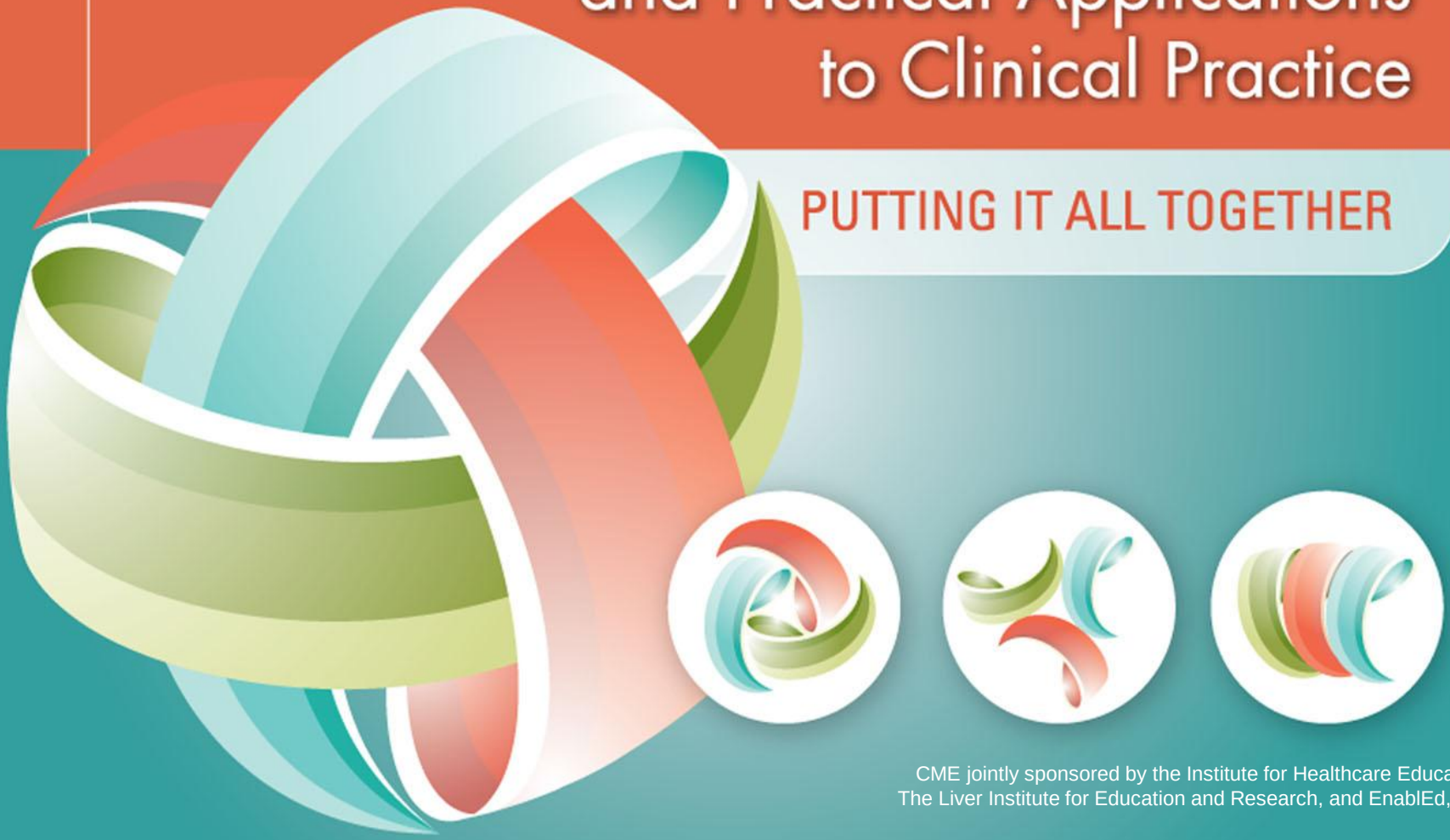
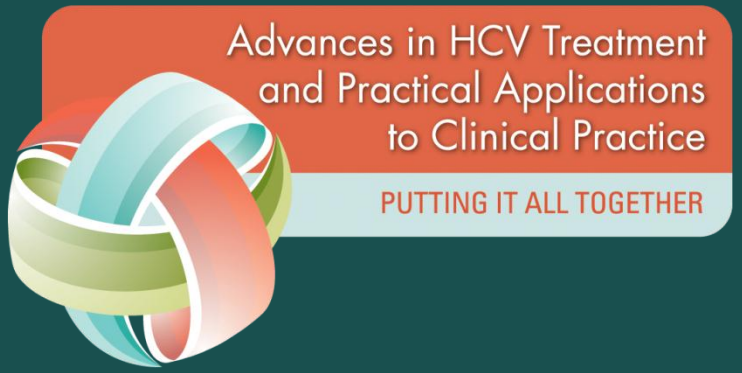
Advances in HCV Treatment and Practical Applications to Clinical Practice

PUTTING IT ALL TOGETHER



CME jointly sponsored by the Institute for Healthcare Education, The Liver Institute for Education and Research, and EnablEd, LLC



Case:
Drug–Drug Interactions

Case: Drug–Drug Interactions

- 62-year-old man evaluated for treatment of chronic HCV, probably acquired 40 years ago
- Medical history
  - Coronary artery disease, currently asymptomatic; 2 bare metal stents placed 3 years ago
  - Hypercholesterolemia
  - Benign prostatic hypertrophy
- Medications
  - Atorvastatin 20 mg/day
  - Aspirin 325 mg/day, clopidogrel 75 mg/day
  - Alfuzosin 10 mg/day
  - Sildenafil 50 mg as needed

Case: Drug–Drug Interactions

- ALT 109 IU/L, AST 98 IU/L
- Albumin 3.8 g/dL
- White blood cells, hemoglobin normal; platelets 140,000/μL
- α-Fetoprotein normal
- HCV genotype 1b
- HCV RNA 902,480 IU/mL
- Ultrasound: heterogeneous echotexture of liver
- FibroSure: 0.68

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Case: Drug–Drug Interactions

- The patient's cardiologist says that aspirin and clopidogrel can be held for 7–10 days

- Would you obtain a liver biopsy?

