Revelation or Hubris?
Using Pharmacogenetics to Forecast Atazanavir-Associated Jaundice

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Atazanavir (ATV)

- Protease inhibitor
- 2011 BC Centre for Excellence Adult Guidelines
  - First line agent (in combo with 2 nRTIs)
  - Combine with low dose ritonavir

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Atazanavir (ATV)

- Drug interactions
  - Inhibits UGT enzymes
    - 1A1, 1A3, 1A4
- Adverse effects
  - Benign accumulation of unconjugated bilirubin
    - Elevated bilirubin: 44%
    - Jaundice or scleral icterus: 5%

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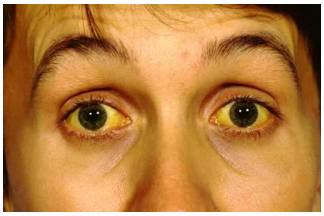
Jaundice



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Genetics Review

- **Allele**: particular form of a gene
- **Genotype**: genetic information determining the phenotype
- **Phenotype**: observed trait
- **Wild-type**: normal/common allele
- **Homozygous**: alleles at a given locus are identical
- **Heterozygous**: alleles at a given locus are different (ie. different on maternal and paternal copy of the gene)
- **Haplotype**: closely linked group of alleles

Chapter 61: Principles of Human Genetics. Harrison's Principles of Internal Medicine. 18th ed. 2012

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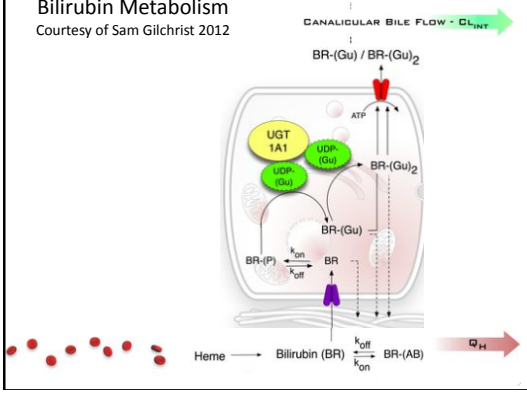
Bilirubin Metabolism

Courtesy of Sam Gilchrist 2012



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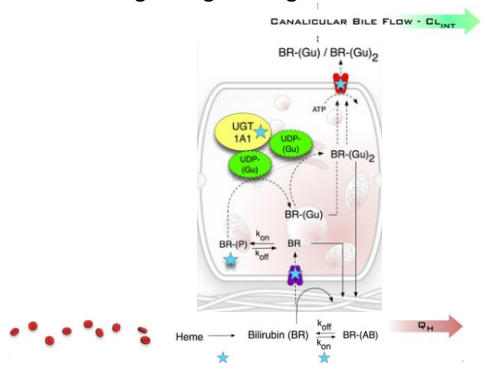
Where things can go wrong…



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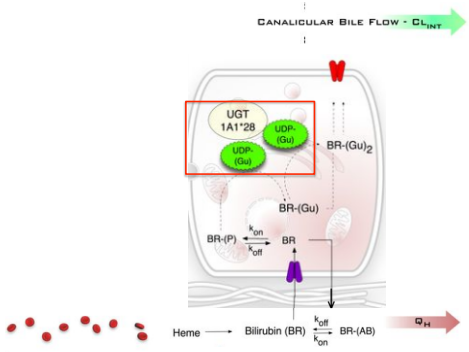
Now add UGT1A1*28 polymorphism..



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Gilbert's Syndrome (UGT1A1*28)

- Polymorphism in the UGT1A1 promoter region
  - Reduced UGT expression
- Benign unconjugated hyperbilirubinemia
- Allelic frequency: ~40%
  - Homozygous prevalence: 7 to 19%
  - Varies by ethnicity
- Exacerbated by triggers
  - Stress, infection, drugs

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Pharmacogenetic (PGx) Testing

- Goal: Personalized drug therapy
- Definition: Test for clinical use intended to provide information that may aid in selection of certain therapeutics
  - May also aid in dosage selection

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PICO Question

P	Adult patients with HIV initiating or receiving ATV boosted or unboosted with ritonavir
I	UGT1A1*28 allele (homozygous or heterozygous)
C	No UGT1A1*28 polymorphism (wild-type)
O	**Safety** •Bilirubin concentrations •Incidence of jaundice •Discontinuation due to hyperbilirubinemia **Efficacy** •Difference in viral load suppression, CD4+ count **Cost**

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Search Strategy

Databases	Medline, Embase, Cochrane, Google, Google Scholar, International Pharmaceutical Abstracts, Clinicaltrials.gov
Search Terms	Glucuronosyltransferase, glucuronosyltransferase 1A1, UGT, atazanavir, atazanavir plus ritonavir, polymorph$
Limits	Humans, English, HIV patients
Results	**7 cohort studies** **•6 full manuscripts** **•1 abstract**

