Transporters: Role in Clinical Development of HCV Compounds

Brian Kirby, PhD
Clinical Pharmacology, Gilead Sciences
Foster City, CA

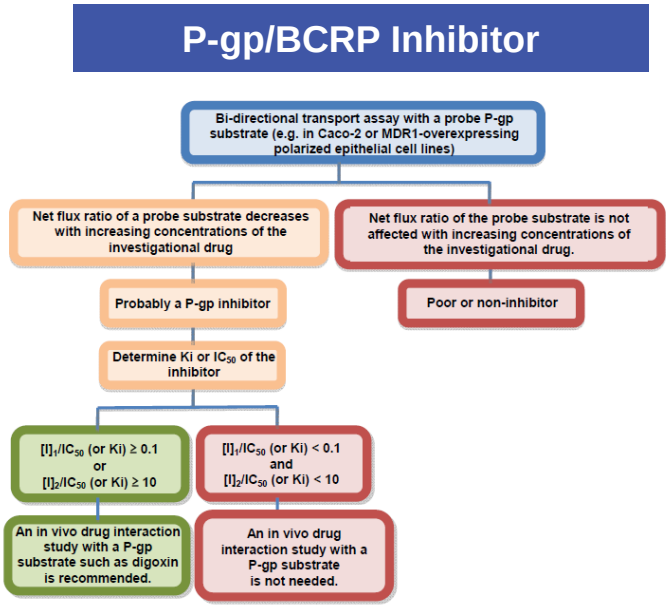
15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy 2014
Washington, DC

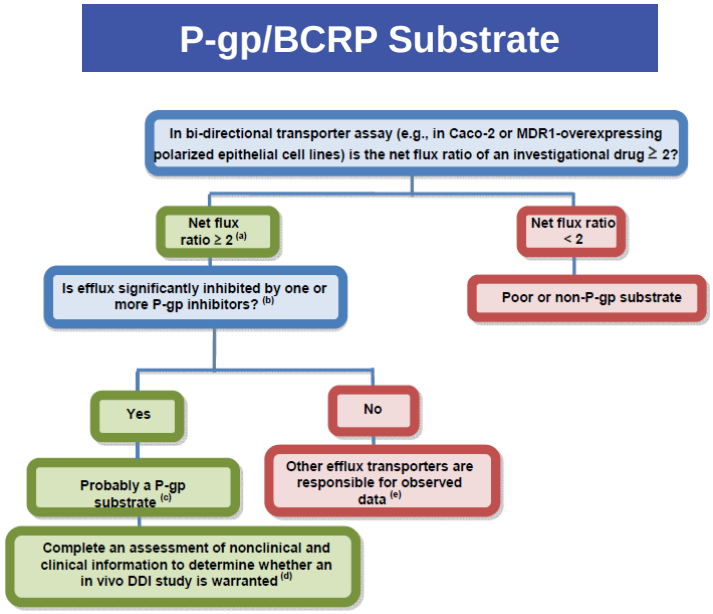
Introduction

- Drug discovery and development is moving away from metabolic liabilities
  - Increasing importance and evaluation of the role of transporters in drug disposition
- Unique challenges for transporter-mediated DDIs
  - Bioavailability vs. systemic clearance vs. distribution
  - Tissue and membrane localization (plasma vs. tissue concentration)
  - Lack of specificity of probe substrates and inhibitors
  - Limited understanding of f_t (similar to f_m for metabolism)
    - Decreases predictability of DDI magnitude
    - Mechanistic extrapolation to other conmeds, regimens and drug combinations

Introduction

- The field is advancing, learning from approaches applied to metabolic DDIs
  - International Transporter Consortium (ITC) white papers
  - US FDA and EU EMA guidance
    - Primary transporters of interest
    - Criteria for evaluation as substrate or inhibitor
    - Study design considerations



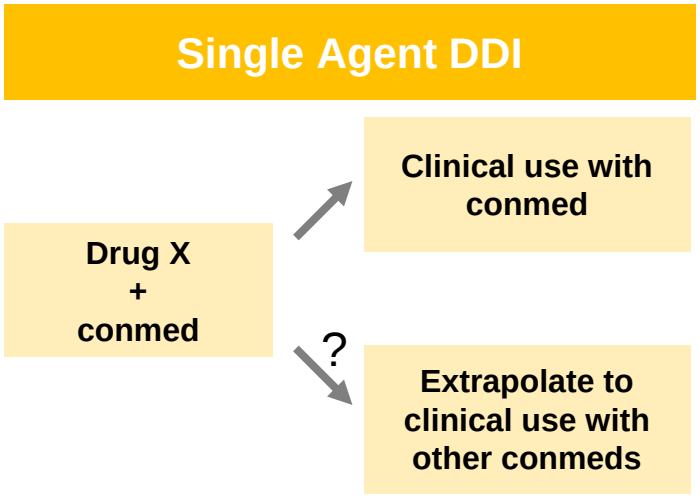


Evolution of DDI Assessments

Polypharmacy required for HIV and HCV have been central to and benefited from this evolution

