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BHIVA 'Best of CROI' Feedback Meetings

London | Midlands | North West England
Edinburgh | North East England

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Co-infection and malignancies

- **TB**
- Cryptococcal meningitis
- Hepatitis C
- Malignancy

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Co-treatment of OI and ART
TB and Cryptococcal meningitis

Potential challenges	Potential benefits
IRIS	Reduced HIV progression
Co-toxicities	Reduced mortality
Drug-drug interactions	Clearance of OI
Absorption	Prevent OI recurrence
Pill burden	
Adherence counseling	

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TB – when to start?

ACTG A5221 STRIDE: An international randomi
trial of immediate vs early antiretroviral therapy
(ART) in HIV+ patients treated for tuberculosis

D Havlir, P Ive, M Kendall, A Luetkemeyer, S Swindells, J
Kumwenda, J Rooney, S Qasba, E Hogg, J Andersen, I Sa

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Frederick Sawe
Mauro Schechter
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CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA
UNAIDS

Optimal timing of antiretroviral therapy during tuberculosis treatment: The SAPiT trial

17th Conference of Retroviruses and Opportunistic Infections
Boston, 28 February 2011

Salim S. Abdool Karim,
Kogieleum Naidoo, Anneke Grobler, Nesri Padayatchi, Cheryl Baxter, Andrew L. Gray, Tanuja Gengiah, Santhanalakshmi Gengiah, Anushka Naidoo, Niraksha Jithoo, Gonasagrie Nair, Wafaa M. El-Sadr, Gerald Friedland and Quarraisha Abdool Karim

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Starting ART at 3 Points in TB
The SAPiT Trial: CAPRISA 003

- **Purpose of study:** To determine the optimal time to initiate ART in TB patients
- **Design:** Open-label 3-arm randomized controlled trial
- **Sample size:** 642 HIV-TB co-infected patients
- **Study site:** CAPRISA eThekwini Clinic, Durban
- **Study Population:** Ambulatory TB smear +ve, HIV +ve (CD4 count < 500 cells/mm^3) and on standard TB treatment regimens. Participants attended the clinic's TB-DOTS program.
- **Endpoints**
  - 1^0 All-cause mortality + AIDS defining illness
  - 2^0 Tolerability, Viral Load, TB outcomes & Immune Reconstitution Inflammatory Syndrome (IRIS)

CAPRISA

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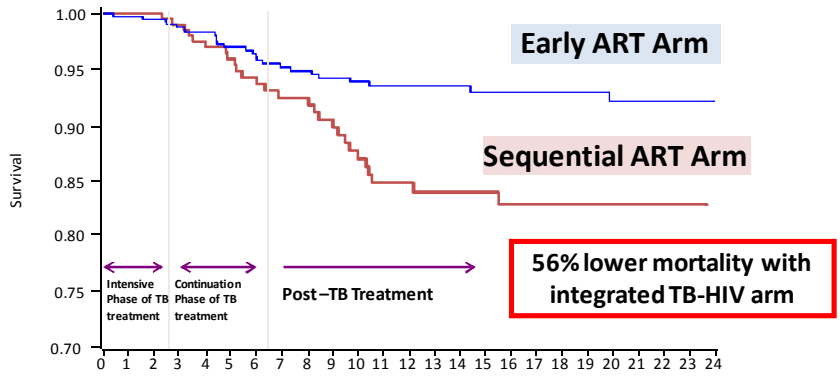
SAPIT Study: Mortality in sequential arm occurred late

Sept 2008: DSMB arm of the SAPIT trial stopped



Reduction in mortality rates was present in patients with CD4 counts above and below 200 cells/mm3

Karim SA et al. CROI 2009. Abstract 36...