Case: Drug–Drug Interactions (DDIs)

- Liver biopsy: Metavir F3 fibrosis
  - Bridging fibrosis with early nodule formation

- Would you treat this patient?
  - If so, with what regimen would you treat?
- Is any modification of the patient's medical regimen required?

Why the Risk of DDIs with Direct-Acting Antivirals (DAA)?

Drug	CYP 450	P-glycoprotein	Non-CYP metabolism
Telaprevir	CYP 3A4: • Substrate • Inhibitor	• Substrate • Inhibitor	–
Boceprevir	CYP 3A4/5: • Substrate • Inhibitor	• Substrate • Inhibitor	AKR • Substrate

CYP = cytochrome P.

Kassera C, et al. CROI 2011. Abstract 118; Garg V, et al. CROI 2011. Abstract 629; Telaprevir/ and boceprevir prescribing information; Kiser JJ, et al. Hepatology 2012;55:1620-28.

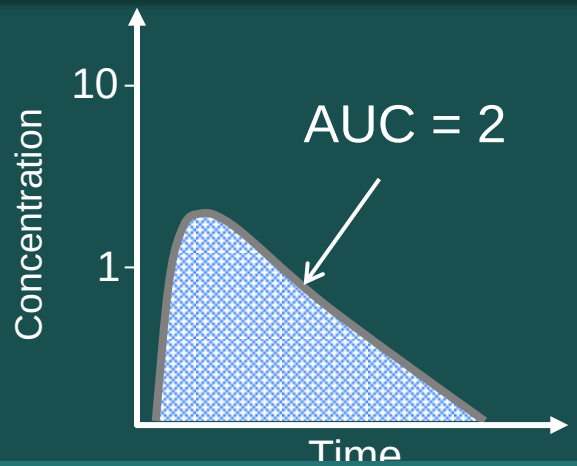
Why Worry About DDIs with DAAs?

- Drug–drug interactions can change the activity of concomitant medications or increase their risk of toxicity
- Drug–drug Interactions can change the antiviral activity of DAAs (loss of efficacy)

Inhibition of Hepatic CYP450

A. Drug alone

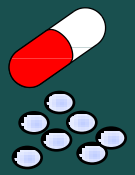
Drug



Drug exposure increased by 2.5-fold

B. Drug + Inhibitor

Drug Inhibitor



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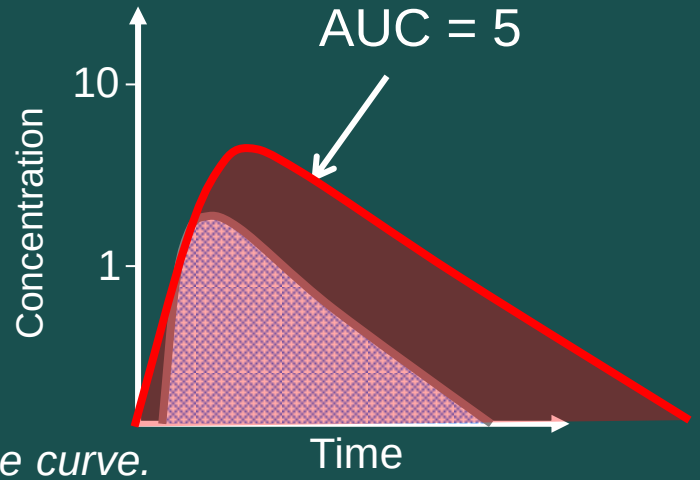


AUC = area under the concentration–time curve.

Drugs Contraindicated with Telaprevir and Boceprevir

Common denominator = Interaction with CYP3A4;

Interactions can occur via inhibition OR induction

- Rifampin
- Alfuzosin
- Ergot derivatives
- Cisapride (limited access)
- St. John's wort
- Lovastatin, simvastatin (telaprevir: atorvastatin)
- Sildenafil or tadalafil for pulmonary artery hypertension
- Oral midazolam, triazolam
- Drosperinone (boceprevir)

Many other potential or established DDIs; recent reports of antiretroviral therapy DDIs with boceprevir

Telaprevir and boceprevir prescribing information.

Telaprevir Increases Exposure to Immunosuppressants (CYP3A Substrates)

