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Question: Should ZDV vs d4T be used for initial ART?

Settings: Multiple locations

Bibliography: 1. Carr A, Chuah J, Hudson J, et al. A randomised, open-label comparison of three highly active antiretroviral therapy regimens including two nucleoside analogues and indinavir for previously untreated HIV-1 infection: the OzCombo I study. *AIDS* 2000; 14:1171-80. 2. Eron JJ Jr, Murphy RL, Peterson D, Pottage J, Parenti DM, Jemsek J, Swindells S, Sepulveda G, Bellos N, Rashbaum BC, Esinhart J, Schoellkopf N, Grosso R, Stevens M. A comparison of stavudine, didanosine and indinavir with zidovudine, lamivudine and indinavir for the initial treatment of HIV-1 infected individuals: selection of thymidine analog regimen therapy (START II). *AIDS*. 2000; 14:1601-10. 3. French M, Amin J, Roth N, Carr A, Law M, Emery S, Drummond F, Cooper D; OzCombo 2 investigators. Randomized, open-label, comparative trial to evaluate the efficacy and safety of three antiretroviral drug combinations including two nucleoside analogues and nevirapine for previously untreated HIV-1 Infection: the OzCombo 2 study. *HIV Clin Trials* 2002; 3:177-85. 4. Gathe J Jr, Badaro R, Grimwood A, Abrams L, Kleszczewski K, Cross A, McLaren C. Antiviral activity of enteric-coated didanosine, stavudine, and nelfinavir versus zidovudine plus lamivudine and nelfinavir. *J Acquir Immune Defic Syndr* 2002; 31:399-403. 5. Geijo Martínez MP, Maciá Martínez MA, Solera Santos J, Barberá Farré JR, Rodríguez Zapata M, Marcos Sánchez F, Martínez Alfaro E, Cuadra García-Tenorio F, Sanz Moreno J, Moreno Mendaña JM, Beato Pérez JL, Sanz Sanz J; GECMEI. Ensayo clínico comparativo de eficacia y seguridad de cuatro pautas de tratamiento antirretroviral de alta eficacia (TARGA) en pacientes con infección por VIH avanzada. *Rev Clin Esp* 2006; 206:67-76. 6. Kumar PN, Rodriguez-French A, Thompson MA, Tashima KT, Averitt D, Wannamaker PG, Williams VC, Shaefer MS, Pakes GE, Pappa KA, ESS40002 Study Team. A prospective, 96-week study of the impact of Trizivir, Combivir/nelfinavir and lamivudine/stavudine/nelfinavir on lipids, metabolic parameters and efficacy in antiretroviral-naïve patients: effect of sex and ethnicity. *HIV Med* 2006; 7:85-98. 7. Robbins GK, De Gruttola V, Shafer RW, Smeaton LM, Snyder SW, Pettinelli C, Dubé MP, Fischl MA, Pollard RB, Delapenha R, Gedeon L, van der Horst C, Murphy RL, Becker MI, D'Aquila RT, Vella S, Merigan TC, Hirsch MS; AIDS Clinical Trials Group 384 Team. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. 2003; 349:2293-303. 8. Squires KE, Gulick R, Tebas P, Santana J, Mulanovich V, Clark R, Yangco B, Marlowe SI, Wright D, Cohen C, Cooley T, Mauney J, Uffelman K, Schoellkopf N, Grosso R, Stevens M. A comparison of stavudine plus lamivudine versus zidovudine plus lamivudine in combination with indinavir in antiretroviral naive individuals with HIV infection: selection of thymidine analog regimen therapy (START I). *AIDS* 2000; 14:1591-600. 9. Li T, Dai Y, Kuang J, Jiang J, Han Y, Qiu Z, Xie J, Zuo L, Li Y. Three generic nevirapine-based antiretroviral treatments in Chinese HIV/AIDS patients: multicentric observation cohort. *PLoS One* 2008;3:e3918.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							ZDV	d4T	Relative (95% CI)	Absolute		
Mortality (follow-up 3 studies at 48 weeks, 1 study at 52 weeks, 1 study at 96 weeks¹)												
6	randomised trials	no serious limitations ²	no serious inconsistency	serious ³	serious ⁴	reporting bias ⁵	3/593 (0.5%)	5/586 (0.9%)	RR 0.74 (0.18 to 2.93)	2 fewer per 1000 (from 7 fewer to 16 more)	⊕⊕⊕ VERY LOW	CRITICAL
Clinical response (follow-up 3 studies at 48 weeks, 2 studies at 52 weeks)												
7	randomised trials	no serious limitations ²	no serious inconsistency	serious ³	no serious imprecision	reporting bias ⁵	8/360 (2.2%)	6/361 (1.7%)	RR 1.26 (0.46 to 3.45)	4 more per 1000 (from 9 fewer to 41 more)	⊕⊕⊕ LOW	CRITICAL
Severe adverse events (follow-up 4 studies at 48 weeks, 3 studies at 52 weeks)												
9	randomised trials	no serious limitations ²	no serious inconsistency	serious ³	no serious imprecision	reporting bias ⁵	137/680 (20.1%)	169/685 (24.7%)	RR 0.85 (0.71 to 1.02)	37 fewer per 1000 (from 72 fewer to 5 more)	⊕⊕⊕ LOW	CRITICAL
Virologic response (follow-up 4 studies at 48 weeks, 3 studies at 52 weeks, 1 study at 96 weeks)												
10	randomised trials	no serious limitations ²	no serious inconsistency	serious ³	no serious imprecision	reporting bias ⁵	396/771 (51.4%)	409/768 (53.3%)	RR 0.97 (0.89 to 1.07)	16 fewer per 1000 (from 59 fewer to 37 more)	⊕⊕⊕ LOW	CRITICAL
Adherence/tolerability/retention (follow-up 4 studies at 48 weeks, 3 studies at 52 weeks, 1 study at 96 weeks, 1 study at 144 weeks)												
12	randomised trials	no serious limitations ²	no serious inconsistency	serious ³	no serious imprecision	reporting bias ⁵	632/1081 (58.5%)	585/1078 (54.3%)	RR 1.08 (0.97 to 1.2)	43 more per 1000 (from 16 fewer to 109 more)	⊕⊕⊕ LOW	CRITICAL

Immunologic response (follow-up 4 studies at 48 weeks, 3 studies at 52 weeks, 1 study at 96 weeks; Better indicated by higher values)												
10	randomised trials	no serious limitations ²	no serious inconsistency	serious ³	no serious imprecision	reporting bias ⁵	771	768	-	MD 9.61 lower (36.82 lower to 17.6 higher)	⊕⊕⊕ LOW	IMPORTANT
Drug resistance (follow-up at 96 weeks)												
1	randomised trials	serious ^{2,6}	no serious inconsistency	serious ³	serious ⁴	none	10/91 (11%)	6/83 (7.2%)	RR 1.52 (0.58 to 4)	38 more per 1000 (from 30 fewer to 217 more)	⊕⊕⊕ VERY LOW	IMPORTANT
Sexual transmission of HIV - not reported												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		

¹ Separate comparison arms from 3 studies (Carr, French, Robbins) contributed more than once for a number of outcomes. There were 9 studies in total.

² 6 out of 9 studies were open-label studies and some studies had large rates of loss to follow-up, but studies were not downgraded based on these facts.

³ 5 out of 9 studies looked at indirect comparisons of drug regimens.

⁴ Number of events <300 and/or confidence intervals include potential harm and benefit.

⁵ 7 out of 9 studies were industry funded, although some were funded simultaneously by competitors.

⁶ Only 1 study (Kumar) reported on drug resistance, suggesting selective reporting.