



Efficacy and Tolerability of Initial Antiretroviral Therapy: a Systematic Review

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Introduction

- HAART efficacy is mainly estimated by intention-to-treat (ITT) analysis of HIV viral load in randomized trials (RCTs) of ART-naïve adults.
- Guideline panels [1-5] recommend particular first-line ART regimens based on sequential review of individual RCTs, not on formal systematic review.
- A systematic review of 53 RCTs and cohorts through July 2004 [6] found that efficacy at 48 weeks was greater with 2 NRTIs + 1 NNRTI or 1 boosted PI and with higher CD4 counts. These variables explained only 35% of the variability in efficacy.
- The Antiretroviral Cohort Collaboration found independent risk factors for progression over 5 years to AIDS or death were higher age, prior AIDS, injection drug use, HIV RNA >100,000, and lower CD4 count [7], but not the type of third drug.
- No study has evaluated other factors encompassing study design and quality, eligibility criteria, participant characteristics and pill dosing that also might affect ART efficacy or tolerability.

Methods

Data sources and search strategy

- PubMed, Current Controlled Trials and Cochrane Clinical Trials Register.
 - Search strategy: "[drug] and (HIV or antiretroviral) and (cohort or randomized trial)"
 - 2006 / 07 CROI, IAS and ICAAC conference websites
 - Studies cited in the US DHHS Adult Treatment Guidelines [2]
 - Drug labels and other documents of the US FDA
 - ClinicalTrials.gov and original study protocols
 - Some sponsors / authors provided unreported eligibility and baseline data
- Studies**
- We included all published (since 1/1996) or presented RCTs and prospective cohorts ≥24 weeks evaluating ≥1 ART regimen that is/was recommended in key guidelines
 - We excluded studies: with no or unspecified ITT data; of children and of primary HIV infection; or if data for each regimen were not separated
 - We excluded treatment groups of: dual-NRTI, 4-drug, alternating or monotherapy ART; non-recommended, triple-NRTI ART; ≥ 1 third drug; or directly-observed ART
 - 1050 potential studies – 119 reviewed – 79 included = 143 groups**
- Endpoints**
- The 1st endpoint was undetectable plasma HIV viral load by ITT analysis.
 - We abstracted TLOVR data preferentially, then ITTNC=F, then ITTM=F.
 - The main 2nd outcome was cessation for an adverse event
- Quantitative data synthesis**
- Predictors of outcomes identified by study size-weighted linear regression
 - Multivariate analysis used forward, stepwise, selection. All variables with univariate p<0.05 were assessed in building multivariate models
 - Hepatitis B/C not assessed in multivariate models due to missing data

References

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Table 1 – Patient characteristics

Characteristics	Groups N=143	Patients N=23067
Study design		
Randomized [%]	yes	89.5 90.4
Phase [%]	2	21.0 8.5
	3	41.2 63.1
	4	37.8 28.4
Sponsor [%]		
	academia	23.1 21.0
	academia+industry	22.4 12.3
	industry	54.6 66.7
Recruitment [%]		
	America	48 56.3
	Europe/Australia	41 25.8
	Asia	4.1 4.2
	Africa	4.6 8.3
Duration [%]		
	6-12 months	7.0 7.5
	12 months	74.8 74.4
	24 months	16.1 13.8
	36 months	2.1 4.3
RNA endpt [%]		
	<50/200	94.4 98.1
Analysis method [%]		
	ITT=M=F	93.0 97.7
	ITTNC=F	30.8 16.4
	TLOVR	42.0 40.2
Publication [%]		
	abstract only	2.8 8.7
	<2002	28.0 17.0
	2003-2005	38.4 40.6
	2006-2007	30.8 35.7
Exclusion criteria based on		
	Genotypic resistance [%]	7.7 8.7
	IDU as source of HIV [%]	2.1 0.3
	Prior AIDS [%]	8.4 6.7
	Low haemoglobin [%]	58.0 58.4
	High ALT [%]	78.3 82.6
Antiretroviral therapy		
	Pills per day (mean)	8.6 8.4
	Doses per day (mean)	2.2 2.2
Dosing vs food [%]		
	fasting only	23.8 13.4
	fasting + food	7.7 10.1
	with food only	35.7 34.0
	no restriction	32.9 42.5
NRTI backbone [%]		
	AZT-3TC	33.6 35.6
	d4T-3TC	15.4 15.7
	d4T-ddI	14.7 11.1
	ABC-3TC	11.9 15.9
	ddI-FTC	1.4 1.4
	ddI-3TC	4.9 2.5
	TDF-FTC	6.3 6.7
	TDF-3TC	4.2 4.1
Third drug [%]		
	unboosted PI	29.4 24.0
	boosted PI	21.7 21.6
	NRTI	7.7 7.5
	NNRTI+PI	1.4 1.7
	other	1.4 1.7
	NNRTI	38.5 43.5
Participants		
	Age (mean years)	36.2 36.0
	Male sex [%]	75.8 73.6
	Race [%]	54.3 62.4
	white	26.9 29.5
	black	26.9 29.5
	HIV risk factor [%]	42.3 44.5
	IDU	12.8 10.5
	heterosexual	42.0 41.5
	Prior AIDS-defining illness [%]	13.1 10.7
	CD4+ count (mean cells/mm ³)	286 268
	HIV RNA (mean log copies/ml)	4.80 4.9
	Hepatitis B surface antigen + [%]	4.6 5.2
	Weight (kg)	70.3 70.3

