Dolutegravir, Abacavir, Lamivudine
Addition to the list

Literature Review Question:
Should dolutegravir (and other treatments used in its regime) be added to the list?

Note: The list currently includes EFV-TDF-FTC (efavirenz, tenofovir, emtricitabine) and a clinician with an interest in HIV care pointed out that current guidelines currently recommend DTG-ABC-3TC (dolutegravir, abacavir, lamivudine).

Literature search:
PubMed, Cochrane: (((HIV) OR human immunodeficiency virus)) AND (((Dolutegravir) OR Abacavir) OR Lamivudine) Filters: Clinical Trial; Review; published in the last 5 years; Humans

SINGLE RCT [1, 2] [3]

Viral suppression (HIV type 1 RNA level)

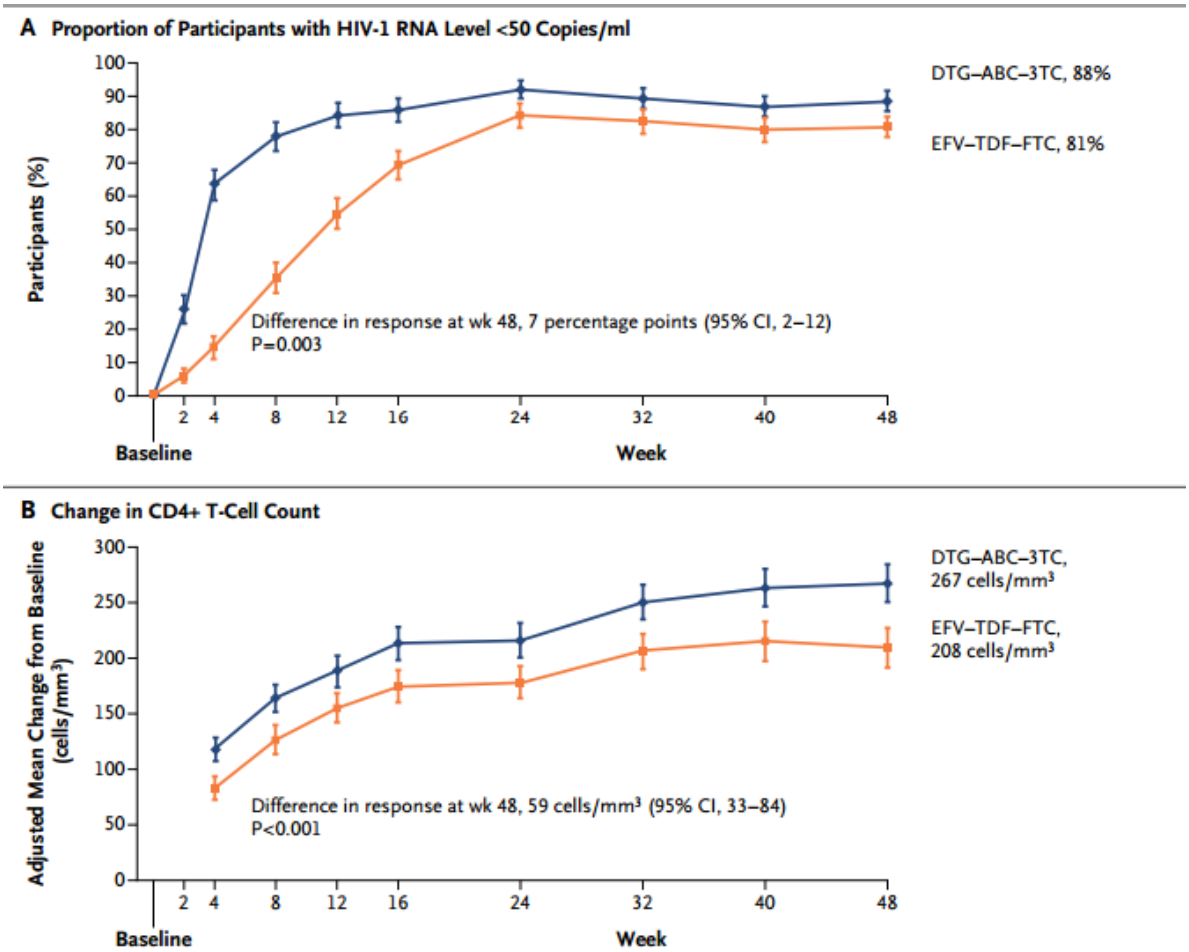

Figure 2. Efficacy Data through Week 48.

