

Abstract #. 631.00



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Effect of ritonavir-boosting on intolerance to atazanavir in Korean HIV patients

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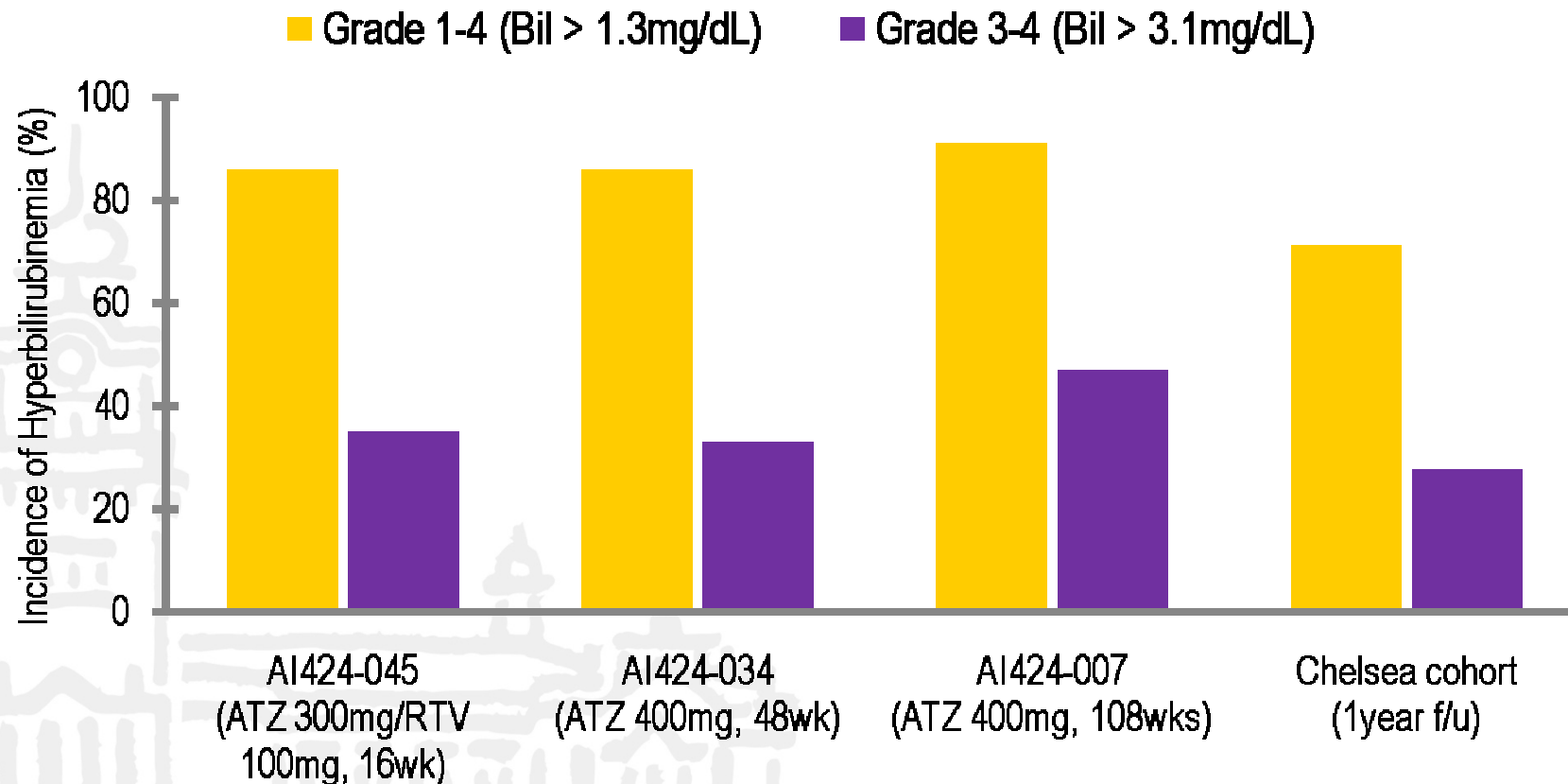
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Atazanavir

- Azapeptide inhibitor of HIV protease
- Dose: 400 mg or 300mg/rit QD
- Favorable potency and resistance profile
- Superior lipid profile to NFV or RTV/SQV
- Safety, efficacy, tolerability demonstrated in clinical trials
 - ◆ Rapidly, durably suppresses HIV RNA
 - ◆ Durably increases CD4 count