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Association of Pharmacogenetic Markers with Premature Discontinuation of First-line Anti-HIV Therapy: An Observational Cohort Study

Rubin Lubomirov,[1,a] Sara Colombo,[1,a] Julia di Iulio,[1] Bruno Ledergerber,[3] Raquel Martinez,[1] Matthias Cavassini,[2] Bernard Hirschel,[4] Enos Bernasconi,[5] Luigia Elzi,[6] Pietro Vernazza,[7] Hansjakob Furrer,[8] Huldrych F. Günthard,[3] Amalio Telenti,[1] and the Swiss HIV Cohort Study

The Journal of Infectious Diseases 2011;203:246–257

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Lubomirov R et al. 2011

Design	Retrospective cohort (total cohort n=577)
P	121 adult HIV patients, antiretroviral-naïve Initiating on ATV/r 300 mg/100 mg Total cohort demographics: Median age 44 yrs, 80% Caucasian, CD4+ 209 cells/µL, Viral load 4.9 $\log_{10}$ copies/mL
I	Homozygous UGT1A1*28
C	Heterozygous UGT1A1*28 Wild-type UGT1A1*28
O	ATV discontinuation rate at 1 year Reason for discontinuation

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Lubomirov R et al. Results

UGT1A1 Genotype	N	Drug Discontinuation at 1 Year (%)
Wild-type or heterozygous	103	19 (18)
Homozygous	18	11 (61)

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Lubomirov R et al. Results

UGT1A1 Genotype	Adjusted HR (95% CI) for drug discontinuation
Wild-type	1 (Reference)
Heterozygous	1.97 (0.77 – 5.03)
Homozygous	9.13 (3.38 – 24.69)

Only statistically significant reason for discontinuation: "Drug-associated toxicity"

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Genetic Factors Influencing Severe Atazanavir-Associated Hyperbilirubinemia in a Population with Low UDP-Glucuronosyltransferase 1A1*28 Allele Frequency

Wan Beom Park,[a] Pyoeng Gyun Choe,[a] Kyoung-Ho Song, Jae Hyun Jeon, Sang Won Park, Hong Bin Kim, Nam Joong Kim, Myoung-don Oh, and Kang Won Choe
Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

Clinical Infectious Diseases 2010; 51(1):101–106

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Park WB et al. 2010

Design	Prospective cohort
P	129 adult Korean HIV patients starting on ATV 400 mg/day (May 2005 – April 2007) Median age 39 years, 91% male, CD4+ 261 cells/µL, Viral load 4490 copies/mL, bilirubin 12.9 µmol/L
I	Homozygous or heterozygous UGT1A1*28
C	Wild-type UGT1A1*28
O	Hyperbiliribunemia at 3 months

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Park WB et al. Results

Genotype	No (%) of patients	Hyperbilirubinemia, no (%) of patients	
		Any grade	Grade 3–4
UGT1A1*28			
Wild-type	103 (79.8)	77 (74.8)	16 (15.5)
Heterozygous	25 (19.4)	22 (88.0)	10 (40.0)
Homozygous	1 (0.8)	1 (100)	1 (100)

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Gilbert Syndrome and the Development of Antiretroviral Therapy–Associated Hyperbilirubinemia

Margalida Rotger,[1] Patrick Taffé,[2] Gabriela Bleiber,[1] Huldrych F. Günthard,[3] Hansjakob Furrer,[4] Pietro Vernazza,[5] Henning Drechsler,[6] Enos Bernasconi,[7] Martin Rickenbach,[2] Amalio Telenti,[1] and the Swiss HIV Cohort Study

The Journal of Infectious Diseases 2005; 192:1381–6

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Rotger M et al. 2005

Design	Prospective cohort
Population	N=21 Already receiving ATV/r 300/100 mg Median age 38.3, 80.2% male, 95.8% Caucasian
Endpoints	Grade of hyperbilirubinemia
Results	Grade 3 hyperbilirubinemia: Wild-type: 4/8 (50) Heterozygous: 3/8 (37.5) Homozygous: 5/5 (100)

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Rotger M et al. 2005

- Control group!
  - Bilirubin concentrations when the same subjects were not receiving ATV
- Multivariate analysis:

Effect	↑bilirubin by
Homozygous *28 (regardless of ATV)	1.58µmol/L
Receiving ATV (regardless of genotype)	2.69µmol/L

- Conclusion:
  - Effect of drug is greater than effect of genotype

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Gilbert's Disease and Atazanavir: From Phenotype to UDP-Glucuronosyltransferase Haplotype

Tim O. Lankisch,[1] Ulrike Moebius,[2] Michael Wehmeier,[3] Georg Behrens,[2] Michael P. Manns,[1] Reinhold E. Schmidt,[2] and Christian P. Strassburg[1]

(HEPATOLOGY 2006;44:1324-1332.)

