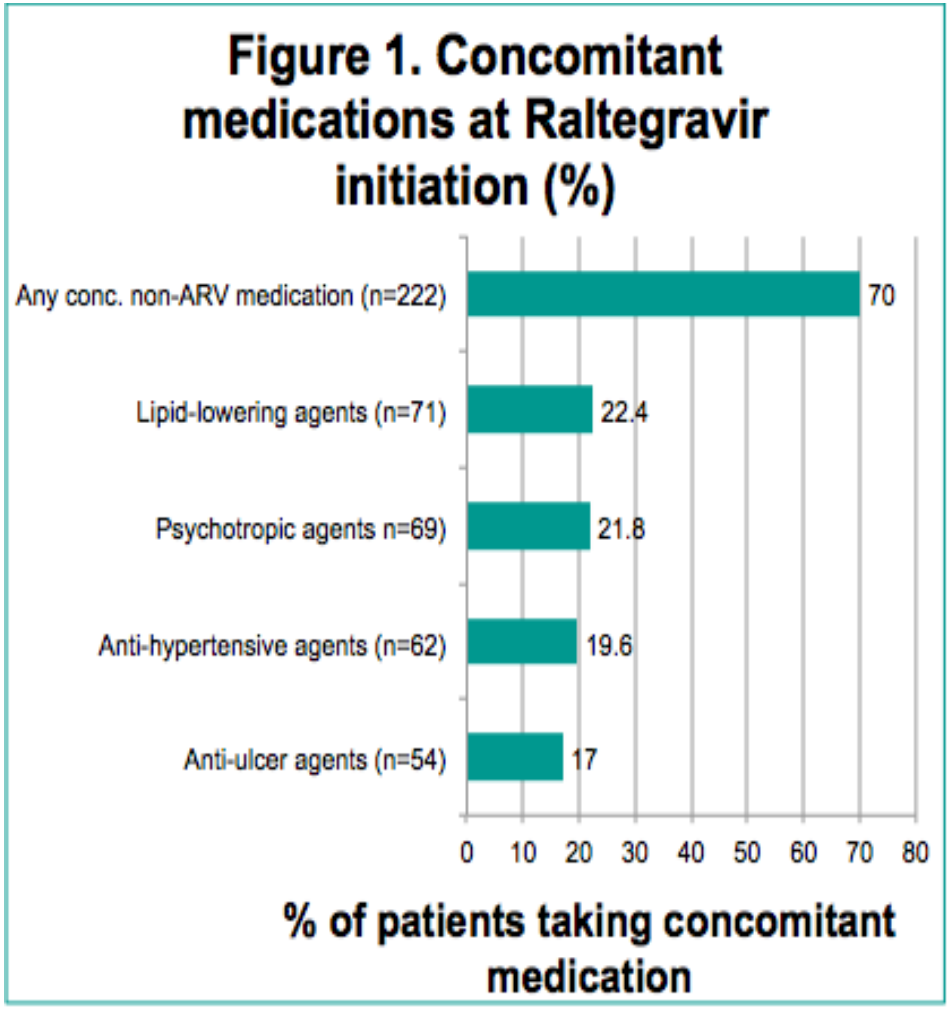
ii Metformin may worsen lipoatrophy.
No data for any oral antidiabetic agents in terms of CVD prevention in HIV-positive persons. Incretins (DDP-4 inhibitors [e.g. linagliptin, saxagliptin (reduce dose when given with a booster), sitagliptin and vildagliptin], GLP-1 agonists [liraglutide, exenatide], and SGLT-2 inhibitors [e.g. dapagliflozin, canagliflozin, empagliflozin] have not been evaluated in HIV-positive persons, but some (e.g empagliflozin, liraglutide) have shown to reduce mortality from CVD; choice of drugs dependent on a variety of individual- & disease-specific factors; no clinically significant drug-drug-interaction or adverse effects on CD4 counts expected; clinical use of pioglitazone questioned by its side effects; HbA1c targets up to 7.5% can be considered for older persons with long-standing type 2 diabetes and evidence of CVD.

iii Consider lower dose in individuals with mild to moderate CKD or individuals receiving DTG.