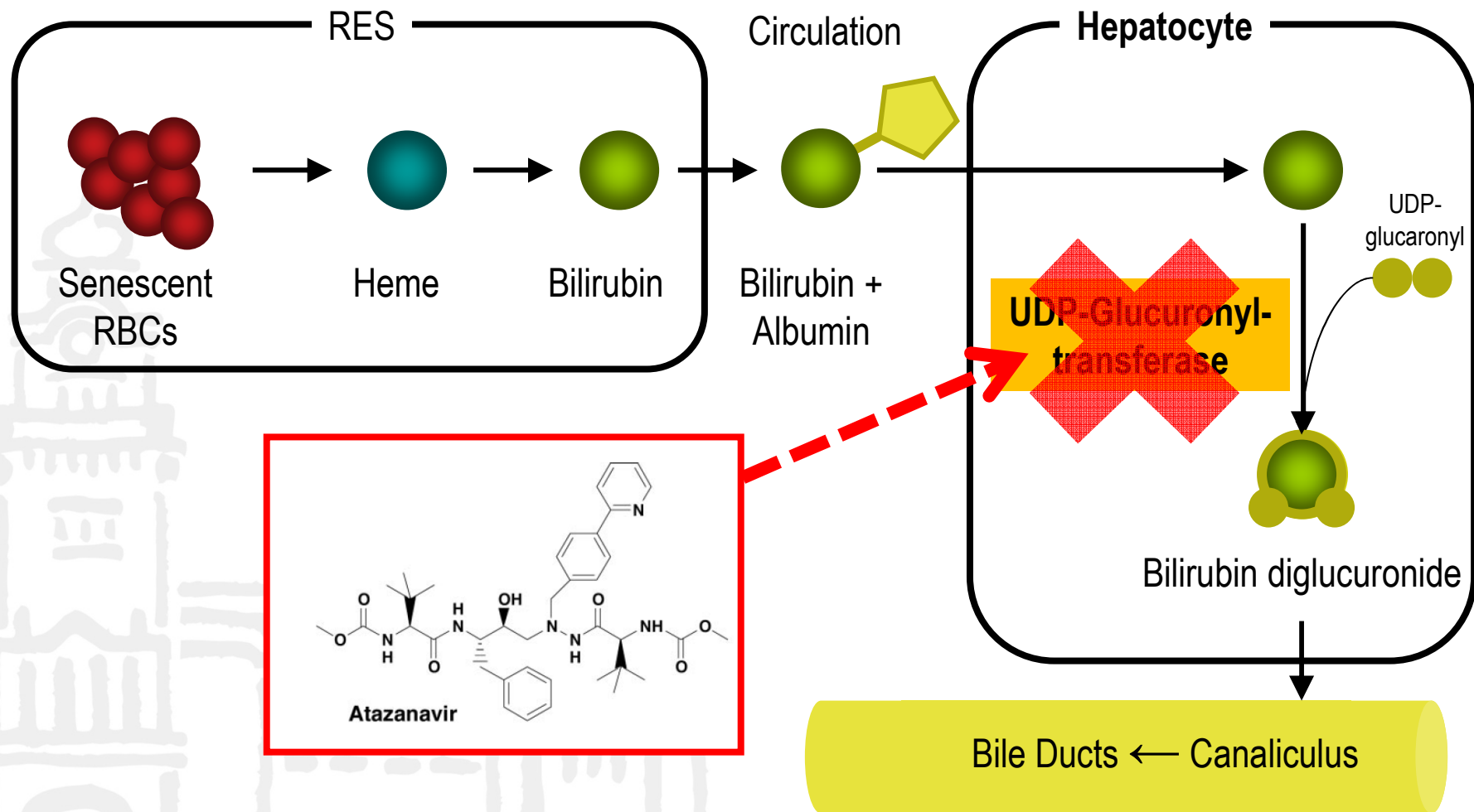


Atazanavir-induced Hyperbilirubinemia



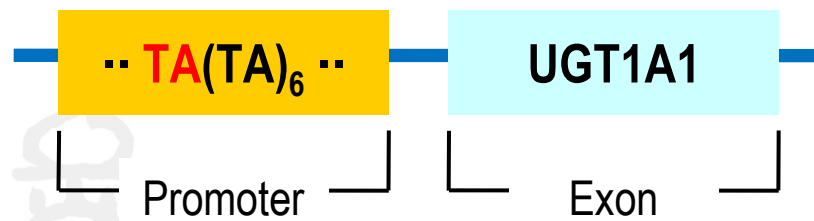
Jonhson *et al. AIDS* 2005; 19:685-694
Squires *et al. J Acquir Immune Defic Syndr* 2004; 36:1011-1019
Sanne *et al. J Acquir Immune Defic Syndr* 2003; 32:18-29
Stebbing *et al. Postgrad Med J* 2006; 82:343-346