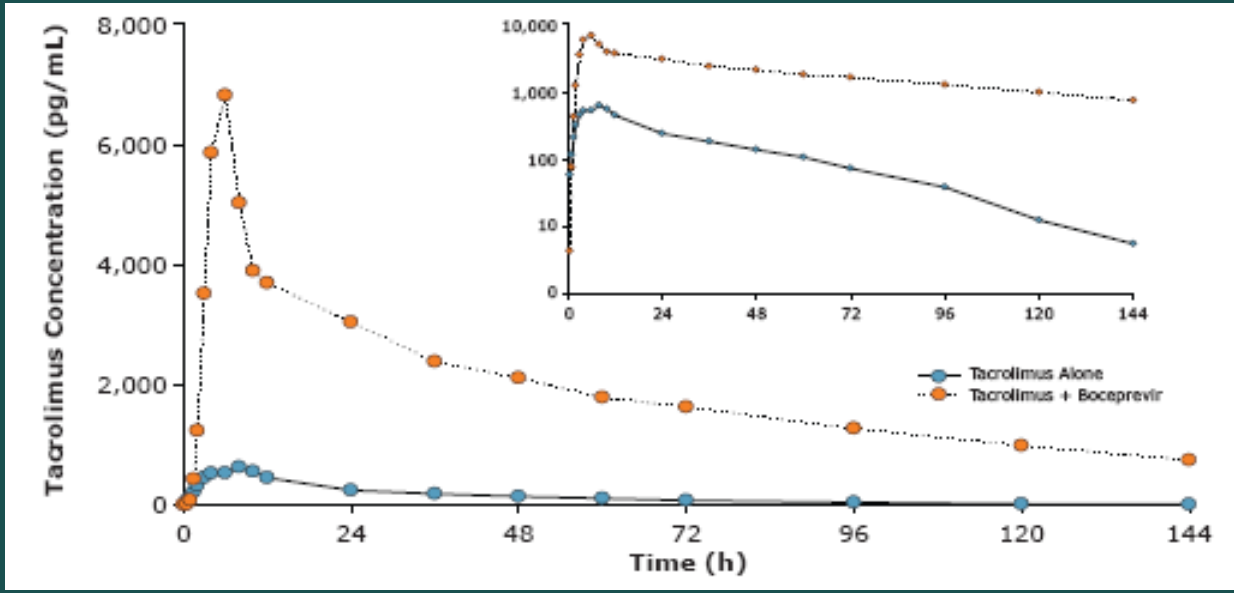
Calcineurin Inhibitor	C_{max}	AUC	$t_{1/2}$
Cyclosporine A	1.3-fold increase	4.6-fold increase	From 12 → 42 hours
Tacrolimus	9.4-fold increase	70-fold increase	From 41 → 196 hours

- Doses of immunosuppressants will require significant reductions; dosing intervals must be prolonged
- Close monitoring required

C_{max} = maximum plasma concentration; t½ = half-life.

Garg V, et al. Hepatology 2011:54:20-7.

Telaprevir Interaction with Tacrolimus

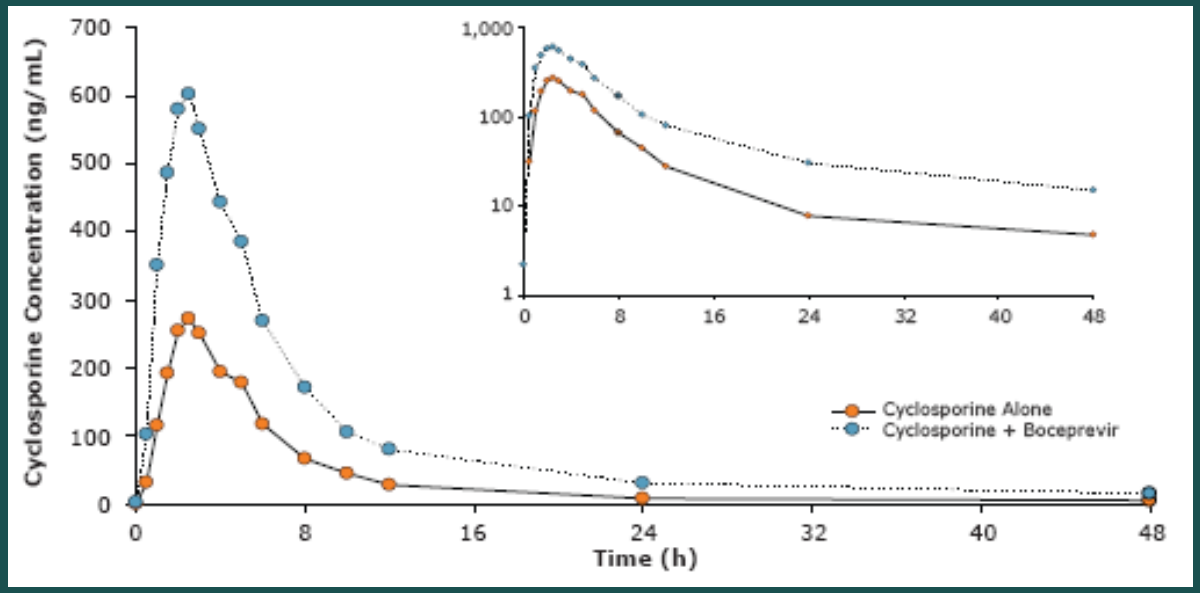


- Doses of immunosuppressants will require significant reductions; dosing intervals must be prolonged
- Close monitoring required

Garg V, et al. Hepatology 2011:54:20-7.

Boceprevir Increases Exposure to Cyclosporine

Mean Plasma Concentration–Time Profiles of Cyclosporine, Alone or with Boceprevir at Steady-State