Raltegravir treatment outcomes among older patients and those with comorbidities: A sub-analysis of the CRICKET study

n=19.215; RAL em 8,3% dos esquemas (n=1.428)

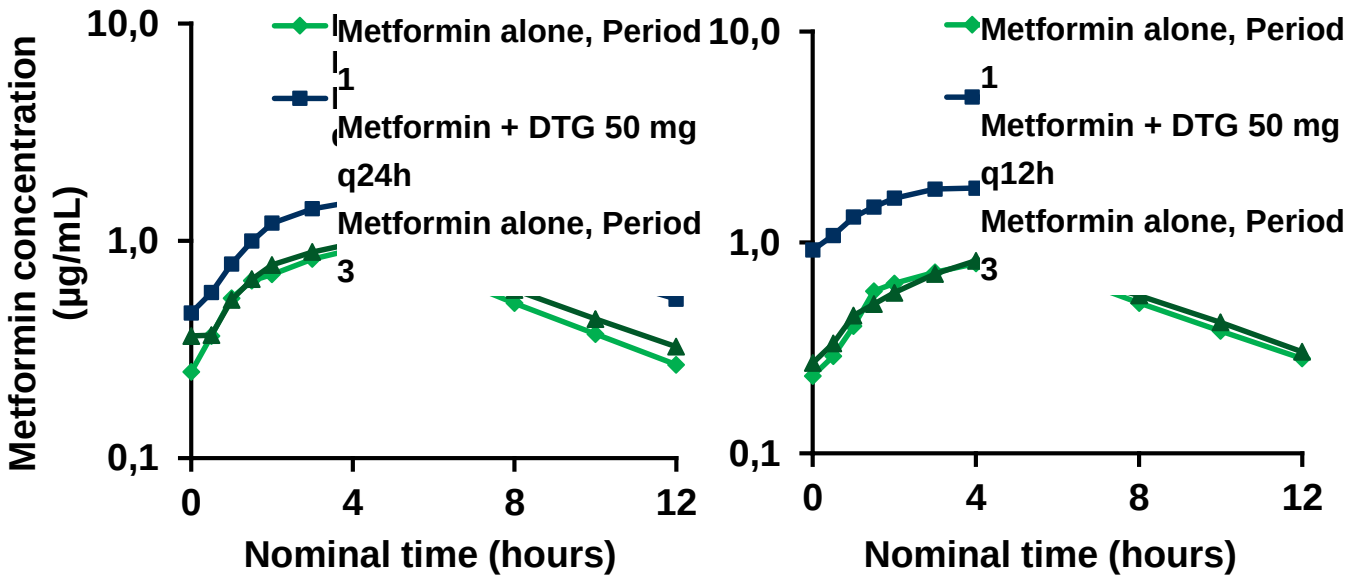
Table 1. Patient demographics and comorbidities among individuals starting raltegravir	
Age N=317 (%)	
<50 years old	205 (64.7)
50 years old and above	112 (35.3)
Mean age - years (standard deviation)	46.3 (9.6)
Sex N=317 (%)	
Male	227 (71.6)
Female	89 (28.1)
Transgender	1 (0.3)
Comorbidities among individuals starting raltegravir N=317 (%)	
Hyperlipidaemia	91 (28.7)
Mental illness	73 (23.0)
AIDS defining illness	67 (21.1)
Hypertension	55 (17.4)
Hep C RNA +ve	45 (14.2)
Acid reflux/GORD/dyspepsia	42 (13.3)
Hep B sAg +ve	21 (6.6)
Active malignancy	18 (5.7)



Nota Informativa nº 007/2017 - DDAHV-SVS-MS
07/Fevereiro/2017

9. As PVHA em uso de RAL por esquema de resgate terapêutico deverão ter este medicamento substituído por DTG a partir de fevereiro de 2017 até 30 de abril 2017.