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Lankisch TO et al. 2006

Design	Retrospective cohort
Population	N=106 adult HIV patients Antiretroviral-naïve Initiating on ATV/r 300 mg/100 mg Median age 45 yrs, 83% male, 92.5% Caucasian Total bilirubin 10µmol/L
Endpoints	Hyperbilirubinemia at 30 days

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Lankisch TO et al. Results Hyperbilirubinemia at 30 days

	Any Grade (%)	Grade 3 – 4 (%)	Grade 4 (%)
Overall	90/106 (84.9)	39/106 (36.8)	6/106 (5.7)
Wild-type	31/40 (77.5)	9/40 (22.5)	0/0 (0)
Hetero-zygous	37/43 (86.0)	12/43 (27.9)	0/0 (0)
Homo-zygous	22/23 (95.7)	18/23 (78.3)	6/6 (100)

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Lankisch TO et al. 2006

- Also assessed Haplotype:
  - UGT1A1*28
  - UGT1A3-57G
  - UGT1A7-66C
  - UGT1A7-129K/131K
- All four variants simultaneous in:
  - 41.2% who had grade 3 or 4 hyperbilirubinemia
  - 100% who had grade 4 hyperbilirubinemia
- Conclusion: other variants may be involved

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Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia

Sonia Rodríguez-Nóvoa[a], Luz Martín-Carbonero[b], Pablo Barreiro[b], Gema González-Pardo[a], Inmaculada Jiménez-Nácher[a], Juan González-Lahoz[b] and Vincent Soriano[b]

AIDS 2007, **21**:41–46

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Rodríguez-Nóvoa et al. 2007

Design	Prospective cohort
Population	N=118, initiating on ATV/r 300 mg/100 mg Median age 42 yrs, 77% male, 100% Caucasian, CD4 497 cells/µL, Viral load 1.9 $\log_{10}$ copies/mL Total bilirubin 13.3µmol/L
Endpoints	Hyperbilirubinemia at week 12
Results	Grade 3 or 4 (%): Wild-type: 10/53 (18) Heterozygous: 17/57 (29) Homozygous: 6/8 (80) Odds Ratio for grade 3 or 4 hyperbilirubinemia by having at least 1 UGT1A1*28 allele: 2.96 (95% CI 1.29 - 6.78)

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Switching to unboosted atazanavir reduces bilirubin and triglycerides without compromising treatment efficacy in UGT1A1*28 polymorphism carriers

Laurenzia Ferraris[1], Ottavia Viganò[1], Anna Peri[1], Maciej Tarkowski[1], Greta Milani[2], Stefano Bonora[3], Fulvio Adorni[4], Cristina Gervasoni[1], Emilio Clementi[2,5], Giovanni Di Perri[3], Massimo Galli[1] and Agostino Riva[1]*

J Antimicrob Chemother 2012; **67**: 2236–2242

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Ferraris L et al. 2012

Design	Open-label, non-randomized
P	51 adult HIV patients, receiving ATV/r 300 mg/100 mg Median age 46 yrs, 73% male, 90% Caucasian, CD4+ 573 cells/µL, Viral load 4.9 $\log_{10}$ copies/mL At least grade 3 hyperbilirubinemia at baseline: Wild-type: 3/24 (13%) Heterozygous: 15/21 (71%) Homozygous: 5/6 (83%)
I	Homozygous (n=6) or heterozygous (n=21) UGT1A1*28 Switched to ATV 400 mg
C	Wild-type UGT1A1*28 Continued ATV/r 300 mg/100 mg (n=24)
O	Bilirubin concentrations 12 months after switch CD4 count, Viral load

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Ferraris L et al. Results

	Baseline bilirubin (µmol/L) (ie. before switch)	Bilirubin at 12 months (µmol/L)
Wild-type (n=24)	24.6 (17.2 – 41.4)	"no change"
Homo- or Heterozygous (n=24)	70.5 (54.1 – 98.8)	31.4 (26.4 – 40.2)

At 48 weeks, all patients' viral load undetectable and no significant change in CD4 count

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Studies' Limitations

- Small sample size
  - Not powered based on genotype
  - ?unbalanced groups
- Observational
- Interpretation & Consideration
  - ?Other alleles involved
  - Risks associated with:
    - Not using first-line HIV medication
    - Experiencing benign reversible hyperbilirubinemia