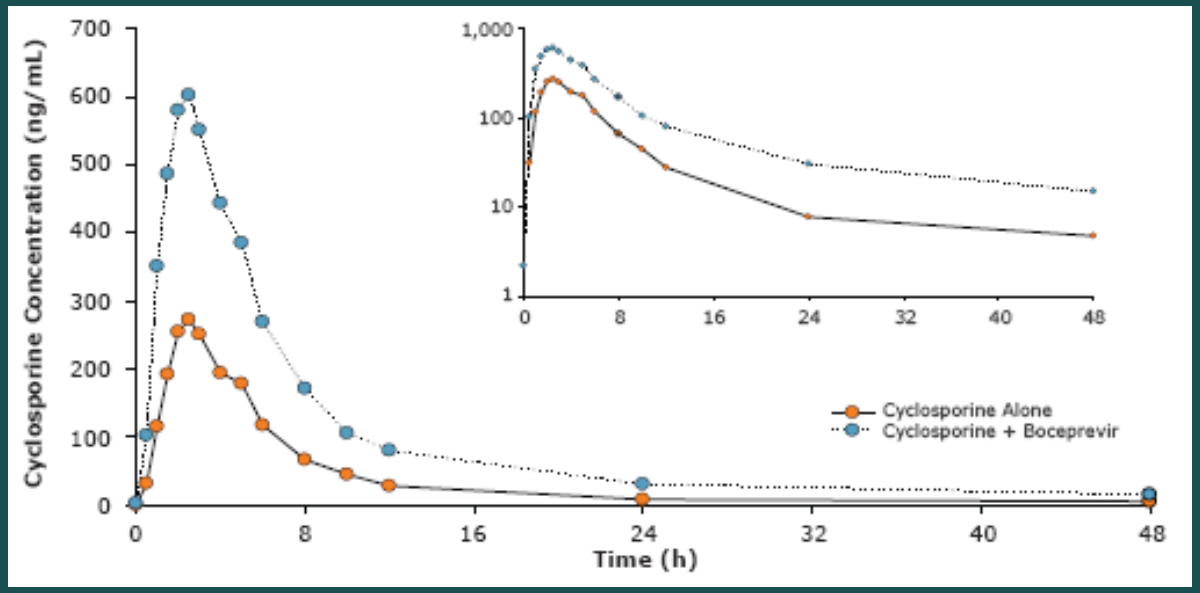


- 2-fold ↑ in C_{max}, 2.7-fold ↑ in AUC_{∞} with cyclosporine/boceprevir coadministration in 32 healthy volunteers (geometric mean ratios)
- Cyclosporine dose adjustments should be expected; close monitoring required

Hulskotte EGJ, et al. HepDART 2011 Poster 123.

Boceprevir Increases Exposure to Tacrolimus

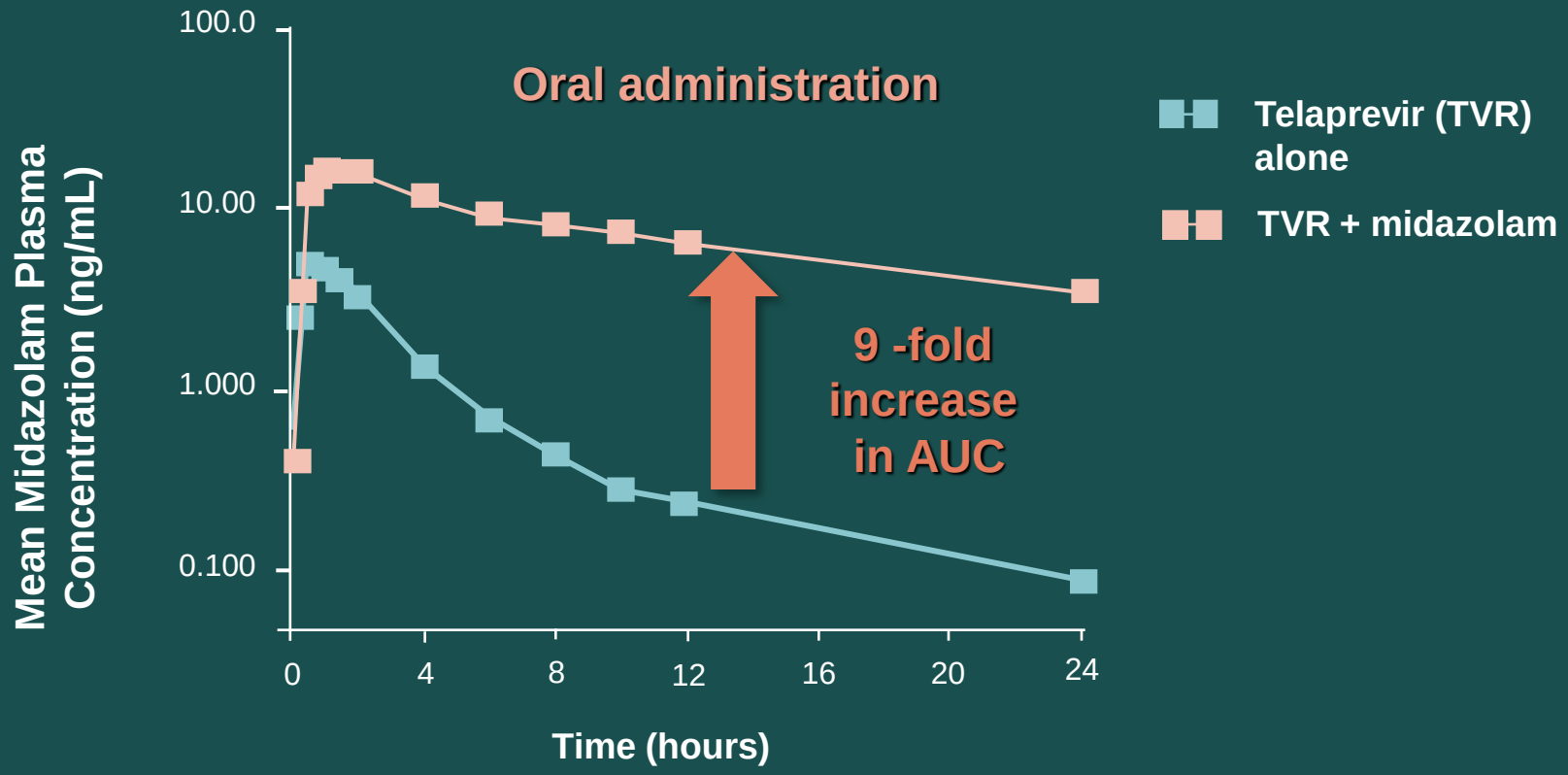
Mean Plasma Concentration–Time Profiles of Tacrolimus, Alone or with Boceprevir at Steady-State



- 10-fold ↑ in C_{max}, 17-fold ↑ in AUC_{∞} with tacrolimus/boceprevir coadministration in 32 healthy volunteers (geometric mean ratios)
- Significant tacrolimus dose reductions, prolonged dosing intervals likely, close monitoring required

Hulskotte EGJ, et al. HepDART 2011 Poster 123.