Mechanism of Hyperbilirubinemia



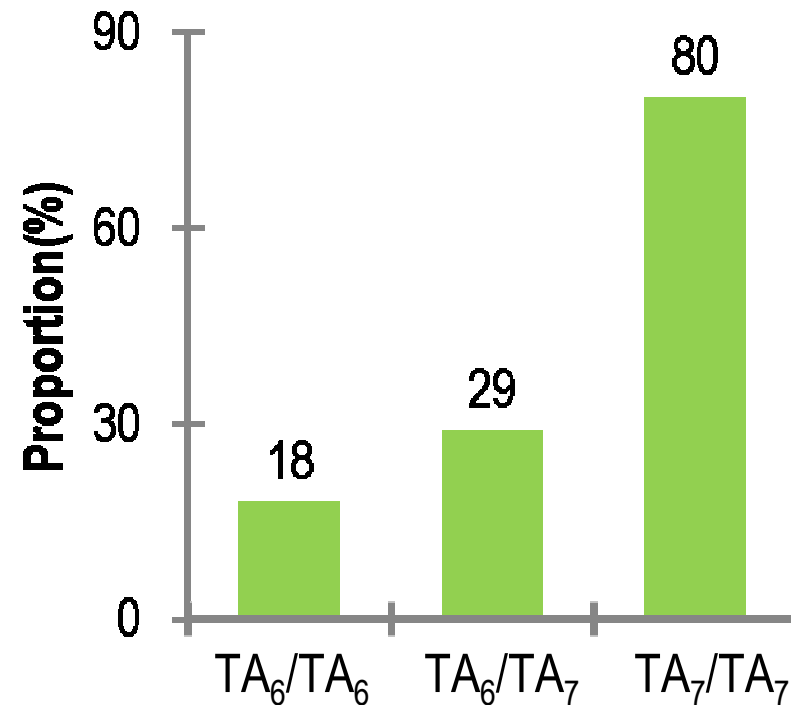
Gilbert Syndrome & Hyperbilirubinemia

- UGT1A1*28 polymorphism

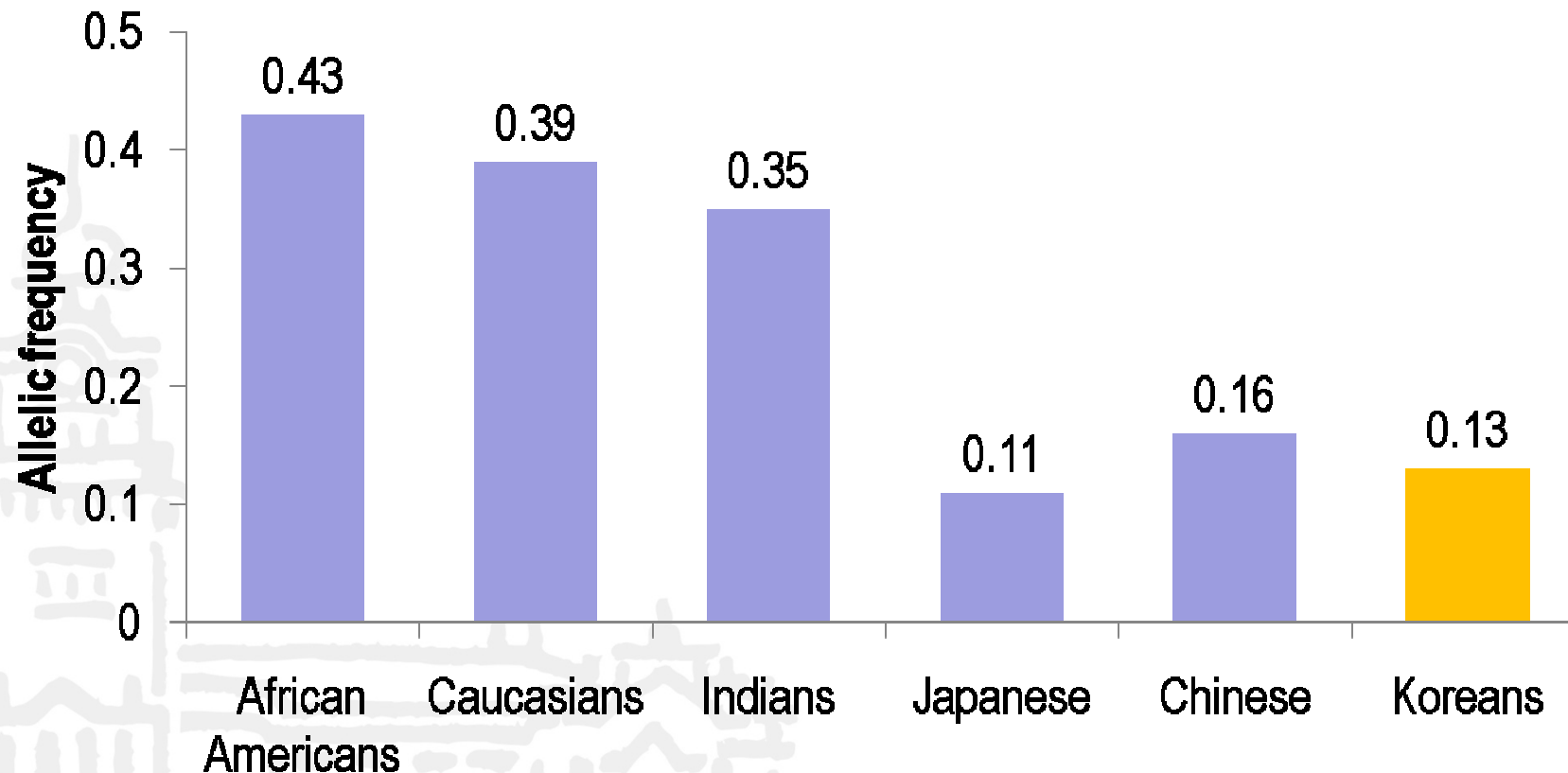


- ◆ Additional TA repeat in the TATA sequence of the UGT1A1 promoter
- ◆ Associated with Gilbert syndrome

- Pts with atazanavir-induced severe hyperbilirubinemia



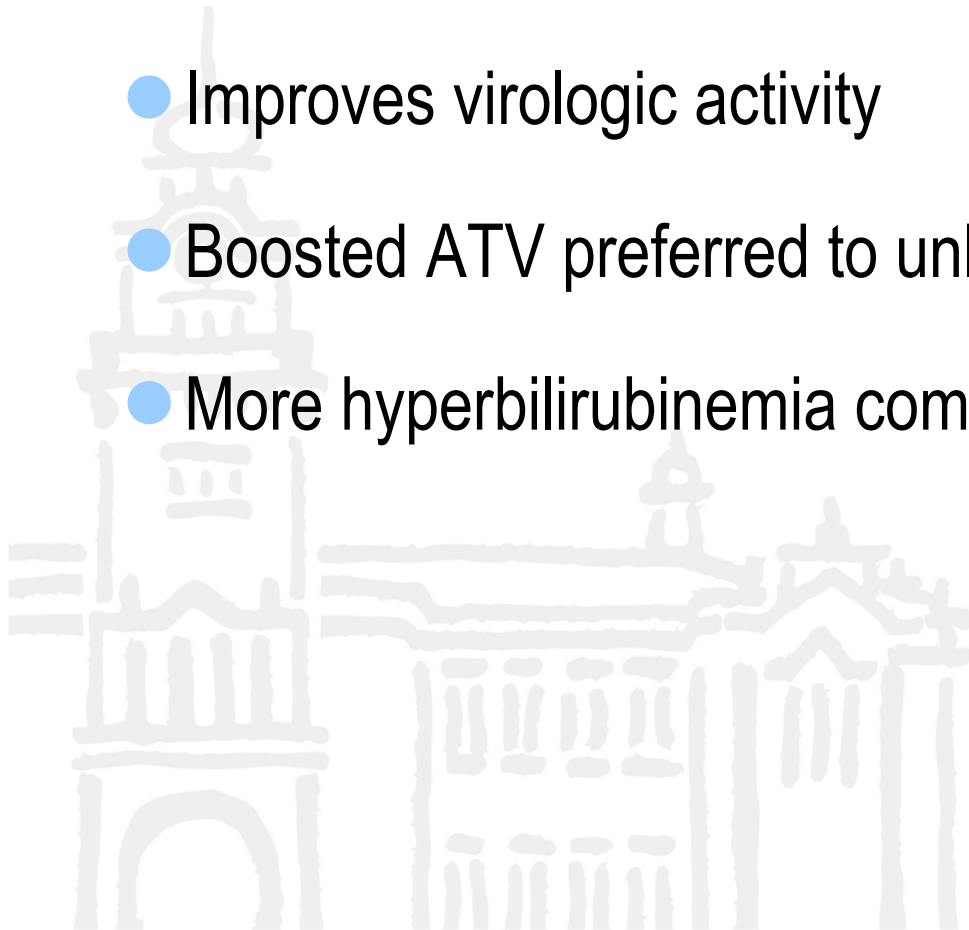
Allelic Frequency of UGT1A1*28



Beutler *et al.* *Proc Natl Acad Sci USA* 1998; 95:8170-4
Mauro *et al.* *Hum Genet* 2004; 115:525-6
Ki *et al.* *Clin Chem* 2003; 49:2078-80

Ritonavir boosting of atazanavir

- Enhances the concentrations of atazanavir
- Improves virologic activity
- Boosted ATV preferred to unboosted ATV
- More hyperbilirubinemia compared with unboosted ATV





Objective

- To assess the incidence of atazanavir-associated hyperbilirubinemia in Korean HIV patients
- To compare the incidence between ritonavir-boosted and ritonavir-unboosted atazanvir
- To evaluate intolerance due to jaundice in real clinical practice setting



Methods

- Study population
 - ◆ Korean HIV-infected patients treated at Seoul National University Hospital from 2005 to 2008
 - ◆ Treated with atazanavir; unboosted/boosted with ritonavir
- Retrospective review of medical records
- Exclusion
 - ◆ Active liver disease
 - Transaminase > 2 times upper normal range
 - ◆ Concomitant drugs with hepatotoxicity

- Total bilirubin levels were measured from serum samples
- Grade of Hyperbilirubinemia

	Total Bilirubin level
Grade 1 (Mild)	23 ~ 32 $\mu\text{mol/L}$ (1.4 ~ 1.9 mg/dL)
Grade 2 (Moderate)	33 ~ 53 $\mu\text{mol/L}$ (2.0 ~ 3.1 mg/dL)
Grade 3 (Severe)	54 ~ 105 $\mu\text{mol/L}$ (3.2 ~ 6.1 mg/dL)
Grade 4 (Serious)	> 105 $\mu\text{mol/L}$ (> 6.1 mg/dL)