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Ribaudo H et al. 2012

Premature Discontinuation of Atazanavir/ritonavir (ATV/r) and UGT1A1 Variants in AIDS Clinical Trials Group (ACTG) Protocol A5202

Heather Ribaudo[1], Eric S. Daar[2], Camlin Tierney[1], Gene D. Morse[3], Katie Mollan[1], Paul Sax[4], Margaret A. Fischl[5], Ann C. Collier[6], David W. Haas*[7], and The AIDS Clinical Trials Group (ACTG)

Unpublished trial (conference poster only)

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Ribaudo H et al. 2012

Design	Prospective cohort (subgroup of large n=1857)
P	N=646 adult HIV patients Antiretroviral-naïve, initiating ATV/r 300 mg/100 mg Median age 39 yrs, 84% male, 45% Caucasian, 31% Black, 24% Hispanic, CD4 235 cells/mL, VL 4.6 $\log_{10}$ copies/mL
I	Homozygous or heterozygous UGT1A1*28 or *37
C	Wild-type UGT1A1
O	•Time to ATV/r discontinuation for any reason •Positive predictive value (PPV) of homozygosity predicting ATV/r discontinuation •Grade 4 hyperbilirubinemia at 24 wks

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Ribaudo H et al. Results ATV/r Discontinuation

	Total Discontinuation	Bilirubin-Associated Discontinuation
Overall	177/646 (27.4)	19/646 (2.9)
Wild-	66/301 (21.9)	3/301 (1.0)
Hetero-	70/253 (27.7)	8/253 (3.2)
Homo-	41/92 (44.6)	8/92 (8.7)

•PPV of homozygosity predicting ATV/r discontinuation: 13% to 32%

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Ribaudo H et al. Results Hyperbilirubinemia at 24 weeks

	Grade 4 (%)
Overall	43/646 (6.7)
Wild-	8/280 (2.8)
Hetero-	15/274 (5.5)
Homo-	20/92 (21.7)

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Ribaudo H et al. Limitations

- Conference abstract only
  - Quality of methodology unknown
- Observational
- Small sample size

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Can we pool the results to determine how well doing a PGx test for UGT1A1*28 can predict hyperbilirubinemia?

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Trials looking at genotype and incidence of ≥ grade 3 hyperbilirubinemia?

Trial	Data of interest provided?
Lubomirov	✗
Park	✓
Lankisch	✓
Rodríguez-Nóvoa	✓
Rotger	✓
Ferraris	✓
Ribaudo	✓ (only grade 4)

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Pooling of Studies: 2x2 Table

		Grade 3 or 4		
		Yes	No	**Total**
Homo-zygous	Yes	55	80	135
	No	122	814	936
	Total	177	894	**1071**

PPV = (Homozygous AND Positive Outcome) / (Total n Homozygous patients)

PPV = 55 / 135 = 41%

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Likelihood Ratios (LR)

Likelihood Ratio		Degree LR shifts pre-test to post-test probability	Implication to Practice
LR(+)	**LR(-)**		
>10	<0.1	Large	Often conclusive change to practice
5 – 10	0.1 - 0.2	Moderate	Likely leads to change
2 – 5	0.5 - 0.2	Small	Sometimes important
1 – 2	0.5 – 1	Very small	Rarely important
1	1	No change	No effect

JAMA 1994;271(9):703

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	Sensitivity	Specificity	LR(+)	LR(-)
Pooled Analysis	31%	91%	3.4	0.75

Interpretation:
LR(+) = small effect on post-test probability
LR(-) = very small effect on post-test probability

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Summary

- Only small trials available to assess value of UGT1A1*28 testing to predict hyperbilirubinemia with ATV
  - Pooled analysis suggests
    - PPV = ~41%
    - LR suggests testing likely not helpful
- Other genetic factors likely involved
- Could result in HIV patient not receiving first-line protease inhibitor

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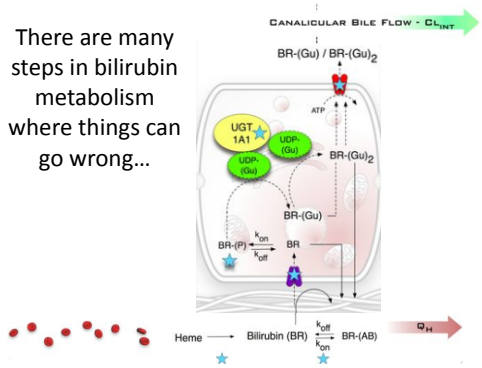
There are many steps in bilirubin metabolism where things can go wrong…



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Bottom Line

- I would not recommend UGT1A1*28 testing before initiating ATV
- Patient education
- Monitor clinically and by bilirubin concentrations
  - Jaundice and hyperbilirubinemia

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