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Study intervention
After Sept 2008, remaining 2 arms continued to end)

- **Randomized to one of 2 arms (continued to trial end):**
  - ***Early integrated-therapy arm***- *antiretroviral therapy to be initiated within 4 weeks of starting tuberculosis treatment,*
  - ***Late integrated-therapy arm***- *antiretroviral therapy to be initiated within 4 weeks of completing the intensive phase of tuberculosis treatment, and*
- **Cotrimoxazole prophylaxis**: provided to all patients
- **ART:** ddI + 3TC + efavirenz – once daily regimen
- **Once-a-day treatment** integrated with TB-DOT

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Overall: AIDS defining illness or death

	Early Integrated arm n = 214	Late Integrated arm n = 215
Number of events	18	19
Person-years	259.4	244.2
Event rate (per 100 person-years)	**6.9**	**7.8**

Incidence Rate Ratio: 0.89 (95% CI: 0.44 to 1.79); p=0.73

Similar rates of AIDS defining illness or death

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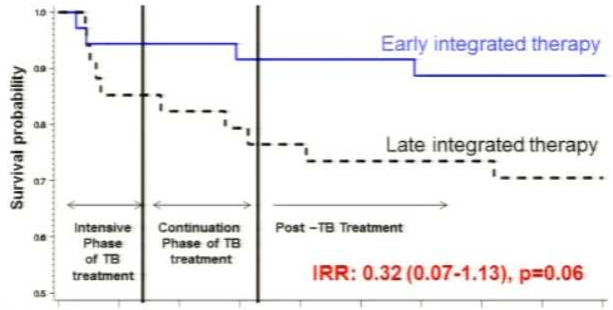
Kaplan-Meier curve for AIDS or death in patients with CD4 <50 cells/mm^3



onths of follow-up	0	6	12	18
ty – Events / # at risk	0/37	2/33	4/31	4/29
e – Events / # at risk	0/35	7/27	9/24	10/21

68% reduction of AIDS / death (p=0.06)

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AIDS / death, IRIS rates, and drug switches stratified by CD4+ count

	Early Integrated Therapy	Late Integrated Therapy	IRR (95% CI)	P-Value
CD4 <50 cells/mm^3	n=37	n=35		
AIDS / death*	8.5	26.3	**0.32** (0.1-1.1)	**0.06**
IRIS*	46.8	9.9	**4.7** (1.5-19.6)	**0.01**
# drug switches	3	0	-	-
CD4 ≥50 cells/mm^3	n=177	n=180		
AIDS / death*	6.6	4.4	**1.51** (0.6-4.0)	**0.34**
IRIS*	15.8	7.2	**2.2** (1.1-4.5)	**0.02**
# drug switches	7	1	**6.8** (0.8-55)	**0.04**

* Rates calculated as events per 100 person-years

CAPRISA

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TB – when to start?

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UNAIDS

Optimal timing of antiretroviral therapy during tuberculosis treatment: The SAPiT trial

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ACTG A5221 STRIDE: An international randomized trial of immediate vs early antiretroviral therapy (ART) in HIV+ patients treated for tuberculosis

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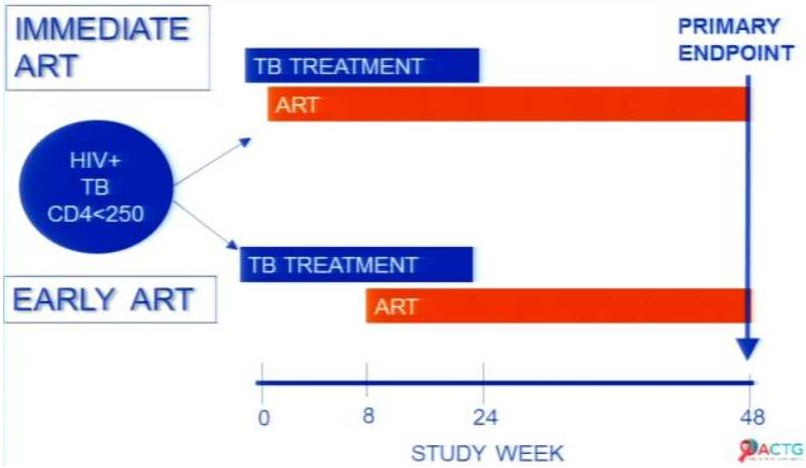
A5221: STRIDE – study design