AIDS Clinical Trials Group guideline

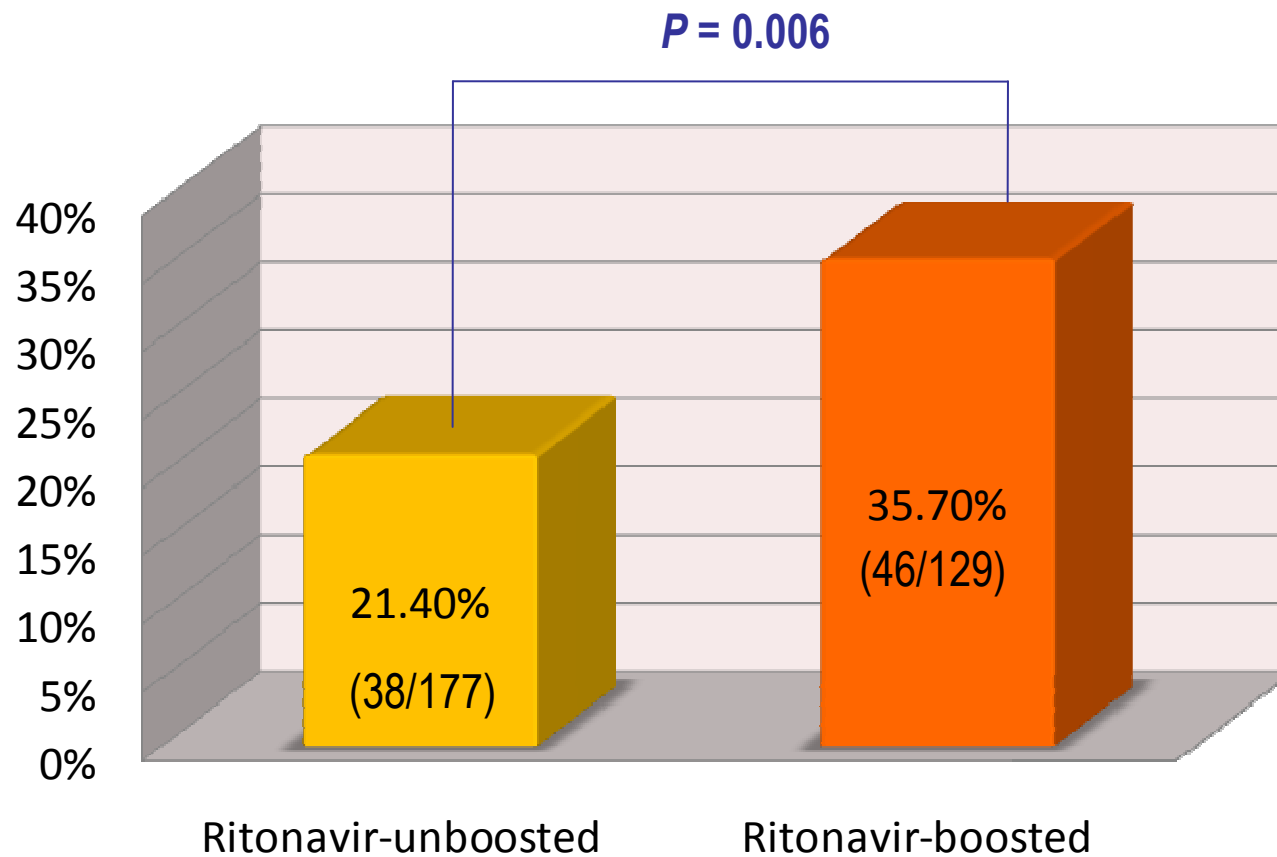
Demographic characteristics

Characteristics	Ritonavir-unboosted (n=190)	Ritonavir-boosted (n=145)	P-value
Age, median (IQR), years	41 (34–53)	42 (35–53)	0.377
Men/women, no. (% men)	173/17 (91.1)	135/10 (93.1)	0.548
Presumed HIV transmission route, n(%)			
Homosexual sex	71 (37%)	60 (41%)	0.456
Heterosexual sex	61 (32%)	51 (35%)	0.555
Blood product	5 (3%)	1 (1%)	0.240
Unknown	53 (28%)	33 (23%)	0.286
Baseline CD4 counts, median (IQR), cells/ μ L	258 (159–416)	398 (257–581)	< 0.001
Baseline viral loads, median (IQR), log ₁₀ copies/mL	3.81 (1.40–4.94)	1.60 (1.40–4.06)	< 0.001
Positive for hepatitis C antibodies, n(%)	9 (5%)	1 (1%)	0.048
Positive for hepatitis B antigen, n(%)	12 (6%)	9 (6%)	>0.999

Incidence of hyperbilirubinemia at 3 months

Grade of hyperbilirubinemia	Number of patients (%)	
	Ritonavir- unboosted (n=177)	Ritonavir-boosted (n=129)
Grade 1 (mild)	39 (22%)	23 (18%)
Grade 2 (moderate)	52 (29%)	43 (33%)
Grade 3 (severe)	36 (20%)	46 (36%)
Grade 4 (serious)	2 (1%)	0
Total	129 (72%)	112/129 (87%)

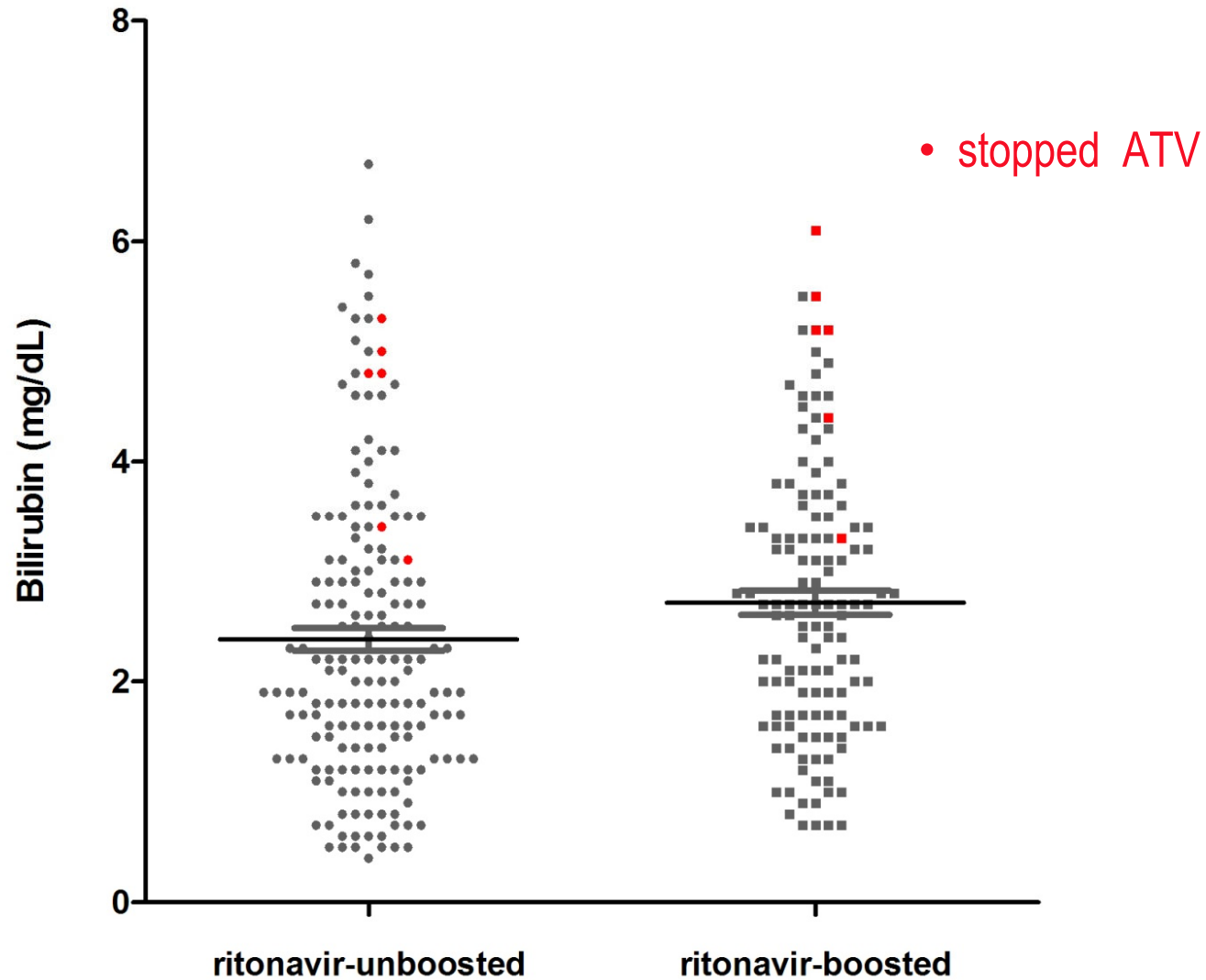
Incidence of severe (grade 3~4) hyperbilirubinemia at 3 months