ARVs → **ARVs + HCV DAAs**

Single Agent DDI Studies (2-way; Victim – Perpetrator)



Benefits

- Direct + specific information for conmeds
- May be best for sensitive substrates

Limitations

- Extrapolation to other conmeds is limited based on the conmeds evaluated
- Extrapolation to multi-drug regimen may be limited

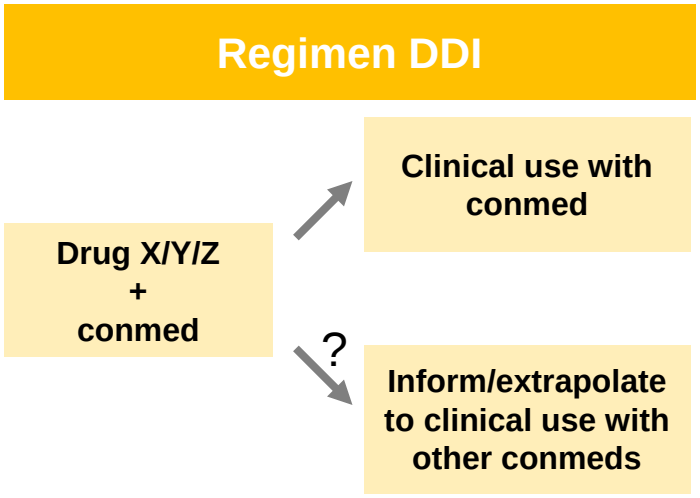
Evolution of DDI Assessments

Polypharmacy required for HIV and HCV have been central to and benefited from this evolution

ARVs → **ARVs + HCV DAAs**

Single Agent DDI Studies (2-way; Victim – Perpetrator)

Regimen DDI Studies (>2-way; specific/applicable data to use)



Benefits

- Direct + specific information for conmeds
- Informs on regimen effects

Limitations

- Extrapolation to other conmeds is limited based on the conmeds evaluated
- Extrapolation to other regimens may be limited
- Large studies ($ due to Bioanalytical)

Evolution of DDI Assessments

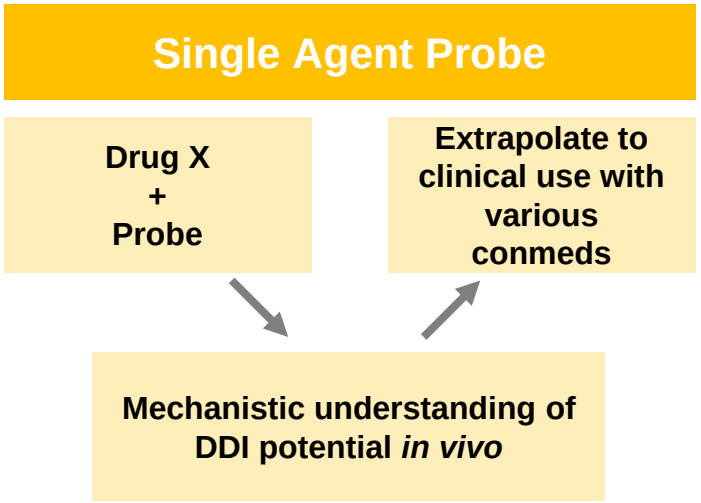
Polypharmacy required for HIV and HCV have been central to and benefited from this evolution

ARVs → **ARVs + HCV DAAs**

Single Agent DDI Studies (2-way; Victim – Perpetrator)

Regimen DDI Studies (>2-way; specific/applicable data to use)

Single Agent Probe Studies (obviate need for DDI studies)



Benefits

- Provides mechanistic understanding of DDI potential in vivo
- Fewer studies required to inform broad conmed recommendations
- Fewer “DDI” studies

