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Dr Andrew Hill

University of Liverpool

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Effects of HIV/HCV co-infection on the efficacy of antiretroviral treatment for HIV

A meta-analysis of 5408 patients in 10 randomised clinical trials

Andrew Hill, Liverpool University, Liverpool, UK
Federico Pulido, Hospital 12 de Octubre, Madrid, Spain
Yvon van Delft, Janssen, Tilburg, The Netherlands
Christiane Moecklinghoff, Janssen, Neuss, Germany

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Background

The effects of HCV co-infection on the efficacy of antiretroviral treatment have not been clearly established.

There have been conflicting results from cohort studies of antiretroviral treatment in HIV/HCV co-infected patients, which have used a range of efficacy endpoints.

Most HIV clinical trials exclude patients with active IV drug use and/or HCV co-infection which could require treatment

Methods

- **A detailed MEDLINE search was conducted to identify HIV cohort studies and clinical trials with published analyses of the efficacy of antiretroviral treatment by HCV co-infection.**
- **The efficacy of antiretroviral treatment by co-infection was summarised in the cohort studies.**
- **A meta-analysis of the clinical trials was conducted, with the standardized endpoint of HIV RNA <50 copies/mL at Week 48**
- **ITT Time to Loss of Virological Response (TLOVR) algorithm used for analysis of the HIV clinical trials.**

Results

- **12 cohort studies were identified**
- **10 clinical trials**
  - seven in treatment-naïve patients,
  - three in pre-treated patients
  - Overall, 637/5408 (12%) patients had HIV/HCV co-infection by HCV antibody tests
  - This percentage was in the lower range of the percentage of HIV/HCV co-infected patients reported in cohort studies in North America and Europe (median 37%, range 9-64%)

Results: HCV and outcomes in 12 cohort studies

Cohort (Country, year)	n	%HCV+	HCV co-infection and outcomes on ARV treatment
ACTG (USA, 2011)	2,495	-	Higher risk of HIV RNA rebound >200 copies/mL
VA (USA, 2004)	12,216	37%	Significantly lower survival
British Columbia (Canada, 2006)	1,186	51%	Smaller rises in CD4 cell count
EuroSida (Europe, 2004)	5,883	34%	No effects on time to first HIV RNA <400 copies/mL; no effects on CD4 cell rises; significantly lower survival
MASTER (Italy, 2011)	3,262	26%	Slower time to HIV RNA <500 copies/mL No effects on CD4 cell rises
National cohort (Denmark, 2006)	2,734	16%	Significantly lower survival
CHIC (UK 2010)	20,365	8.9%	No effects on HIV RNA suppression or CD4 cell rises
Russian study (Russia, 2011)	416	64%	Smaller rises in CD4 cell count
AHOD (Australia, 2003)	2,086	13.1%	Smaller rises in CD4 cell count No effects on HIV RNA suppression or survival
Outpatient clinics (Vietnam, 2011)	1,806	27%	Smaller rises in CD4 cell count Higher loss to follow up
Treat Asia (SE Asia, 2007)	2979	10%	No effects on time to first HIV RNA <400 copies/mL, CD4 cell rises or survival
PEPFAR (Tanzania, 2010)	4,935	1.4%	Smaller rises in CD4 cell count No effects on survival

Results – Clinical trials of treatment naïve patients
Difference = -11.1% (95% CI -6.5% to -15.6%)

Clinical trial	Treatment arm	% HCV+	HIV RNA <50 copies/mL HCV+	HIV RNA <50 copies/mL HCV-
Naive patients				
Gilead 934	ZDV/3TC/EFV	7%	7/16 (44%)	164/228 (72%)
	TDF/FTC/EFV	4%	8/10 (80%)	186/233 (80%)
ECHO/THRIVE	2NRTI/EFV	9% (B/C)	50/63 (79%)	497/602 (83%)
	2NRTI/RPV	7% (B/C)	36/49 (74%)	528/621 (85%)
SENSE	2NRTI/EFV	10%	5/8 (63%)	53/70 (76%)
	2NRTI/ETR	11%	5/9 (56%)	55/70 (79%)
KLEAN	ABC/3TC/FPV/r	12%	20/47 (43%)	277/358 (77%)
	ABC/3TC/LPV/r	9%	23/38 (61%)	282/386 (73%)
ARTEMIS	TDF/FTC/DRV/r	8%	32/42 (76%)	255/300 (85%)
	TDF/FTC/LPV/r	9%	32/48 (67%)	239/299 (80%)
CASTLE	TDF/FTC/ATV/r	9%	42/61 (69%)	300/378 (79%)
	TDF/FTC/LPV/r	7%	37/51 (73%)	301/397 (77%)

Results – Clinical trials of pre-treated patients
difference = -13.2%, (95% CI -4.6% to -21.1%)

Pre-treated Patients	Treatment arm	% HCV co-infection	HIV RNA <50 copies/mL HCV+	HIV RNA <50 copies/mL HCV-
TITAN	2NRTI/DRV/r	13% (B/C)	35/52 (67%)	193/244 (79%)
	2NRTI/LPV/r	12% (B/C)	19/37 (51%)	179/259 (69%)
MONET	2NRTI/DRV/r	9%	10/12 (83%)	103/117(88%)
	DRV/r	17%	16/22 (71%)	94/105 (89%)
OK-04	2NRTI/LPV/r	50%	37/50 (74%)	39/48 (81%)
	LPV/r	44%	31/44 (70%)	46/56 (82%)

Limitations of the analysis

- HCV co-infected patients enrolled in clinical trials may have a better outcome than those who are not enrolled (eg. active IV drug users).
- With the TLOVR algorithm for analysing HIV RNA <50 copies/mL, a high proportion of non-responders (50-70%) can be discontinuations of treatment for adverse events or other reasons
- No data on rises in CD4 count or survival in the clinical trials
- Hepatitis C co-infection is based on antibody testing only. Ten to 30% of the patients with positive serology against HCV do not have actual replication of HCV as measured by viral load assays, suggesting spontaneous clearance of HCV

Conclusions

- **In the meta-analysis of the 10 clinical trials, treatment efficacy as (HIV RNA<50 copies/mL at Week 48) was 11.5% lower in HIV/HCV co-infected patients compared to those with HIV infection alone (p<0.001)**
- **The cause of the lower efficacy of antiretroviral treatment in HIV/HCV co-infected patients is unclear. The TLOVR algorithm includes discontinuations for adverse events or other reasons as failure endpoints.**
- **The low percentage of HIV/HCV co-infected patients in this analysis (12%), compared with published cohort studies (37%), suggests that HCV co-infected patients are under-represented in HIV clinical trials**