Reasons for discontinuation of atazanavir during first 3 months

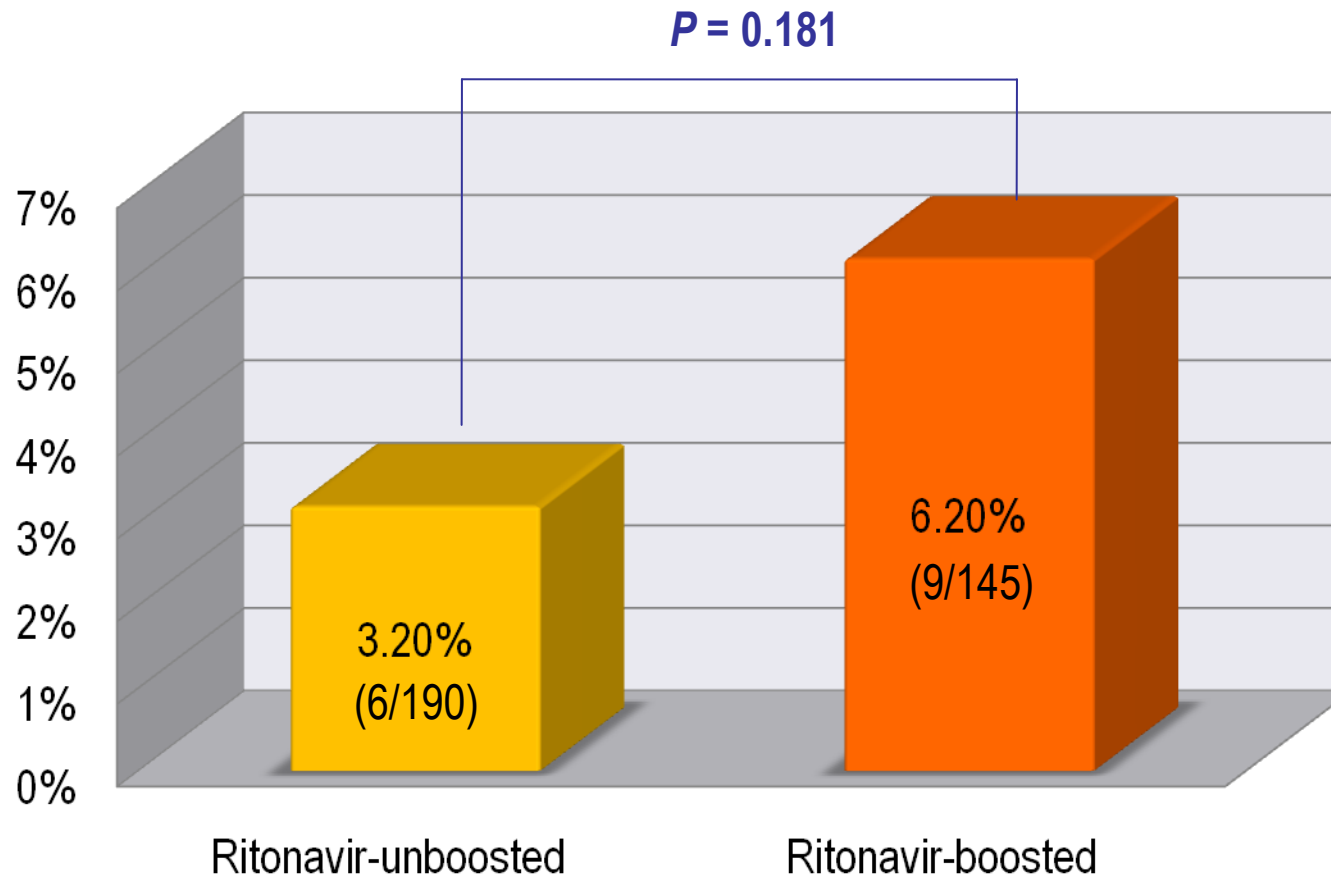
Reason for discontinuation	Ritonavir-unboosted (n = 190)	Ritonavir-boosted (n = 145)	P-value
Jaundice	6 (3.2%)	9 (6.2%)	0.181
Gastrointestinal discomfort	1 (0.5%)	6 (4.1%)	0.046
Others	6 (3.2%)	3 (2.1%)	0.541
Total	13 (6.8%)	18 (12.4%)	0.081