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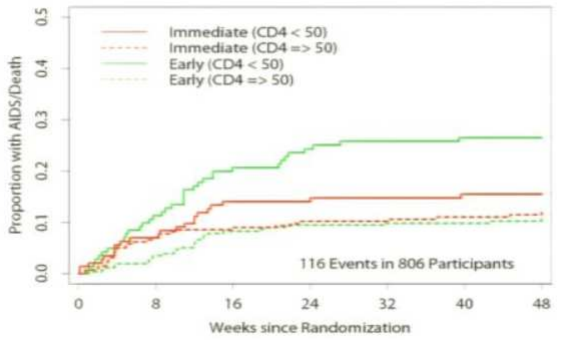
Time-to-New AIDS-Defining Illness or Death by CD4 Stratum



N at risk

Immed 405	368	346	341	335	324	226
Early 401	371	342	329	325	318	218

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Frequency and Predictors of MTB IRIS

	Frequency[1] # MTB IRIS
Immediate ART	43 (11%)
Early ART	19 (5%)

[1]P=0.002

Predictor	Hazard (95% CI)[1]	P Value
Immediate ART	2.5 (1.4, 4.2)	0.001
HIV RNA Higher	1.8 (1.2, 2.7)	0.007
Confirmed TB[2]	3.6 (2.0, 6.6)	<0.001

[1]Cox analysis, multivariate analysis
[2]versus probable/not TB

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ART timing studies in TB studies

Study	Participants	Early	Deferred	Major finding
SAPiT (Two integrated arms)	Smear positive PTB CD4 < 500	Within 4 weeks of starting TB treatment	Within 4 weeks of completing intensive phase	No difference in AIDS/death, but in subanalysis of those with CD4 < 50 early ART reduced AIDS/death by 68%
ACTG 5221 STRIDE	Confirmed or suspected TB CD4 < 250	2 weeks	8-12 weeks	No difference in AIDS/death, but in subanalysis of those with CD4 ≤ 50 earlier ART reduced AIDS/death by 42%

Abdool Karim, CROI 2011 Abstract 39LB
Havlir, CROI 2011 Abstract 38

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Paper # 650

Pharmacokinetic Evaluation of Different Rifabutin Dosing Strategies in African TB Patients on Lopinavir/ritonavir-based ART

Suhashni Naiker1, C Conolly1, L Weisner2, D Phillips1, A Harries3, C Lienhardt4, H McIlleron2, and A Pym1
1MRC, Durban, South Africa; 2Univ of Cape Town, South Africa; 3Intl Union Against Tuberculosis and Lung Disease, Paris, France; and 4WHO, Geneva, Switzerland

What is already known:

- healthy volunteer study suggested optimal dosing of RBT with LPV/r was 150mg 3x/week
- 1 study from US showed suboptimal RBT Cmax (target >300ng/mL) in 9 / 10 HIV + patients, and most patients were below AUC target to prevent rifamycin monoresistance (1 patient developed resistance)

S Naiker[1], C Conolly[2], L Weisner[3], D Phillips[1], AD Harries[4], C Lienhardt[5], H McIlleron[3] and AS Pym[1]

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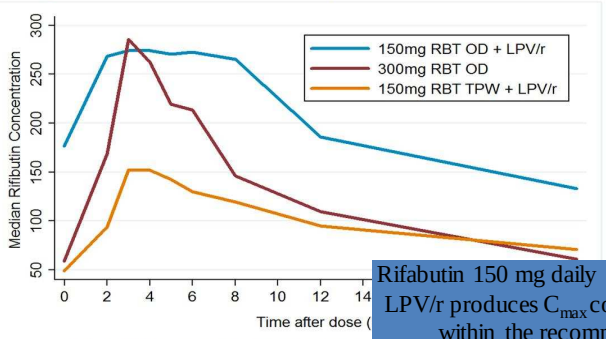
Figure 1. RBT median concentration-time profile before and after LPV/r-based ART



Rifabutin 150 mg daily combined with LPV/r produces C_{max} concentrations within the recommended target range of 300 to 900 ng/mL.

Table 1. RBT Pharmacokinetic Parameters from No

	n	AUC_{0-24} Median (iqr)	C_{max} Median (iqr)
RBT 300mg	14	3052.9 (2650.2-3431.5)	291.5 (250-377)
RBT 150mg daily	14	4766 (3950.5-6099.5)	311 (258-376)
RBT 150mg TPW	14	2307.5 (1767.5-3884)	167.5 (87.8-294)

AUC_{0-24}
RBT 300mg vs RBT 150mg daily: P= 0.0052
RBT 150mg daily vs RBT 150mg TPW : P= 0.0015

C_{max}
RBT 300mg vs RBT 150mg TPW : P= 0.0015
RBT 150mg daily vs RBT 150mg TPW : P= 0.0035

Optimal exposures. Safety data ?