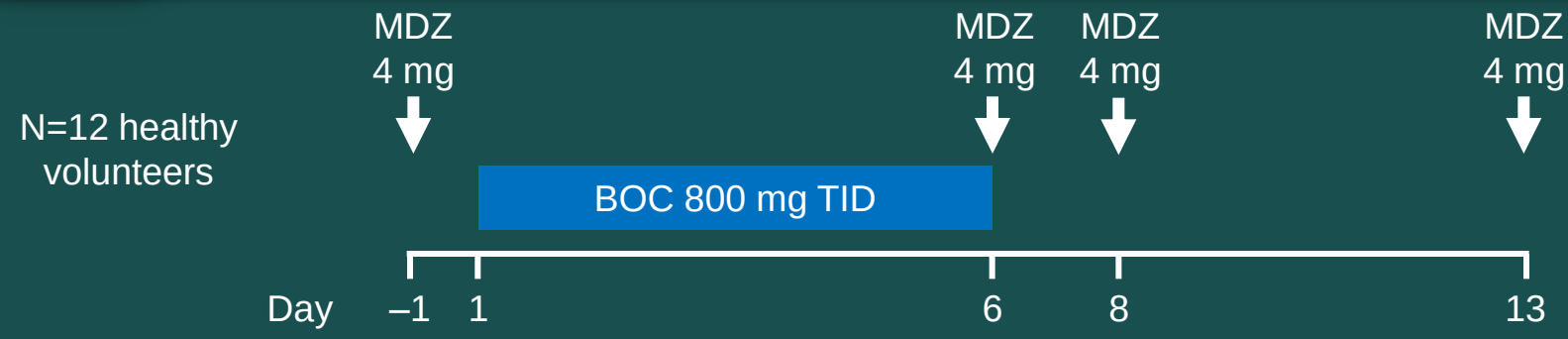
Telaprevir Increases Exposure to Oral Midazolam (CYP3A4 Substrate)



- Oral midazolam contraindicated with telaprevir

Garg V, et al. IWCPHT 2011. Abstract PK_12; telaprevir prescribing information.

Boceprevir Increases Oral Midazolam Exposure (CYP3A4 Substrate)