Serum Bilirubin Concentration at 3 months



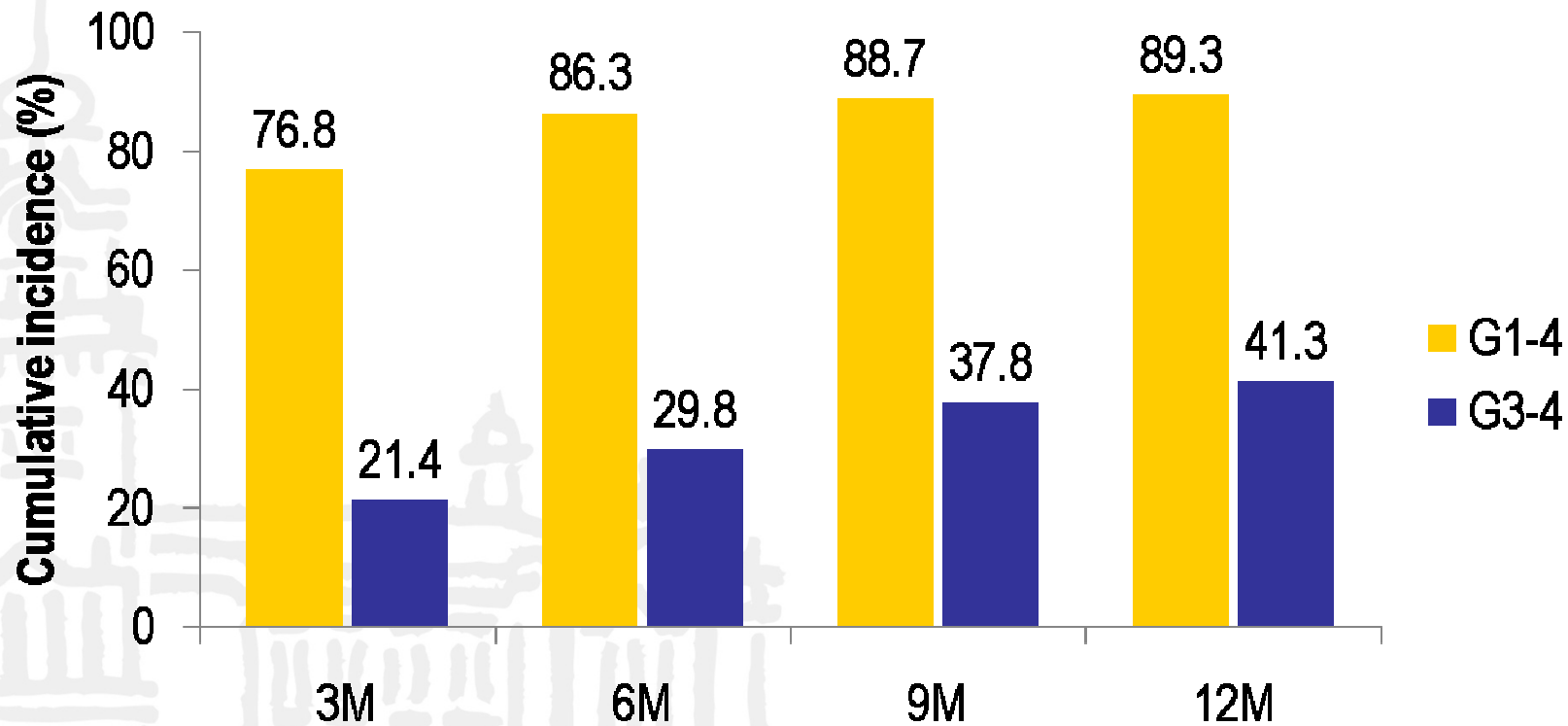
Due to clinical jaundice, 3 patients in boosted group stopped atazanavir before 3 months.

Atazanavir discontinuation due to jaundice during 3 months



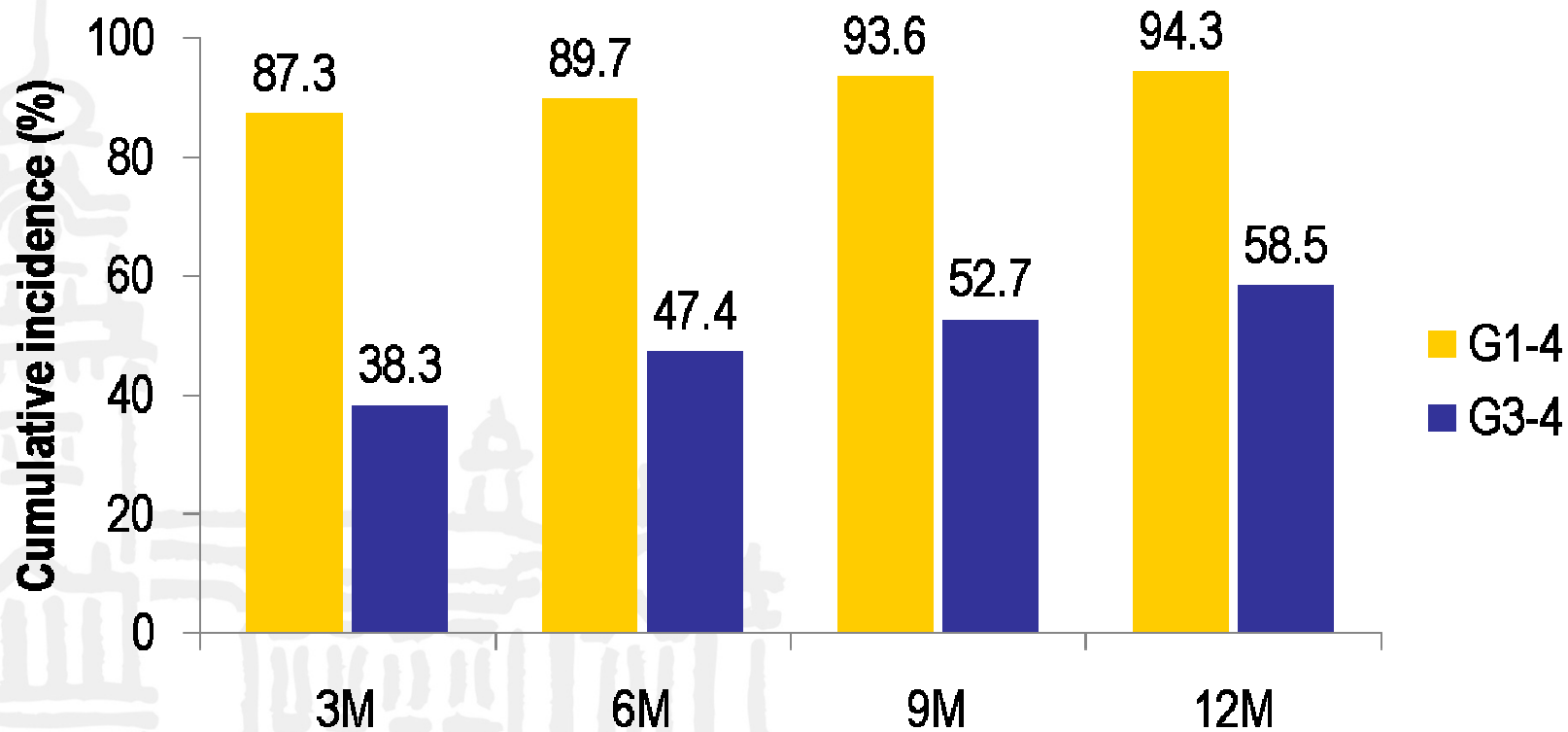
Cumulative incidence of Hyperbilirubinemia