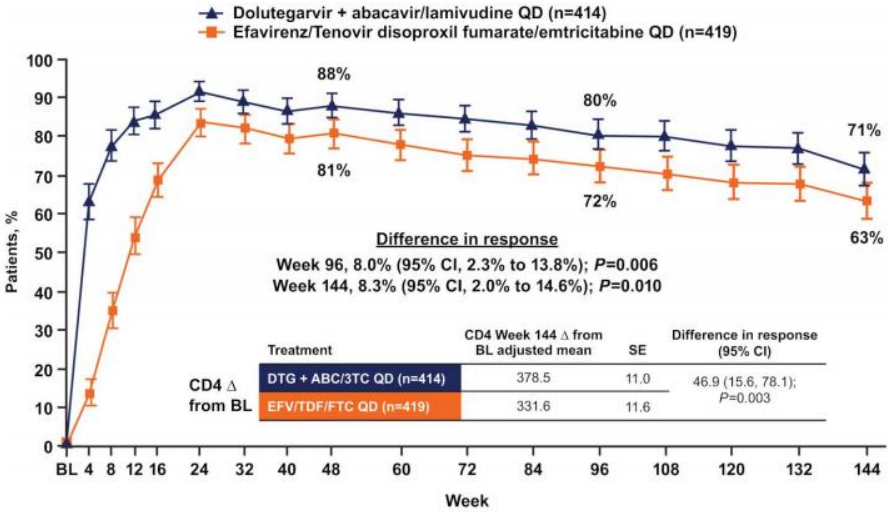

FIGURE 1. Proportion <50 copies per milliliter (95% CI) and CD4 change from baseline. BL, baseline; DTG + ABC/3 TC, dolutegravir + abacavir/lamivudine; EFV/TDF/FTC, efavirenz/tenofovir disoproxil fumarate/emtricitabine; QD, once daily; SE, standard error.

Table 1 Efficacy of dolutegravir plus abacavir/lamuvidine in the treatment of antiretroviral therapy-naive adults with HIV-1 infection. Results from the SINGLE trial at weeks 48 [19], 96 [20] and 144 [47]; some data are from abstracts and a poster [20, 47]

Parameter	Regimen[a]	Week 48	Week 96	Week 144
Plasma HIV-1 RNA <50 copies/mL (% of pts)[b]	DTG + ABC/3TC	88*	80*	71*
	EFV/TDF/FTC	81	72	63
	Difference (95 % CI)	7 (2–12)	8.0 (2.3–13.8)	8.3 (2.0–14.6)
Median time to virological suppression (days)[c]	DTG + ABC/3TC	28**		
	EFV/TDF/FTC	84		
	Hazard ratio (95 % CI)	2.32 (2.00–2.68)		
CD4+ cell count adjusted mean change from baseline (median baseline) [cells/μL]	DTG + ABC/3TC	267 (334.5)**	325 (334.5)*	378 (334.5)*
	EFV/TDF/FTC	208 (339.0)	281 (339.0)	332 (339.0)
	Difference (95 % CI)	59 (33–84)	44.0 (14.3–73.6)	47 (16–78)
Virological failure (% of pts)[d]	DTG + ABC/3TC	4	6	9
	EFV/TDF/FTC	4	6	8

3TC lamivudine, *ABC* abacavir, *DTG* dolutegravir, *EFV* efavirenz, *FTC* emtricitabine, *pts* patients, *TDF* tenofovir disoproxil fumarate

* $p \leq 0.01$, ** $p < 0.001$ vs. EFV/TDF/FTC

[a] Pts received once-daily DTG 50 mg plus ABC/3TC 600/300 mg ($n = 414$) or once-daily EFV/TDF/FTC 600/300/200 mg ($n = 419$)

[b] Primary efficacy endpoint at week 48 (data presented from the intention-to-treat population); superiority testing was conducted after noninferiority was established in the intention-to-treat and per-protocol populations (lower boundary of two-sided 95 % CI for treatment difference was <10 %)

[c] Defined as HIV-1 RNA level <50 copies/mL

[d] Protocol-defined virological failure; statistical analysis for between-group differences were not reported