Dose do DTG interfere nos níveis de Metformina



Há aumento da exposição plasmática da metformina quando coadministrada com DTG e o efeito produzido (PK) no nível de metformina é dose-dependente do DTG

Conduta e Resultados

Abril/2017

Troca de RAL por DTG; ajuste da dose de metformina (1g/dia)

Modificado esquema de antihipertensivos para Losartana e Anlodipino

Maio/2017

- CV < 40 Trigl150 Colesterol LDL100
- Creatinina 1,2 (com 1 mês de DTG)
- Clearance normal
- Assintomático até o presente (março/18); CV<40; Exames laboratoriais normais

Efeitos adversos relacionados ao SNC nos estudos em pessoas virgens de terapia

Cases, n (%)	SPRING-2		FLAMINGO		SINGLE*		ARIA	
	DTG N=411	RAL (n=411)	DTG (n=242)	DRV/r (n=242)	DTG (n=414)	EFV (n=419)	DTG/ (n=248)	ATV/r (n=247)
Insomnia								
Overall	25 (6)	20 (5)	20 (8)	16 (7)	71 (17)	52 (12)	10 (4)	8 (3)
Drug-related†	6 (1.4)	3 (0.7)	4 (1.7)	5 (2.1)	43 (10.4)	28 (6.7)	5 (2.0)	1 (0.4)
Led to withdrawal†	**0**	**0**	**0**	**0**	**1 (0.2)**	**4 (1.0)**	**1 (0.4)**	**0**
Anxiety								
Overall	17 (4)	23 (6)	13 (5)	9 (4)	28 (7)	30 (7)	5 (2)	8 (3)
Drug-related†	1 (0.2)	2 (0.5)	1 (0.4)	0	4 (1.0)	11 (2.6)	0	1 (0.4)
Led to withdrawal†	**0**	**0**	**0**	**0**	**0**	**4 (1.0)**	**0**	**0**
Depression								
Overall	29 (7)	21 (5)	16 (7)	12 (5)	35 (8)	44 (11)	9 (4)	11§ (4)
Drug-related†	1 (0.2)	2 (0.5)	0	0	13 (3.1)	19 (4.5)	1(0.4)	1 (0.4)
Led to withdrawal†	**0**	**0**	**0**	**0**	**1 (0.2)**	**6 (1.4)**	**0**	**0**
Suicidality								
Overall	4 (<1)	6 (1)	4 (2)	1 (<1)	3 (<1)	7 (2)	3 (1)	4 (2)
Drug-related†	0	0	1 (0.4)	0	0	4 (1.0)	1 (0.4)	0
Led to withdrawal†	**0**	**2 (0.5)**	**1 (0.4)**	**0**	**0**	**1 (0.2)**	**0**	**0**

All third agents were part of a three-drug regimen containing two NRTIs
*Higher rates in SINGLE trial could potentially be attributed to proactive CNS questionnaire use and double-blind comparison with EFV; †Proportion of population

Dolutegravir + Lamivudina

- ACTG A5353
  - Estudo Piloto com DTG/3TC em pacientes virgens de ARV
  - 120 participantes envolvidos
  - 31% com HIV RNA >100.000
  - Com 34 semanas, 96% adquiriram supressão viral máxima (HIV RNA<50)

Dois ensaios clínicos avaliando esse esquema vs terapia tripla inicial em pacientes virgens de tratamento (GEMINI-1 and GEMINI-2)

Taiwo BO, et al. ACTG A5353: A pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV- 1-infected participants with HIV-1 RNA <500,000 copies/ml. IAS 2017: Conference on HIV Pathogenesis
Treatment and Prevention, Paris, France
July 23-26 2017

Dolutegravir + Lamivudina

- LAMIDOL
  - 104 participantes já experimentados que fizeram trocas para DTG+3TC
  - 101 mantiveram supressão viral com 40 semanas

Joly V et al. *Promising results of dolutegravir + lamivudine maintenance in ANRS 167 Lamidol trial*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 458, 2017.