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Co-infection and malignancies

- TB
- **Cryptococcal meningitis**
- Hepatitis C
- Malignancy

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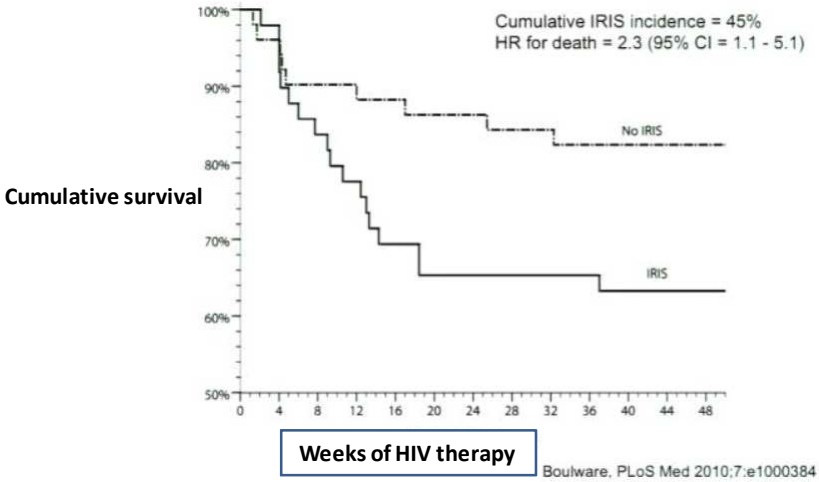
Prospective study of patients with cryptococcal meningitis starting ART



Boulware, PLoS Med 2010;7:e1000384

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Cryptococcal Meningitis

1) Adjunctive Interferon-γ immunotherapy

- RCT of 2 dose or 6 dose IFN-γ schedule vs. standard AMB/5-FC alone in 90 patients in Cape Town
- Faster CSF fungal clearance in both IFN-γ arms, but no effect on mortality (31% at 10 weeks)

2) Determinants of acute outcome & long term survival

- Cohort of 523 patients in 5 countries
- Fungal burden, weight, abnormal mental status & rate of fungal clearance predict acute outcome
- Mortality 32% at 10 weeks, 41% at 1 year
- Fungal burden at 2 weeks, but not early ART predictive of IRIS

1) Jarvis *et al*, 40 2) Bicanic *et al*, 892

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Cryptococcal Meningitis

3) Comparison of second drugs given with AMB

- 80 patients randomised to 4 different treatments for 2 weeks :– 5-FC, fluconazole – 800 mg or 1200 mg, or voriconazole 300 mg (all + AMB 0.7-1 mg/kg)
- No significant differences in rate of fungal clearance, mortality or toxicity between groups

4) Short-course AMB with high dose fluconazole

- Open label study of 2 weeks fluconazole 1200 mg with AMB for first 5 days, in 30 patients in Uganda
- Rapid fungal clearance with no reduction after stopping AMB

3) Loyse *et al*, 893 4) Muzoora *et al*, 894

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Co-infection and malignancies

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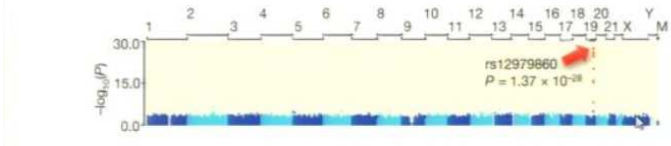
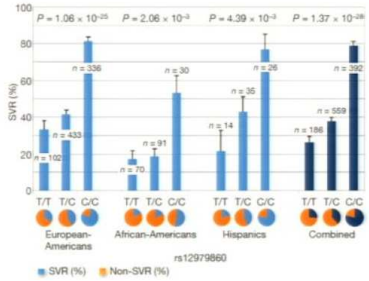
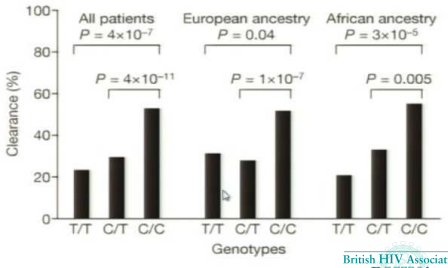
IL28B gene association with HCV clearance and recovery