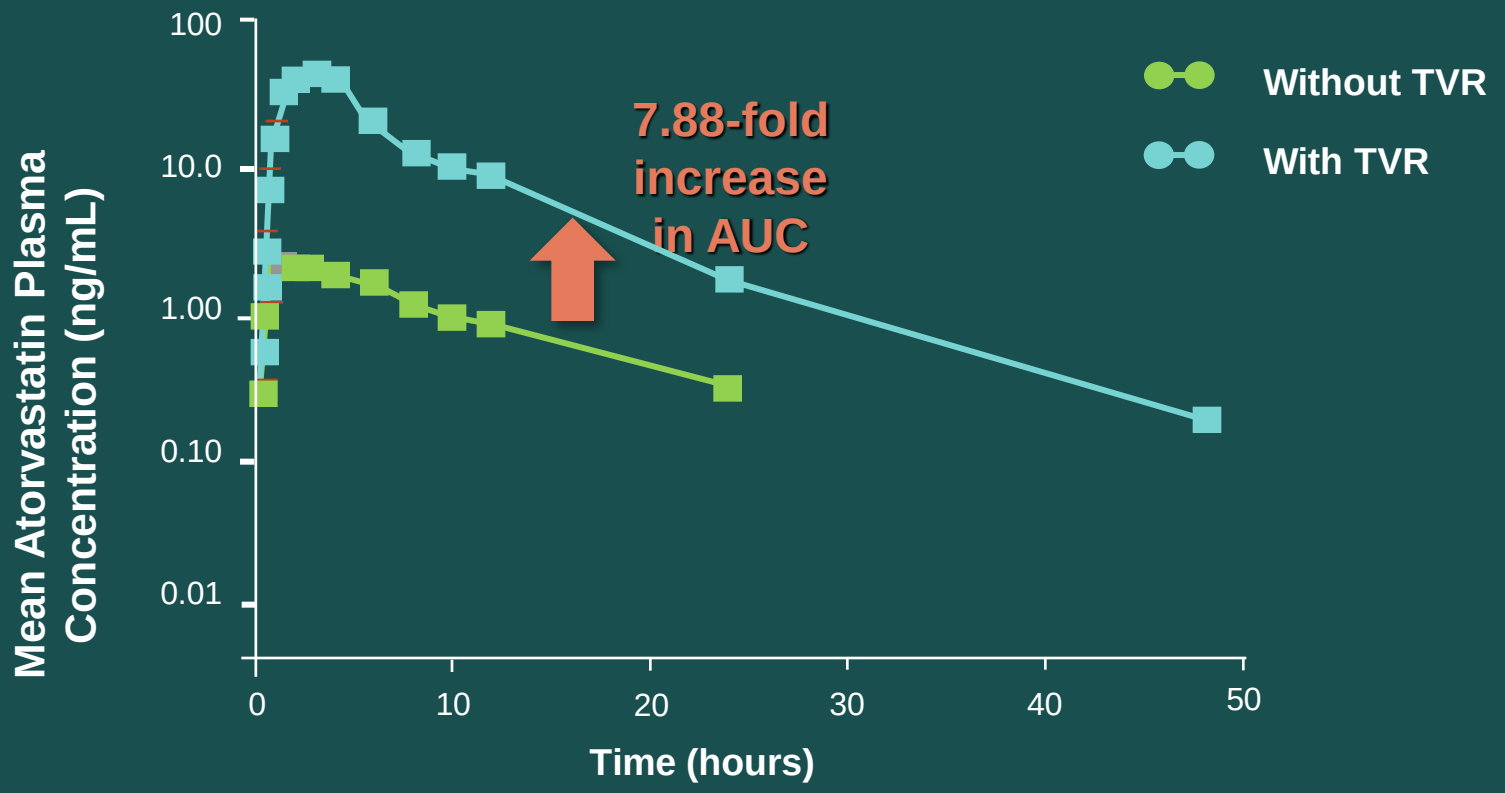


	Treatment	LSmean
MDZ $AUC_{0–12h}$, ng•h/mL	MDZ Day -1	**52.94**
	MDZ + BOC Day 6	**280.7**
	MDZ Day 8	**56.10**
	MDZ Day 13	**43.83**

BOC = boceprevir; LSmean = least-squares mean; MDZ = midazolam; TID = 3 times daily.

Modified from Kassera C, et al. CROI 2011. Abstract 118.

Telaprevir Increases Exposure to Atorvastatin (CYP3A4 Substrate)



- Telaprevir contraindicated with atorvastatin

Lee JE, et al. Antimicrob Agents Chemother 2011;55:4569-74; telaprevir prescribing information.

Telaprevir Decreases Exposure to Ethinyl Estradiol (CYP Substrate)

Oral Contraceptive	Effect of telaprevir on AUC
Ethinyl estradiol	↓ 28%
Norethindrone	↓ 11%

- 2 additional methods of nonhormonal contraception should be used
- Hormonal contraceptives can be continued, but they may be unreliable during and for up to 2 weeks after cessation of telaprevir therapy

Garg V, et al. J Clin Pharmacol. 2011 Oct 30. [Epub ahead of print]

Boceprevir Interaction with Oral Contraceptives

	Treatment	LSmean
Drospirenone $AUC_{0–8h}$, ng•h/mL	OC	655
	OC + BOC	1304
Ethinyl estradiol $AUC_{0–24h}$, ng•h/mL	OC	659
	OC + BOC	499

- Caution should be exercised in patients taking drospirenone who are predisposed to hyperkalemia or are taking potassium-sparing diuretics
- Alternative contraceptives should be used

OC = Oral contraceptives.

Modified from Kassera C, et al. CROI 2011. Abstract 118; boceprevir prescribing information.

Boceprevir: Interactions with HIV Protease Inhibitors (PIs)

- Interactions with 3 ritonavir-boosted (/r) PIs described
- Coadministration not recommended

Antiretroviral PI	AUC Antiretroviral	AUC Boceprevir
Atazanavir/r	-35%	No change
Darunavir/r	-44%	-32%
Lopinavir/r	-34%	-45%

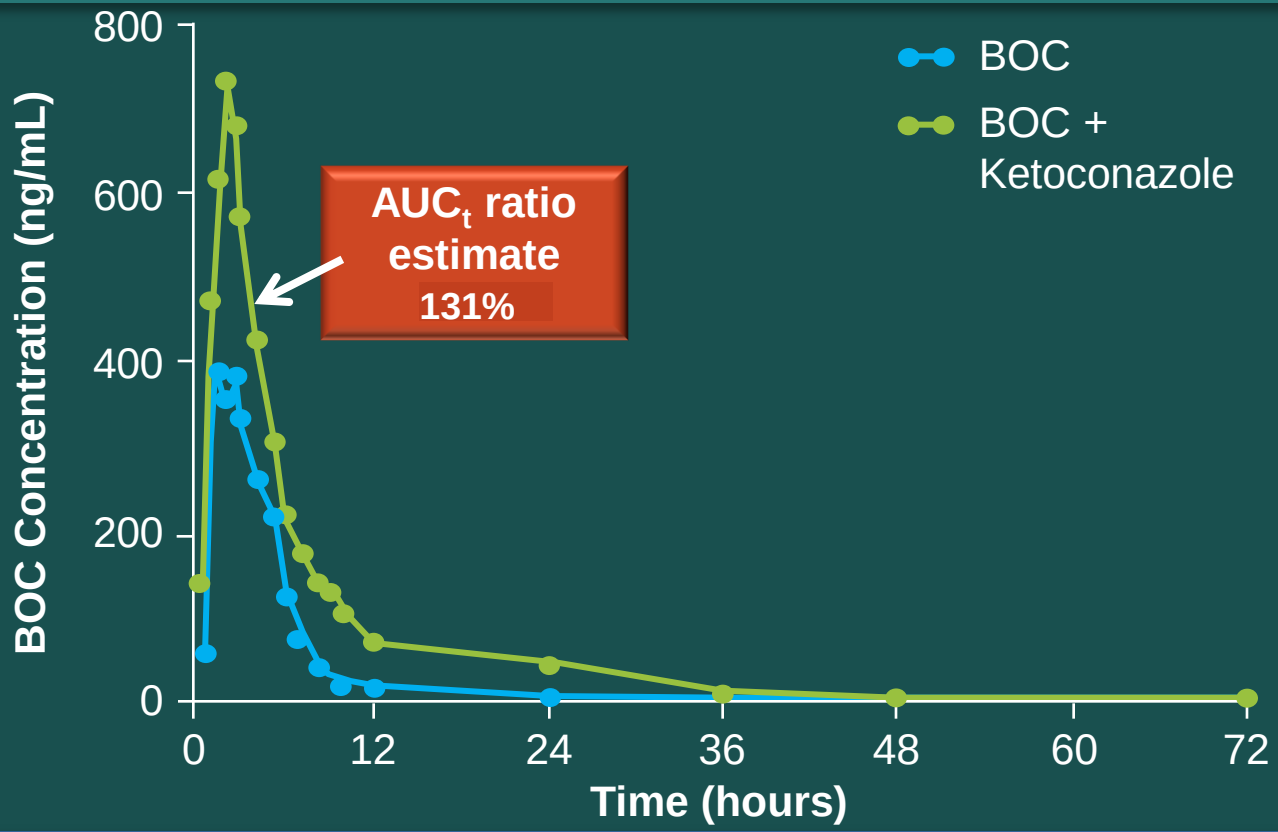
Hulskotte CROI 2001 Abstract 771LB.