- ATV 400mg containing regimen

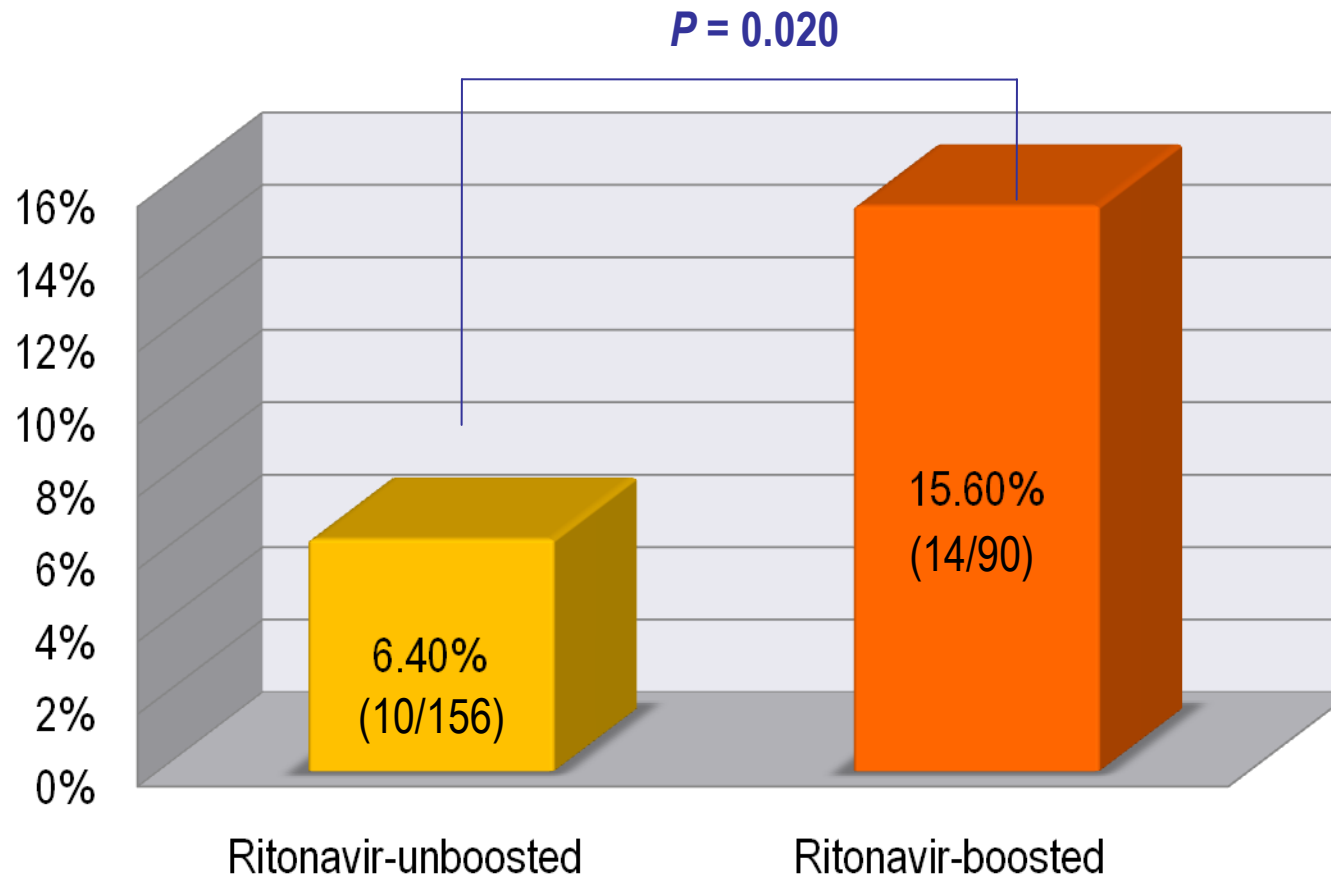


Cumulative incidence of Hyperbilirubinemia

- ATV 300mg/RTV 100mg containing regimen

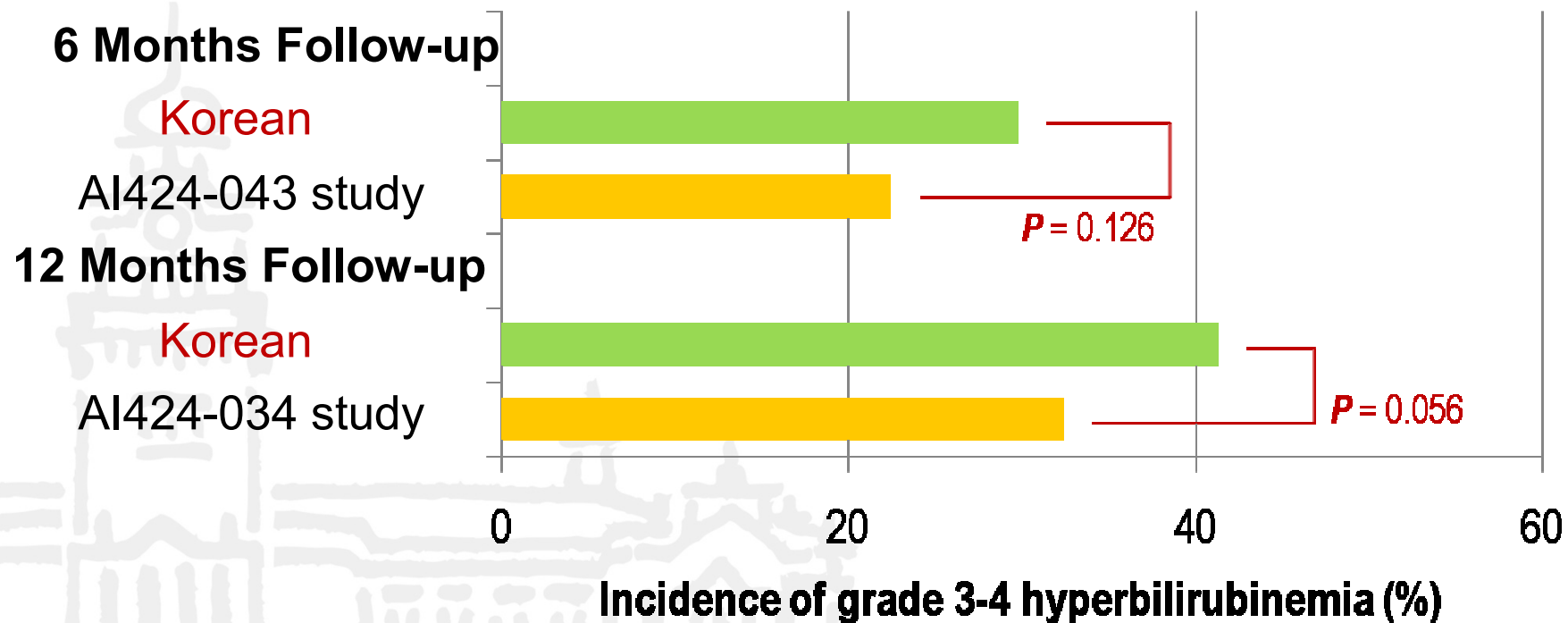


Atazanavir discontinuation due to jaundice during 12 months



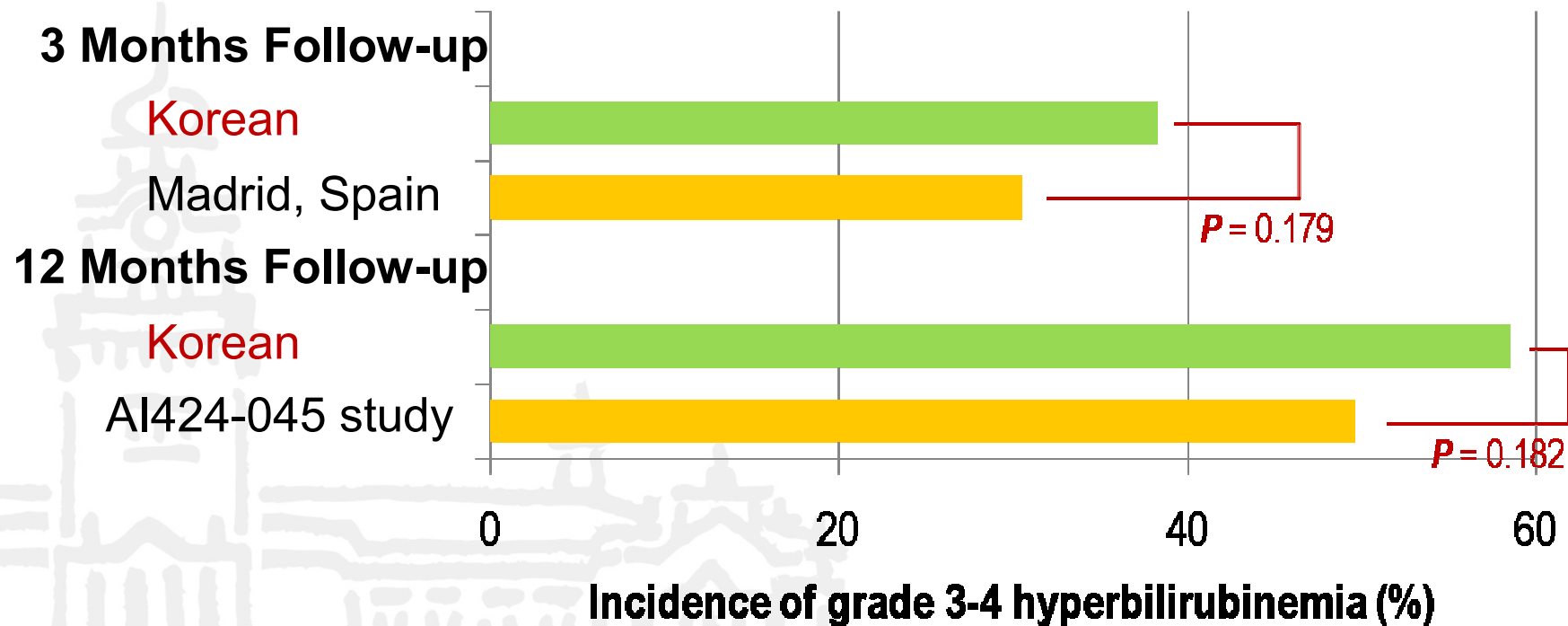
Korean versus Caucasian

- ATV 400mg containing regimen



Korean versus Caucasian

- ATV 300mg/RTV 100mg containing regimen



Risk factors for atazanavir discontinuation due to jaundice during 12 months

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>P</i>	aOR (95% CI)	<i>P</i>
Age	0.96 (0.93 – 1.00)	0.034	0.96 (0.93 – 1.00)	0.040
Female sex	1.37 (0.38 – 4.97)	0.635	-	-