C allele is associated with response to PegIFN and RBV



C allele associates with higher probability of spontaneous clearance of HCV



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IL 28 summary slide

- The combined use of IL-28B GT, HCV GT, and HCV-RNA load enables identification of patients with very high and low likelihood of SVR - #945

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Background III

Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference

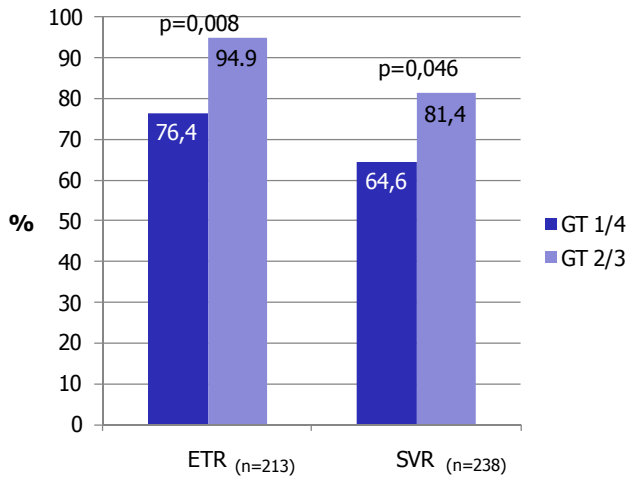
The European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel

AIDS 2011, **25**:399–409

Material and Methods

- 238 HIV-infected patients from 4 European countries (UK, France, Germany, Austria) with diagnosed acute HCV infection were treated early with pegylated interferon (pegIFN) and ribavirin (RBV) (n=207) or pegylated interferon alone (n=31), followed prospectively since 2002 and evaluated for SVR.
- In 85% of cases (175/207) weight-adapted dosage of ribavirin (wt <75kg: 1000mg/wt >75kg: 1200mg/d) was used.

ETR & SVR



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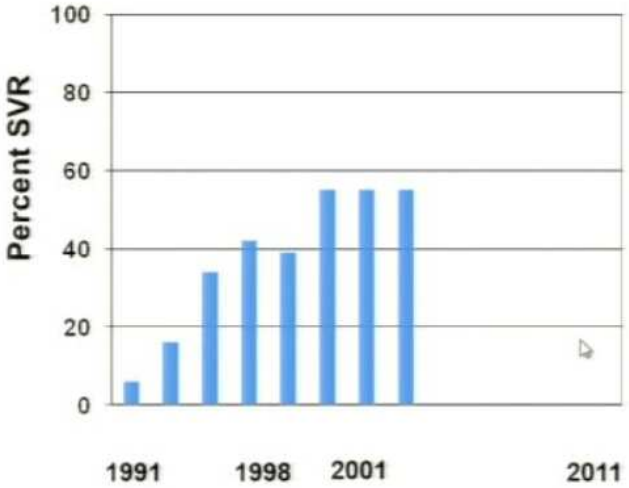
Progress in treatment of HCV has stalled!



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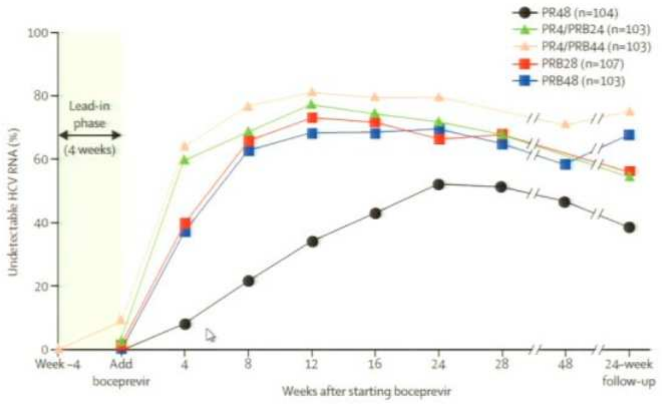
Bocepravir – efficacy in naïve patients: SPRINT 2 study