Limitations

- Extrapolation to multi-drug regimens may be complex

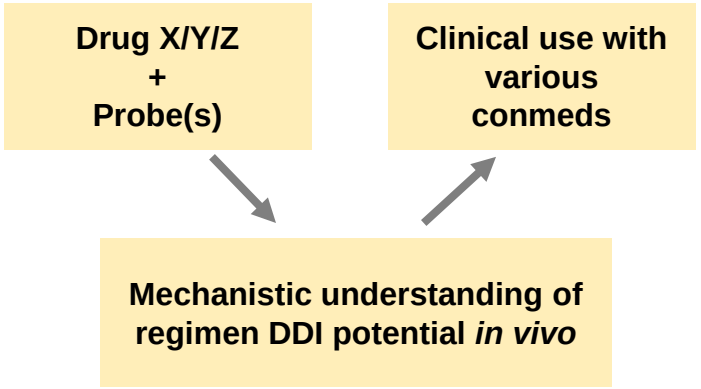
Evolution of DDI Assessments

Polypharmacy required for HIV and HCV have been central to and benefited from this evolution

ARVs → **ARVs + HCV DAAs**

- Single Agent DDI Studies (2-way; Victim – Perpetrator)
- Regimen DDI Studies (>2-way; specific/applicable data to use)
- Single Agent Probe Studies (obviate need for DDI studies)
- Regimen Probe/Cassette Studies (can evaluate many questions)

Regimen Probe/Cassette



Benefits

- Mechanistic understanding of DDI potential of the regimen in vivo
- Fewer studies required to inform broad conmed recommendations

Limitations

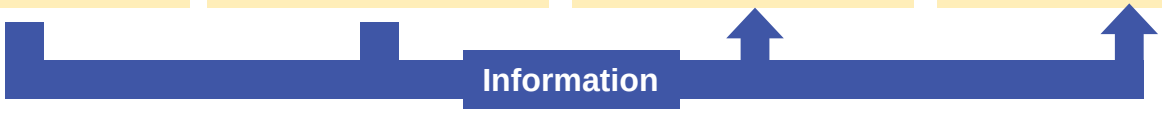
- Extrapolation to other multi-drug or single-agent regimens may be complex

GSI HCV DAA Clin Pharm Approach to DDIs

Fit For Purpose

Compound / [Development Program]

	GS-9451/LDV/TGV (NS3/4 PI, NS5A, NS5B non-nuc)	SOF (NS5B Nuc)	LDV (NS5A) [LDV/SOF]	GS-5816 (pan-GT NS5A) [GS-5816/SOF]
Transporter DDI Profile: Non-Clinical + Early Clinical	GS-9451: efflux/uptake/ metabolism LDV: P-gp/BCRP TGV: P-gp **Intra-regimen DDI**	P-gp/BCRP substrate	P-gp/BCRP substrate/inhibitor	P-gp/BCRP/OATP substrate/inhibitor
Approach to Transporter DDIs	**Regimen Probes** Digoxin Rosuvastatin Pravastatin Cyclosporine Verapamil Rifampin	**Single Agent DDIs** Cyclosporine Tacrolimus Methadone ARV regimens ARV single agents OCs	**Single Agent DDIs** ARV regimens OCs *[Applied to LDV/SOF Regimen]*	**Single Agent Probes** Digoxin Rosuvastatin Pravastatin Cyclosporine Ketoconazole Rifampin



P-gp Mediated DDI: Informing Post-Transplant

Single Agent + Probe (high dose CsA) DDIs

CsA/Tac–SOF DDI Study

- Regimens
  - CsA: 600 mg single dose
  - Tac: 5 mg single dose
- To inform conmed restrictions in post-transplant setting
- Test “worst-case” scenario for transporter inhibition (P-gp/BCRP)

PK Results

		Perpetrator	AUC	C_{max}
Object	SOF	CsA	↑353%	↑154%
		Tac	↑13%	↓ 4%
	GS-331007	CsA	↔	↓ 40%
		Tac	↔	↔
	Cyclosporine	SOF	↔	↔
	Tacrolimus		↑9%	↓ 27%

- CsA and TAC can be administered with SOF without SOF dose adjustment

Post-Transplant Phase 2

- Recurrent HCV post-liver transplant (n=40)
- 24 weeks of SOF + RBV

PK Results

- Subjects on CsA (n=10) vs non-CsA (N=30) containing immunosuppressant regimens had similar SOF (↑15%) and GS-331007 (↔) AUC_{tau}
- No clinically significant differences in SOF or GS-331007 PK compared with historical data
  - ~2-fold higher GS-331007 AUC_{tau}; decreased renal function in post-transplant setting

Mathias, et al. AASLD 2012.