Telaprevir: DDIs with HIV Antiretrovirals

HIV antiretroviral	Recommendation
Atazanavir/r	Clinical and laboratory monitoring for hyperbilirubinemia is recommended
Darunavir/r Fosamprenavir/r Lopinavir/r	Coadministration not recommended
Efavirenz	TVR dose increase needed (1125 mg every 8 hours)
Raltegravir	No dose adjustment required
Tenofovir	Increased clinical and laboratory monitoring is warranted

Telaprevir prescribing information; van Heeswijk R, et al. CROI 2011 Paper #119; van Heeswijk R, et al. ICAAC 2011, Abstract A1-1738a.

Boceprevir Exposure Increased by CYP3A4/P-Glycoprotein Inhibitor



- Caution should be used when boceprevir is combined with ketoconazole or azole antifungals (itraconazole, posaconazole, voriconazole)

Modified from Kassera C, et al. CROI 2011. Abstract 118; boceprevir prescribing information.

Rifampin Reduces Telaprevir Exposure

Comedication	Effect on Telaprevir	
	AUC	C_{max}
Rifampin	- 92%	- 86%

- Mechanism: rifampin is a potent CYP3A4 inducer
- Rifampin reduces exposure to telaprevir by 92%
- Rifampin is contraindicated with telaprevir

Vertex FDA Briefing Document April 2011; telaprevir prescribing information.

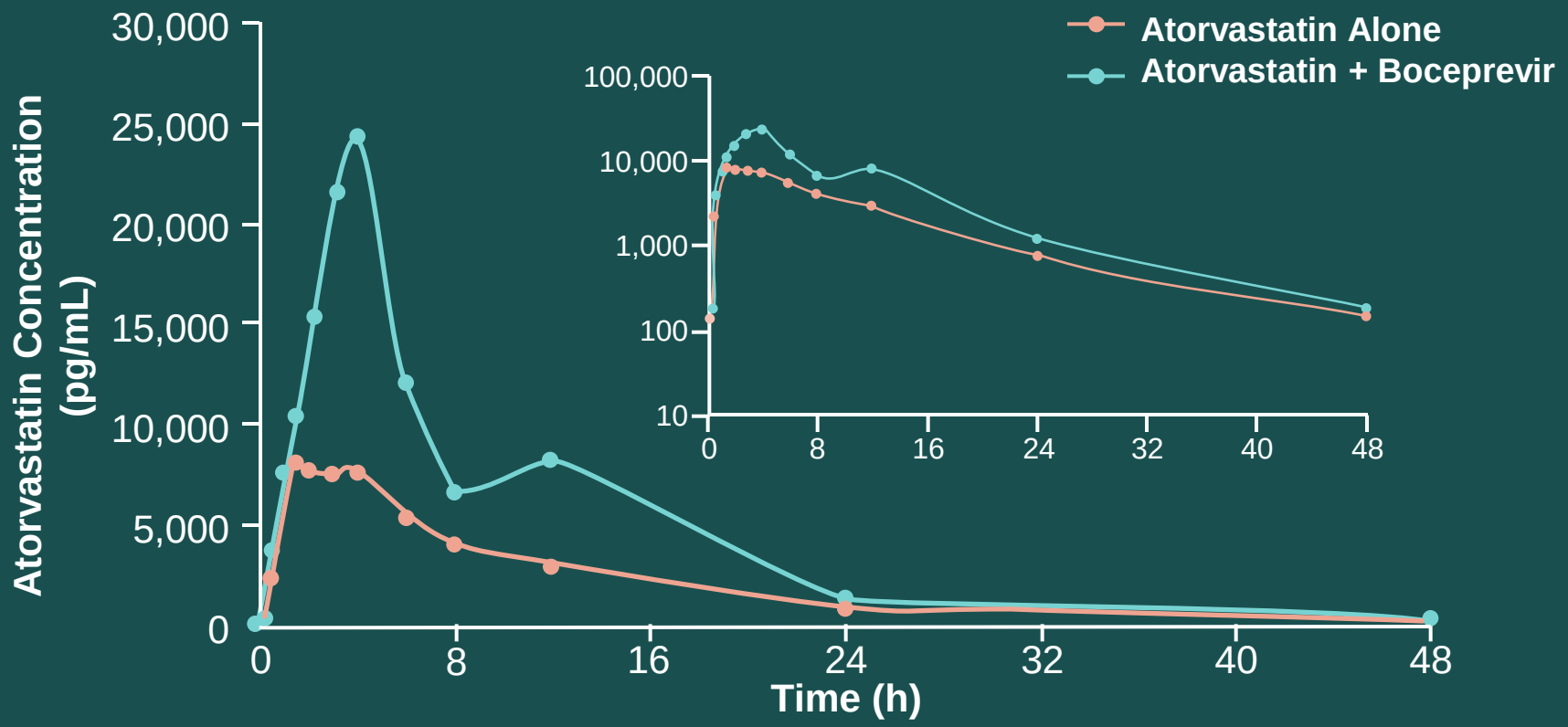
Boceprevir Exposure Decreased by Efavirenz

	Treatment	LSmean*
BOC $AUC_{0–8h}$, ng•h/mL	BOC	6913
	BOC + Efavirenz	5630
Efavirenz $AUC_{0–24h}$, ng•h/mL	Efavirenz	78667
	Efavirenz + BOC	94655

- Clinical implications of reduced boceprevir trough concentrations are unclear

Kassera C, et al. CROI 2011. Abstract 118.