Kwo Lancet 2010;

HCV plenary; CROI abstract 115 and CROI abstract LB 146 TPV in HIV/HCV coinfected

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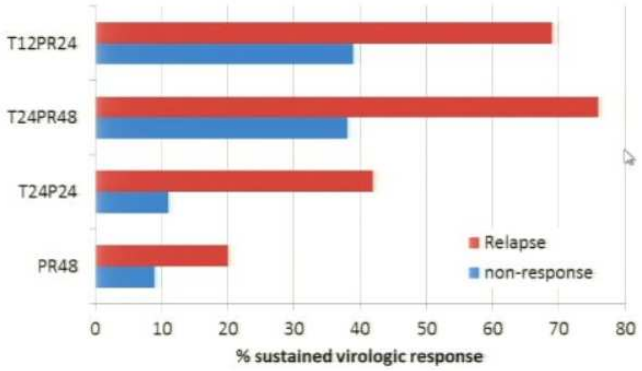
Bocepravir – efficacy in retreatment of PEG-IF/RBV failures: RESPOND 2



McHutchison NEJM 2010

2011 CROI 116

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Pharmacokinetic Interactions Between Antiretroviral Agents and the Investigational HCV Protease Inhibitor Telaprevir in Healthy Volunteers

R van Heeswijk,[1] A Vandevoorde,[1] G Boogaerts,[1] T Vangeneugden,[1] E de Paepe,[1] R Polo,[1] R Van Solingen-Ristea,[1] K de Backer,[1] V Garg,[2] and M Beumont[1]

[1]Tibotec BVBA, Beerse, Belgium; [2]Vertex Pharmaceuticals Incorporated, Cambridge, MA, USA

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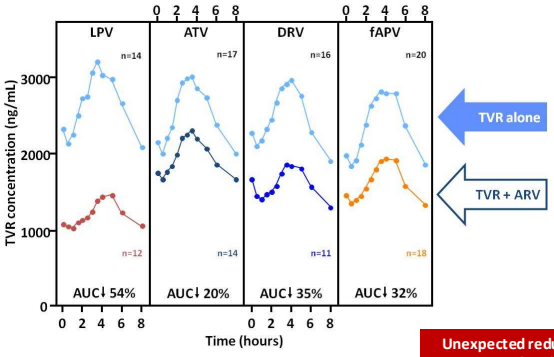

Unexpected reduction in TVR levels

	TVR	TVR AUC	ARV AUC
LPVr	750mg tds	↓54%	↔
ATVr	750mg tds	↓20%	Cmin increased
DRVr	750mg tds	↓35%	↓40%
fAPVr	750mg tds	↓32%	↓47%
EFV (+ TDF)	1125mg tds or 1500mg bd	Small changes (↓15-20%) TVR	
TDF (+EFV)	1125mg tds or 1500mg bd	1500bd Ctrough ↓48%	↑10%

Unexpected reduction in ARV levels

1125mg tds progressed to clinical trial with EFV

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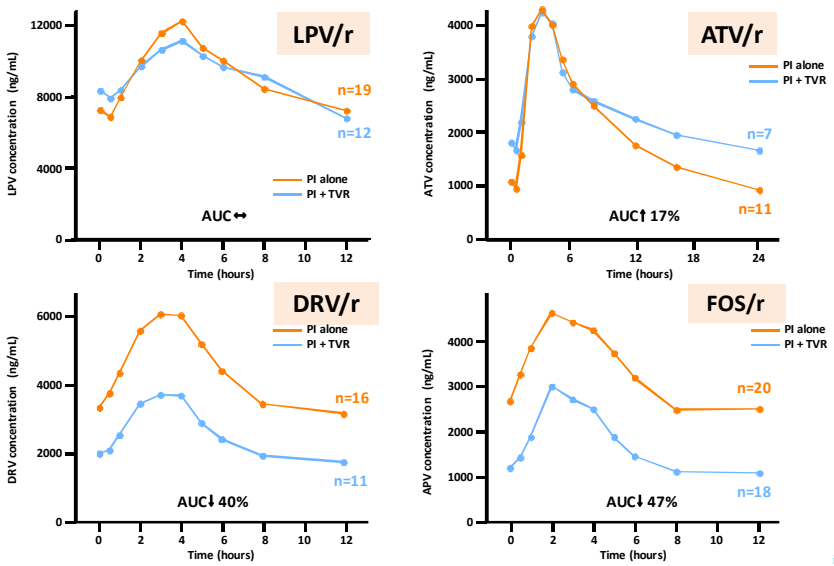
Mean HIV PI PK Profiles