- A total of 844 patients who had not previously received antiretroviral therapy (ART) were included in the analysis. Participants were randomly assigned to dolutegravir at a dose of 50 mg plus abacavir–lamivudine once daily (**DTG–ABC–3TC group**) or combination therapy with efavirenz–tenofovir disoproxil fumarate (DF)–emtricitabine once daily (**EFV–TDF–FTC group**) [1].
- At week 48, the proportion of participants with an HIV-1 RNA level of less than 50 copies per milliliter was significantly higher in the **DTG–ABC–3TC group** than in the **EFV–TDF–FTC group** (88% vs. 81%, P=0.003) [1]. The adjusted treatment difference between the two groups was 7 percentage points (95% confidence interval [CI], 2 to 12), with dolutegravir and abacavir–lamivudine meeting

the non-inferiority criterion (non-inferiority margin was 10 percentage points) [1]. In addition, the DTG–ABC–3TC group had a shorter median time to viral suppression than did the EFV–TDF–FTC group (28 vs. 84 days, P<0.001) (Figure 2) [1].

- A higher proportion of participants in the **DTG–ABC–3TC group** than in the **EFV–TDF–FTC group** arm maintained HIV-1 RNA levels of 50 copies per milliliter through week 96 (80% vs. 72%; P = 0.006); this difference was maintained at week 144 (71% vs. 63%; P = 0.01) (Figure 1) [2].

Change in CD4+ cell count

- At week 48, the DTG–ABC–3TC group had a greater increases in CD4+ T-cell count than did the EFV–TDF–FTC (267 vs. 208 per cubic millimeter, P<0.001) (Figure 2) [1].
- Change from baseline in CD4+ cell counts was consistently greater in the **DTG–ABC–3TC group** than in the **EFV–TDF–FTC group. (**At week 96, 325 vs. 281 per cubic millimeter, p=0.004; At week 144, 378 vs. 332 per cubic millimeter, p=0.003) (Figure 1) [2].

