Author(s): Ameeta Singh/Tom Wong
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Question: Should 2nd line or subsequent ART regimens containing TDF and 3TC (or FTC) vs 2nd line or subsequent ART regimens containing 3TC or FTC or TDF as the only HBV drug be used for HIV/HBV co-infected individuals > 5 years old?
Settings: Multiple
Bibliography: 1. Benhamou Y, Fleury H, Trimoulet P et al. Anti-hepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients. Hepatol 2006;43:548-55. 2. Schmutz G, Nelson M, Lutz T et al. Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection. AIDS 2006;20:1951-54. 3. Matthews GV, Seaberg E, Dore GJ et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals. AIDS 2009;23:1707-15. 4. Alvarez-Uria G,Ratcliffe L, Vilar JF. Long term outcome of tenofovir-disproxil fumarate use against hepatitis B in an HIV-infecetd cohort. HIV Med 2009;10:269-73

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	2nd line or subsequent ART regimens containing TDF and 3TC (or FTC)	2nd line or subsequent ART regimens containing 3TC or FTC or TDF as the only HBV drug	Relative (95% CI)	Absolute	Quality	Importance
Mortality 1, 2 and 5 years (follow-up median 34 months; death during follow up period)												
4	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/43 (0%)	0/16 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
HIV disease progression - not reported												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		
HBV disease progression (cirrhosis, HCC) (follow-up median 12 months)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	0/65 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Severe treatment associated adverse events (follow-up median 12 months; see note[5])												
1	observational studies	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	1/65 (1.5%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
CD4 recovery - not measured[8]												

0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		
Other non-AIDS morbidities - not reported												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		
Other HBV related morbidities - not reported												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		
HIV viral load response (follow-up median 34 months; HIV RNA < 2.6 log 10 copies/ml)												
1	observational studies	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	43/64 (67.2%)	29/62 (46.8%) 0%	RR 1.44 (1.05 to 1.97)[11]	206 more per 1000 (from 23 more to 454 more) 0 more per 1000 (from 0 more to 0 more)	VERY LOW	IMPORTANT
HBV viral load response (follow-up median 34 months[12]; HBV DNA < 200 copies/ml)												
4	observational studies	serious[13]	no serious inconsistency	no serious indirectness	serious[14]	none	31/52 (59.6%)[15]	0/0 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	IMPORTANT
HBV drug resistance (follow-up median 34 months; virologic breakthrough[16])												
1	observational studies	serious[17]	no serious inconsistency	no serious indirectness	serious[18]	none	9/59 (15.3%)	0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
HIV drug resistance (follow-up median 34 months; HIV drug resistance test)												
1[19]	observational studies	serious[20]	no serious inconsistency	no serious indirectness	serious[21]	none	1/52 (1.9%)[22]	0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	IMPORTANT
Adherence (follow-up median 34 months; rebound in HIV RNA on treatment)												
1	observational studies	serious[23]	no serious inconsistency	no serious indirectness	serious[24]	none	1/52 (1.9%)[25]	0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	IMPORTANT

[1] See Footnote 1
[2] Studies varied in duration of follow up - study by Alvarez Uria longest and included here. None specifically reported on mortality but no deaths reported in this study with longest duration of follow up.
[3] See 4 above

[4] See 4. above
[5] Single patient on TDF developed renal tubulopathy (co-existing Castelman disease and non Hodgkin's lymphoma) at month 20. Developed Fanconi type syndrome without renal failure. Recovered few weeks after TDF withdrawal.
[6] Retrospective observational study
[7] See 8. above
[8] ARV treatment experienced patients; CD4 change not reported
[9] See 8. above
[10] See 8. above
[11] RR not reported; p=0.01; RR calculated using Epi Info
[12] Variable median follow up in studies - Alvarez Uria included here (median FU 34 months). Other studies: Schmutz: median 116-129 weeks; Matthews: time since HAART initiation 6.7 months on LAM or FTC alone, 8.2 months on TDF alone and 8.2 months on TDF and LAM/FTC; Benhamou: median duration ARV 6 years
[13] See 1 above re details of studies
[14] See 1 above re details of studies
[15] No significant difference between LAM naive and LAM experienced groups
[16] no signiificant differences in characteristics (gender, age, HBeAg positive,preexisiting cirrhosis, CD4 nadir or end of study CD4, previous duration of LAM, concomitant use of LAM or PI) in patients experiencing virologic breakthrough and those not
[17] Alvarez Uria retrospective observational study design
[18] Alvarez Uria study retrospective observational
[19] Alvarez Uria retrospective observational study design
[20] see 22. above
[21] see 2.. above
[22] Type of resistance in the single patient note reported except to say showed resistance mutations against the HIV ARV regimen the patient was on. Patient's HIV RNA was 3168 copies/ml.
[23] Alvarez Uria retrospective observational study design
[24] Alvarez Uria retrospective observational study design
[25] Adherence indirectly measured and reported based on development of rebound HIV RNA in 1 of 9 patients with HBV virologic breakthrough