APV = amprenavir

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Interim Analysis of a Phase 2a Double-Blind Study of Telaprevir in Combination with PEG-IF Alfa-2a and Ribavirin in HIV/HCV Coinfected Patients

Mark S. Sulkowski, Douglas T. Dieterich, Kenneth E. Sherman, Juergen K. Rockstroh, Nathalie Adda, Lisa Mahnke, Varun Garg, Shahin Gharakhanian, Scott McCallister, and Vincente Soriano

On behalf of the Study 110 Team

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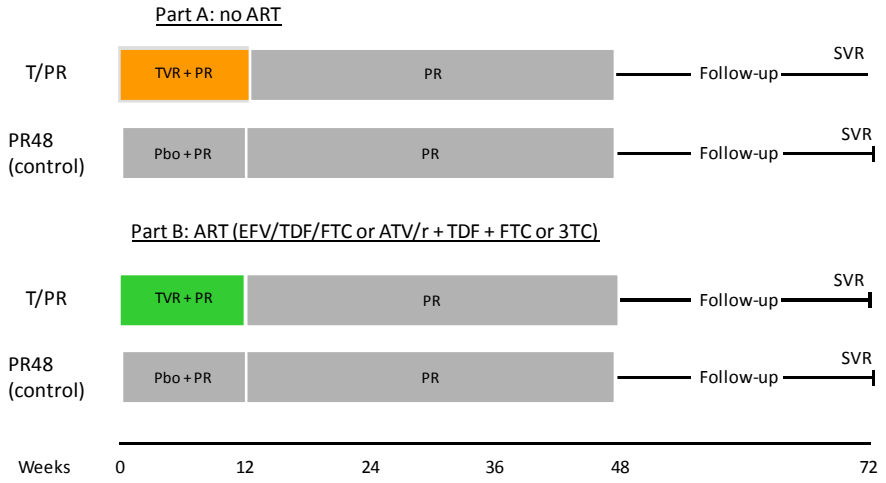
Study Design



(EFV)=efavirenz; (TDF)=tenofovir; (FTC)=emtricitabine; (ATV/r)=ritonavir-boosted atazanavir; (3TC)=lamivudine;
(T) TVR=telaprevir 750 mg q8h or 1125 mg q8h (with EFV); Pbo=Placebo; (P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk; (R) RBV=ribavirin 800 mg/day or weight-based (1000 mg/day if weight <75 kg, 1200 mg/day for if weight ≥75 kg; France, Germany)
Roche COBAS® TaqMan® HCV test v2.0, LLOQ of 25 IU/mL (pts with values below 25IU/mL were reported as <25 detectable or undetectable)

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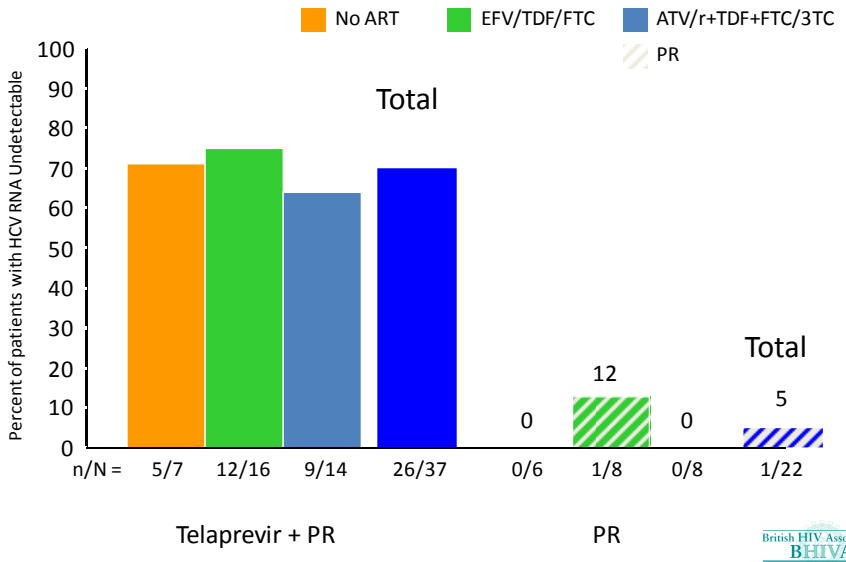
Undetectable HCV RNA at Week 4 (ITT)