Adverse event

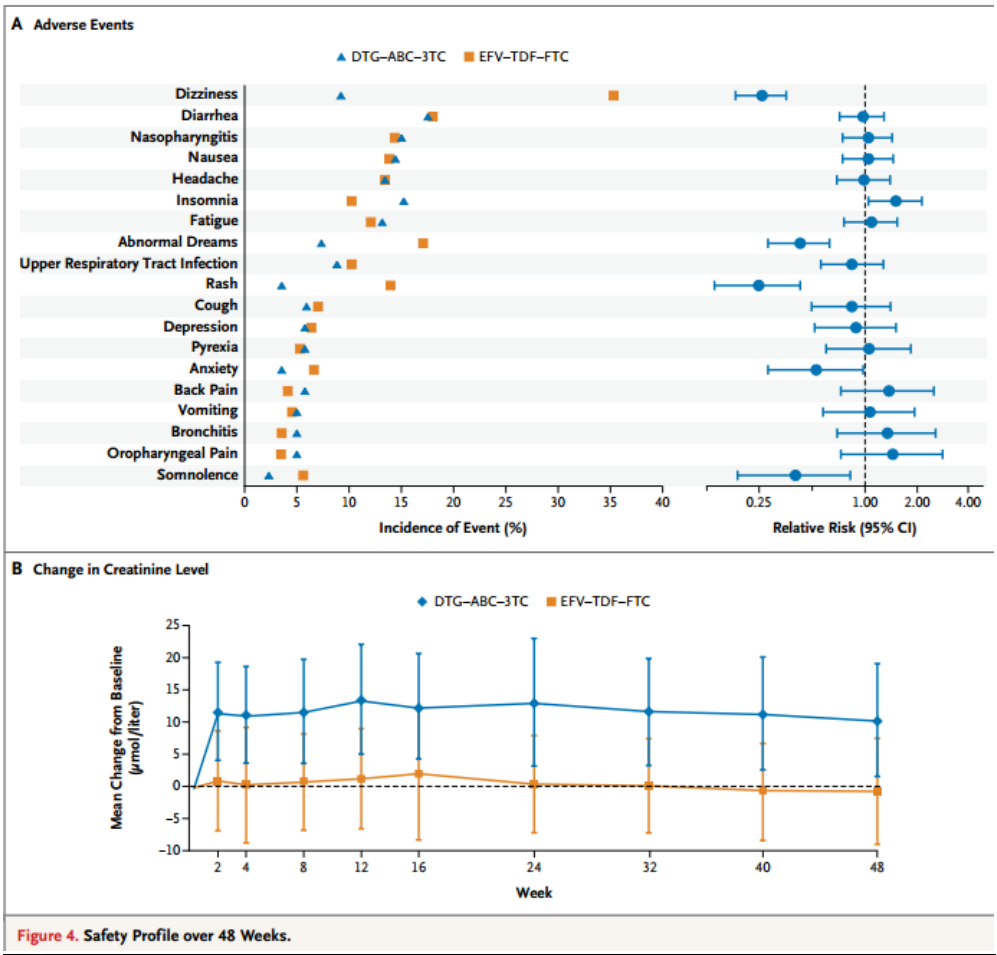

Figure 4. **Safety Profile over 48 Weeks.**

- During the 48-week observation period of this study, diarrhea, nasopharyngitis, nausea, headache, and fatigue were among the most commonly reported clinical adverse events. Overall, the 48-week safety profile of dolutegravir and abacavir–lamivudine was generally favorable, as compared with that of efavirenz–tenofovir –emtricitabine.

- Rash and neuropsychiatric events (including abnormal dreams, anxiety, dizziness, and somnolence) were significantly more common with efavirenz–tenofovir DF–emtricitabine, whereas insomnia was reported more frequently with dolutegravir and abacavir–lamivudine (Figure 4A).
- Participants receiving dolutegravir and abacavir–lamivudine had small mean increases in the serum creatinine level. The mean increases, which ranged from 10.2 to 13.4 µmol per liter (0.12 to 0.15 mg per deciliter), were evident by week 2 and subsequently remained stable through week 48 (Figure 4B).

Systematic review and network meta-analysis [4]

- A total of 31 studies including 17,000 patients were combined in the analysis. The objective of this study is to estimate the efficacy and safety of DTG relative to other guideline recommended agents in a Bayesian network meta-analysis.

Viral suppression and CD4+ cell count change

	Estimated Probability of Virologic Suppression at week 48 Mean (95% CrI)				Estimated CD4+ cell count change from baseline to week 48 Mean (95% CrI)			
Third agent	TDF/FTC	ABC/3TC	Other	Backbone unadjusted	TDF/FTC	ABC/3TC	Other	Backbone unadjusted
	N = 26 studies	N = 26 studies	N = 26 studies	N = 22 studies	N = 28 studies	N = 28 studies	N = 28 studies	N = 24 studies
DTG	0.86 (0.81,0.90)	0.85 (0.80,0.88)	0.82 (0.77,0.87)	0.84 (0.79,0.87)	224.7 (205.6,243.7)	240.9 (224.3,257.7)	187.7 (166.5,209.1)	226.8 (210.7,242.6)
EFV	0.77 (0.74,0.79)	0.75 (0.72,0.78)	−0.72 (0.68,0.75)	0.75 (0.74,0.76)	186.8 (179.5,194.0)	203.0 (193.2,212.9)	149.7 (135.0,164.5)	179.1 (175.1,183.1)

- Adjusting for the effect of NRTI backbone, treatment with dolutegravir (DTG) resulted in significantly higher odds of virologic suppression (HIV RNA, 50 copies/mL) and increase in CD4+ cells/mL versus efavirenz (EFZ)

Adverse event

Table 2. Mean odds ratio (95% CrI) of AEs and discontinuation due to AEs.

DTG compared to	Adverse Events N = 11 studies	Discontinuation due to AEs N = 18 studies
EFV	0.57 (0.38, 0.81)*	0.26 (0.14, 0.43)*

- Odds of experiencing an adverse event were significantly lower for dolutegravir (DTG) compared to efavirenz (EFV).

Guidelines review

Department of Health and Human Services (DHHS) Panel guidelines [5]

The 2015 Department of Health and Human Services (DHHS) Panel guidelines indicate a preference for the following regimens for initial treatment.

- **Dolutegravir (50 mg)-abacavir (600 mg)-lamivudine (300) mg** once daily in patients who are HLA-B*5701-negative
- **Dolutegravir (50 mg) once daily plus tenofovir disoproxil fumarate (300 mg)-emtricitabine (200 mg)** once daily
- Elvitegravir (150 mg)-cobicistat (150 mg)-emtricitabine (200 mg)-tenofovir disoproxil fumarate (300 mg) once daily in patients with an estimated glomerular filtration rate greater than or equal to 70 mL/min/1.73 m2
- Elvitegravir (150 mg)-cobicistat (150 mg)-emtricitabine (200 mg)-tenofovir alafenamide (10 mg) once daily in patients with an estimated glomerular filtration rate greater than or equal to 30 mL/min/1.73 m2
- Raltegravir (400 mg) twice daily plus tenofovir disoproxil fumarate (300 mg)-emtricitabine (200 mg) once daily