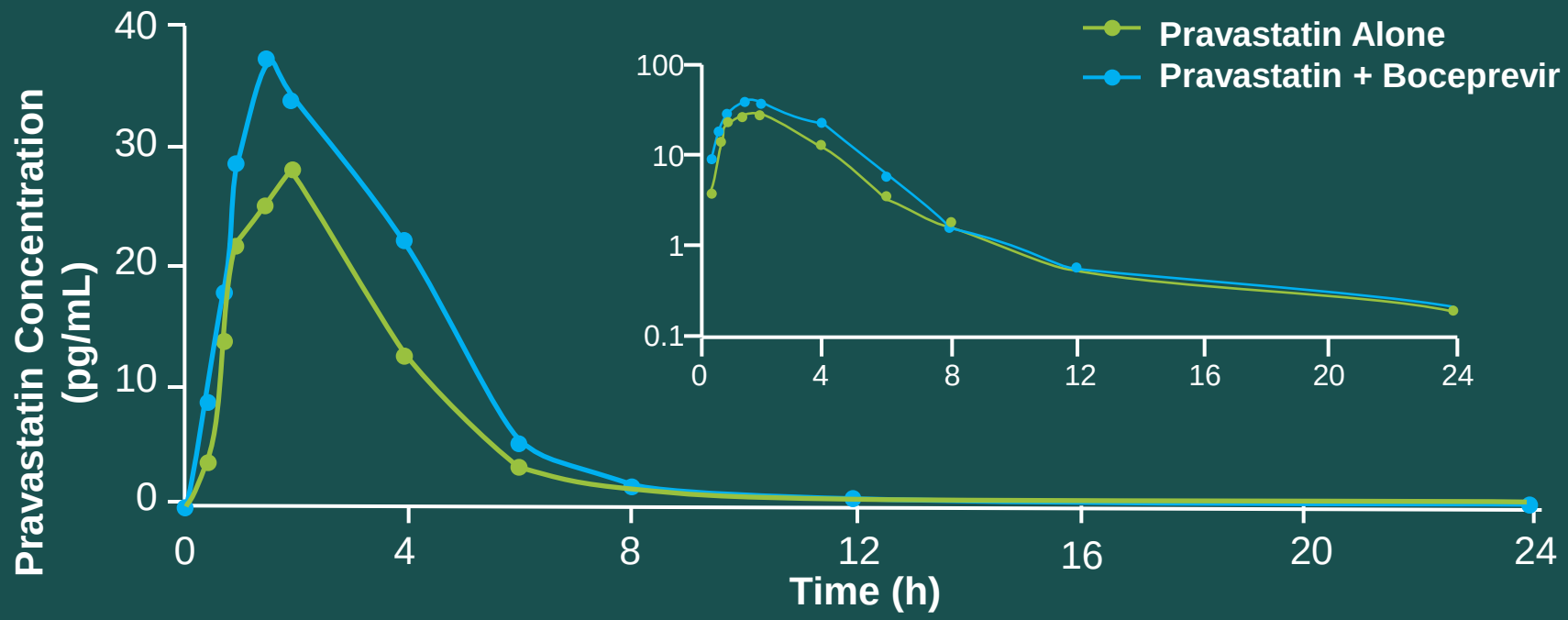
Boceprevir with Atorvastatin



- Atorvastatin C_{max} increased by ~2.7-fold; AUC_{inf} increased by ~2.3-fold (geometric mean ratios)

Hulskotte HepDART 2011 Abstract.

Boceprevir with Pravastatin



- Pravastatin C_{max} increased by ~1.5-fold; AUC_{inf} increased by ~1.6-fold (geometric mean ratios)

Hulskotte HepDART 2011 Abstract.

Case: Drug–Drug Interactions

- Patient is started on telaprevir with peginterferon and ribavirin
- His cardiologist prefers that he not stop his lipid-lowering therapy
- Medication adjustments:
  - Atorvastatin switched to rosuvastatin
    - Rosuvastatin metabolized by CYP450 2C9
  - Alfuzosin switched to finasteride
  - Sildenafil decreased from 50 mg to 25 mg

Rosulastatin prescribing information.

Conclusions

- Be vigilant for DDIs when starting new therapies
- Review all new medications before initiation
- Instruct patients to contact you before they take medications prescribed elsewhere
- HIV-infected patients and liver transplant patients are at high risk of DDIs
- Know where to locate information about interactions
  - Online
  - Health care resources (e.g., pharmacists)

Do Not Hesitate to Use Web Resources!

- List of CYP substrates, inhibitors, inducers
  - http://medicine.iupui.edu/clinpharm/ddIs
- Drug interactions
  - http://www.drugs.com/drug_interactions.html
  - http://www.medscape.com/druginfo/druginterchecker
  - http://www.drugstore.com/pharmacy/drugchecker/
- HIV coinfection
  - http://www.hiv-druginteractions.org
- Hepatitis coinfection
  - http://www.hep-druginteractions.org