Table 2 - Factors associated with higher efficacy (RNA ND by ITT; overall rate 59.1% at mean 14.3 months) Overall model r² = 0.83

Parameter	r ²	Multivariate analysis			
		Estimate	95% CI	P	
Study design					
Nonrandomized	0.07	2.39	-4.70, 9.48	0.50	
Year started	<1997	0.25	0.59	-9.6, 10.8	0.50
	1997-1999		3.60	-2.69, 9.92	
	2000-2002		-0.50	-5.59, 4.59	
	>2002		Ref		
African recruitment	0.05	-0.02	-0.12, 0.08	0.63	
Duration (months)					
	6-12	0.07	15.64	7.22, 24.07	0.0004
	12		3.87	-2.85, 10.59	
	24		2.69	-4.61, 9.99	
	36		Ref		
Analysis method	ITT=M=F	0.09	5.06	0.51, 9.62	0.082
	ITTNC=F		1.29	-2.94, 5.53	
	TLOVR		Ref		
Publication	<2002	0.23	3.40	-3.27, 10.07	0.52
	2003-2005		0.49	-3.64, 4.63	
	2006-2007		Ref		
Eligibility criteria					
Genotypic resistance	no	0.05	3.46	-2.93, 9.85	0.28
	yes		Ref		
Haemoglobin	any vs none	0.05	6.19	2.72, 9.66	0.0006
Antiretroviral therapy					
Pills per day		0.12	0.42	-0.05, 0.89	0.079
Doses per day		0.35	1.02	-2.25, 4.30	0.54
Dosing vs food					
	fasting only	0.26	-4.23	-10.74, 2.28	0.0011
	fasting + food		-14.08	-21.47, -6.68	
	with food only		-1.91	-7.93, 4.10	
	no restriction		Ref		
NRTIs					
	other	0.27	-2.36	-11.43, 6.71	0.0018
	AZT-3TC		-6.40	-13.39, 0.59	
	d4T-3TC		-6.68	-13.95, 0.58	
	d4T-ddI		-2.60	-11.69, 6.50	
	ABC-3TC		-6.40	-13.25, 0.44	
	ddI-FTC		12.95	-0.66, 26.56	
	ddI-3TC		6.03	-8.27, 20.33	
	TDF-FTC		4.12	-3.77, 12.01	
	TDF-3TC		Ref		
Third drug					
	boosted PI	0.51	2.31	-4.32, 8.94	<0.0001
	unboosted PI		-12.58	-17.61, -7.54	
	NRTI		-16.63	-21.96, -11.3	
	NNRTI+PI		-7.97	-25.01, 9.07	
	other		-1.02	-10.43, 8.39	
	NNRTI		Ref		
Participants					
Age (years)		0.03	0.77	-0.49, 2.03	0.22
White race (vs other)		0.10	-0.13	-0.21, -0.05	0.002
CD4 count (cells/mm ³)		0.12	-0.03	-0.06, -0.01	0.014
HIV viral load (log)		0.07	4.98	-5.20, 15.17	0.33
Hepatitis B sAg+		0.10	-1.22	-3.61, 1.18	0.30

- All parameters in Tables 2 and 3 were significant on univariate analysis; those not shown were not. Rows shaded in blue were significant on multivariate analysis.
- Sensitivity analyses for efficacy and adverse events using only data from published studies, RCTs or week-48 studies yielded similar results (data not shown).
- The only adverse event significantly associated with a lower treatment efficacy was a higher rate of grade 1+ nausea (r=0.273; p=0.028).