The International Antiviral Society-USA panel (IAS-USA) guidelines[6]

Table 2. Recommended Initial Antiretroviral Regimens[a]

Type of Regimen	Antiretroviral Drug Combination	Rating	Comments
Integrase strand transfer inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Dolutegravir[b] plus tenofovir/emtricitabine	AIa	Dolutegravir is dosed once daily. Associated with modest increases in creatinine level due to inhibition of creatinine secretion.
	Dolutegravir[b] plus abacavir[c]/lamivudine	AIa	No evidence that abacavir/lamivudine performs less well at HIV-1 RNA levels >100 000 copies/mL when given with dolutegravir. A fixed-dose combination is in late-stage development.
	Elvitegravir[b]/cobicistat/tenofovir/emtricitabine	AIa	Once-daily fixed-dose combination. Cobicistat is associated with modest increases in creatinine level due to inhibition of creatinine secretion; has similar drug interactions to ritonavir.
	Raltegravir[b] plus tenofovir/emtricitabine	AIa	Raltegravir is taken twice daily.

- Dolutegravir is a once-daily INSTI that does not require pharmacological boosting and has similar activity and safety to raltegravir when combined with tenofovir/emtricitabine or abacavir/lamivudine.

European AIDS Clinical Society [7]

Initial Combination Regimen for ART-naïve Adult HIV-positive Persons

A) Recommended regimens (one of the following to be selected)[*,**]

Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC/DTG[(i, ii)]	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
TDF/FTC[(iii, iv)] + DTG	TDF/FTC 300[(viii)]/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd	None	
TDF/FTC/EVG/c[(iii, iv, v)]	TDF/FTC/EVG/c 300[(viii)]/200/150/150 mg, 1 tablet qd	With food	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
TDF/FTC[(iii, iv)] + RAL	TDF/FTC 300[(viii)]/200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).

ABC: Abacavir, 3TC: Lamivudine, DTG: Dolutegravir

World Health Organization[8]

- The 2013 guidelines specified a single preferred first-line regimen of tenofovir, lamivudine (or emtricitabine), and efavirenz for all HIV-infected adults who initiate ART, including pregnant and breastfeeding women. (Dolutegavir is not recommended by these guidelines completed before the SINGLE RCT.)

What ARV regimens to start with

Topic and population	Recommendations

First-line ARV regimens for adults	• First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI).
	  • TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART *(strong recommendation, moderate-quality evidence).*
	  • If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following options is recommended:
	  • AZT + 3TC + EFV
	  • AZT + 3TC + NVP
	  • TDF + 3TC (or FTC) + NVP
	  (strong recommendation, moderate-quality evidence).
	• Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities *(strong recommendation, moderate-quality evidence).*

Essential medications list

Medication	Uses	Contraindications (CI), drug interactions (DI) or cautions	Adverse Effects (common and severe)	Initial dose; typical dose	Monitoring
efavirenz/ emtricitabine/ tenofovir	antiviral: HIV-1 infection	CI: pediatrics DI: anti-retrovirals, carbamazepine, anticonvulsants, rifabutin, and rifampin, CCBs, antidepressants, antifungals, statins, hormonal contraceptives	Lactic acidosis, severe hepatomegaly with steatosis, diarrhea, nausea, fatigue, depression, dizziness, sinusitis, upper respiratory tract infection, rash, headache, insomnia, abnormal dreams, anxiety, nasopharyngitis	1 tab one time a day on an empty stomach (Combo pill 600mg-200mg-300mg) Dose adjust Efavirenz with Rifampin	

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2. Walmsley, S., et al., *Brief Report: Dolutegravir Plus Abacavir/Lamivudine for the Treatment of HIV-1 Infection in Antiretroviral Therapy-Naive Patients: Week 96 and Week 144 Results From the SINGLE Randomized Clinical Trial.* J Acquir Immune Defic Syndr, 2015. **70**(5): p. 515-9.
3. Greig, S.L. and E.D. Deeks, *Abacavir/dolutegravir/lamivudine single-tablet regimen: a review of its use in HIV-1 infection.* Drugs, 2015. **75**(5): p. 503-14.
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5. *Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* . 2016, Department of Health and Human Services.

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7. *European AIDS Clinical Society Guidelines*, in *v8*. 2015, European AIDS Clinical Society
8. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing hiv infection - recommendation s for a public health approach*. 2013, World Health Organization