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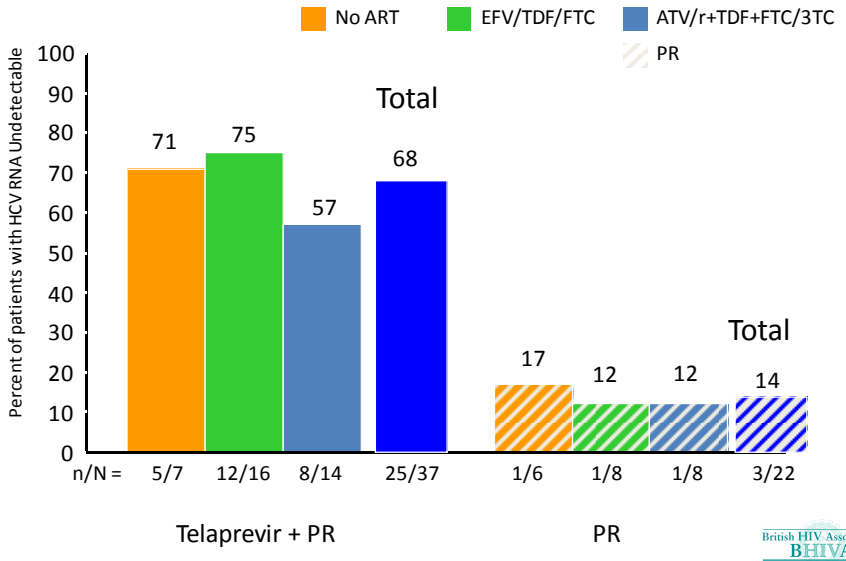
Undetectable HCV RNA at Week 12 (ITT)



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Interim Analysis Summary

- In this interim analysis, the most common adverse events in telaprevir patients with or without concurrent ART were fatigue, nausea, and headache; no severe rash events were reported
- Patients in the T/PR arms in both parts exhibited a higher on-treatment HCV RNA response at week 4
  - T12/PR: 26 of 37 patients (70%)
  - PR: 1 of 22 patients (5%)
- No unexpected trends in HIV viral loads and/or CD4 counts were observed
- No clinically significant PK interactions were observed

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Co-infection and malignancies

- TB
- Cryptococcal meningitis
- Hepatitis C
- **Malignancy**

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Multicentric Castleman's disease

- MCD
  - Dramatic improvement in prognosis if rituximab (+/- chemotherapy) used in treatment
  - 24% risk of non-Hodgkin's lymphoma by 2 years
- If rituximab used in treatment, 3% risk of NHL by 5 years
- Risk of flares of KS in minority of patients
  - France, UK, some US clinicians

Hoffman, CROI 2011, Abstract 861
Michot, CROI 2011, Abstract 83

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Burkitt's lymphoma

- GMALL B-ALL
  - Rituximab
  - Ifosfamide
  - Cytarabine
  - High dose methotrexate
- 78 patients
  - CR 62/77 (81%)
  - 3-year survival 68% (Spain), 78% (Germany)
- 14 infection-related deaths (fungal)
- CD4 <200 main risk for mortality in MV analysis
  - OR 2.8 (1-7.4)

London data:
CODOX-M/IVAC 52% 3-year survival
(Montoto et al. AIDS 2010)

Fätkenheuer, CROI 2011, Abstract 860

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- **Hepatitis C**
- **Malignancy**

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