Table 3 - Factors associated with a greater cessation for adverse events (overall rate 9.0%) Overall model r² = 0.76

Parameter	r ²	Multivariate analysis				
		Estimate	95% CI	P		
Study design						
Phase	2	0.08	-6.14	-9.80, -2.47	<.0001	
	3		1.52	-1.64, 4.68		
	4		Ref			
Sponsor						
	academic	0.09	0.58	-2.69, 3.86	0.0005	
	academic + industry		-5.11	-8.30, -1.91		
	industry		Ref			
Recruited						
	Europe / Australia	0.09	0.07	0.04, 0.11	<.0001	
	Asia		0.03	0.04	-0.01, 0.10	0.14
Duration (months)						
	6-12	0.07	-14.83	-20.17, -9.49	<.0001	
	12		-12.23	-18.03, -6.43		
	24		-12.91	-18.91, -6.92		
	36		Ref			
HIV RNA endpoint	<20 vs <50	0.18	20.95	15.47, 26.42	<.0001	
Analysis method						
	ITT=M=F	0.05	1.24	-2.25, 4.73	0.032	
	ITTNC=F		3.47	0.61, 6.33		
	TLOVR		Ref			
Publication	abstract	0.04	-0.76	-4.42, 2.90	0.68	
	journal		Ref			
Eligibility criteria						
Low ALT	Any	0.03	-1.26	-4.22, 1.70	0.39	
Antiretroviral therapy						
Dosing vs food	fasting	0.08	-0.79	-4.61, 3.02	0.67	
	fasting+food		0.79	-2.84, 4.42		
	food		-1.11	-3.64, 1.42		
	no restriction		Ref			
NRTIs						
	other	0.11	4.10	-6.87, 15.07	0.0002	
	AZT-3TC		4.23	-6.36, 14.92		
	d4T-3TC		3.73	-6.85, 14.32		
	d4T-ddI		7.05	-3.70, 17.81		
	ABC-3TC		1.07	-9.71, 11.84		
	ddI-FTC		0.85	-10.9, 12.58		
	ddI-3TC		-4.95	-16.54, 6.64		
	TDF-FTC		-1.15	-12.24, 9.94		
	TDF-3TC		Ref			
Participant characteristics						
Age (years)		0.14	1.24	0.69, 1.79	<.0001	
Male		0.07	0.05	-0.02, 0.12	0.16	
White race		0.10	0.00	-0.06, 0.07	0.87	

Limitations

- Source data:**
 - AE data presented in <50% of reports
 - <30% participants female, 10% prior IDU, and only 12% from resource-limited settings
 - Viral hepatitis status, adherence and non-opportunistic conditions were rarely reported
 - Follow-up only 14 months, so ignores long-term, ART-related toxicities
 - Abacavir studies did not test HLA-B*5701
- Analysis:**
 - Used aggregate not individual-patient data
 - No analysis of individual NNRTIs or PIs

Key findings

- The above, newly-identified factors explain most of the variability in both ART efficacy (83%) and tolerability (76%). This may allow for better design and comparison of ART studies.
- ART studies are too short and report too few AE data.
- DDI + 3TC/FTC appeared more effective and better tolerated than the more recommended AZT-3TC, which suggests that guideline panel recommendations might be improved by systematic review of all available data.
- DDI is a largely ignored but effective, cheap, first-line ART option, with immediate relevance to resource-limited settings.
- Unlike the ACC [7], we found greater success with higher age and lower CD4 count, and no association with prior IDU or AIDS. Therefore, factors apart from those determining ART success at 14 months may affect progression to AIDS or death at 5 years.

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