Didier, et al. EASL 2014.

P-gp–Mediated DDI: Informing HIV/HCV Co-infection

Regimen + Single Agent DDIs

HIV ARV–SOF DDIs

- ARVs: Atripla (ATR), DRV/r, RAL, RPV
- To support ARV-DAA combinations in HIV/HCV co-infection

% Change in PK Parameter		Perpetrator	AUC	C_{max}	C_{tau}
Object	SOF	ATR	↔	↓ 19%	N/A
		DRV/r	↑34%	↑ 45%	
		RAL	↔	↔	
		RPV	↔	↑ 21%	
	GS-331007	ATR	↔	↓ 23%	
		DRV/r	↔	↔	
		RAL	↔	↔	
		RPV	↔	↔	
	EFV	SOF	↔	↔	↔
	FTC		↔	↔	↔
	TFV		↔	↑25%	↔
	DRV		↔	↔	↔
	RTV		↔	↔	↔
	RAL		↓ 27%	↓ 43%	↔
	RPV		↔	↔	↔

- SOF can be co-administered with EFV, RPV, DRV/r, RAL or the NRTI FTC/TDF backbone

Phase 3 Co-infection (PHOTON-1)

- HIV/HCV co-infected subjects (n=223) treated with SOF + RBV for 12 or 24 weeks
- Allowed HIV ARV regimens included FTC/TDF combined with any of following
  - ATV/r, DRV/r, EFV, RAL, RPV

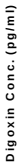
PK Results

- Similar SOF and GS-331007 exposure across HIV ARV regimens
- No clinically significant differences in SOF or GS-331007 PK compared with mono-infected HCV subjects

Kirby, et al. AASLD 2012.

P-gp–Mediated Probe Studies Across Programs

GS-9451/LDV/TGV



Effect on digoxin is mainly pre-systemic and modest

(AUC ↑ 34%)

LDV: Weak P-gp inhibitor

LDV

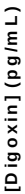
LDV as Perpetrator:

OCs

ARVs

Weak intestinal P-gp inhibition

GS-5816



Effect on digoxin is mainly pre-systemic and modest.

(AUC ↑ 34%)

GS-5816: Weak P-gp inhibitor

[LDV/SOF]

[GS-5816/SOF]

P-gp substrates allowed, caution warranted for narrow therapeutic (Digoxin)

Mogalian, et al. IWCPHHT 2014.

OATP–Mediated DDIs

Background

- OATPs mediate hepatic uptake, thus DDIs in the setting of HCV therapy are of particular interest
- Many conmeds/substrates are not specific OATP probes: multiple transporters and/or enzymes
  - Pravastatin: OATP1B1
  - Rosuvastatin: OATP1B1/3 and BCRP
  - No specific BCRP probe
- Goal: dissect contribution of multiple transporters by using multiple probes

OATP-Mediated DDIs Across Programs

GS-9451/LDV/TGV

LDV

Pravastatin Conc (ng/ml)

Rosuvastatin Conc (ng/ml)

LDV as Perpetrator:
HCV DAA
Weak OATP inhibition

Pravastatin (OATP):
AUC ↑ 168%
C_{max} ↑ 166%

Rosuvastatin (OATP/BCRP):
AUC ↑ 699%
C_{max} ↑ 1670%

LDV: weak OATP inhibitor → **[LDV/SOF]**

Pravastatin allowed,
Rosuvastatin not recommended

OATP-Mediated DDIs Across Programs

GS-5816 (NS5A)

[Pravastatin] (ng/mL)

[Rosuvastatin] (ng/mL)

Pravastatin (OATP):
AUC ↑ 35%
C_{max} ↑ 28%

Rosuvastatin (OATP/BCRP):
AUC ↑ 169%
C_{max} ↑ 161%

[GS-5816/SOF]

GS-5816: Weak OATP Inhibitor
Moderate BCRP inhibitor

→ **Pravastatin allowed,** Rosuvastatin dose limited to <10 mg/day

- Weak inhibition of OATP by GS-5816 corroborates assertion of weak (or less) inhibition of OATP by LDV.

Mogalian, et al. IWCPHHT 2014.

Summary

- Transporters are here to stay and our understanding is increasing
  - Multiple tools: conmed DDIs and probes will inform
- DDI or probe study design (Single Agent vs Regimen) tailored to the projected regimen and known or potential liabilities
- Data from regimen DDI or probe studies may be extracted to inform single agent or other multi-drug regimens
- Multiple mixed probes can be used to dissect contribution of individual transporters