Baseline CD4	0.98 (0.96 – 1.00)	0.113	0.98 (0.95 – 1.00)	0.040
HBV or HCV	1.62 (0.44 – 5.95)	0.468	-	-
Ritonavir boosting	2.69 (1.14 – 6.34)	0.024	4.04 (1.58 -10.35)	0.004



Conclusions

- The incidence of atazanavir-associated severe hyperbilirubinemia in Korean HIV patients was over 40% at 12 months, similar to those reported in other racial groups.
- Severe hyperbilirubinemia was more common in ritonavir-boosted atazanavir regimen than in ritonavir-unboosted regimen.
- Atazanavir-induced jaundice often led to treatment discontinuation, especially in boosted regimen.



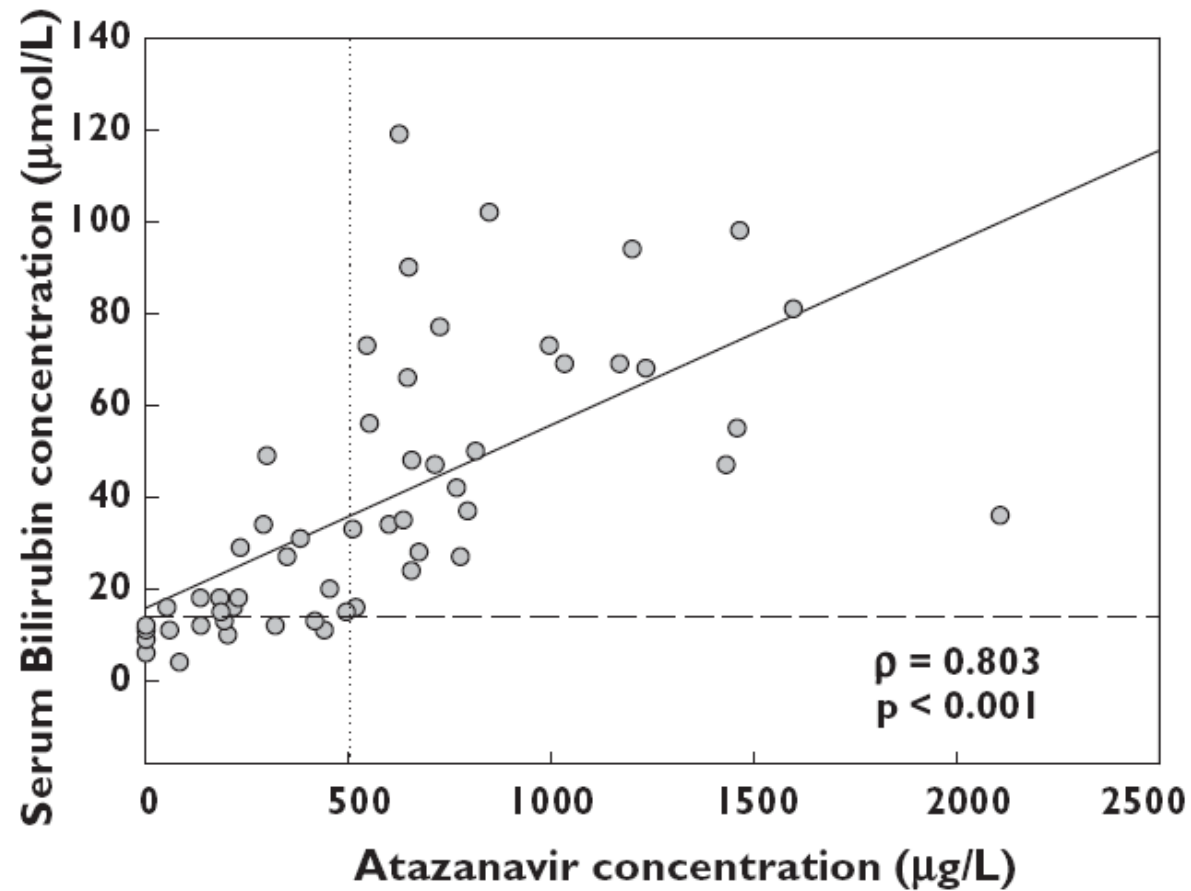
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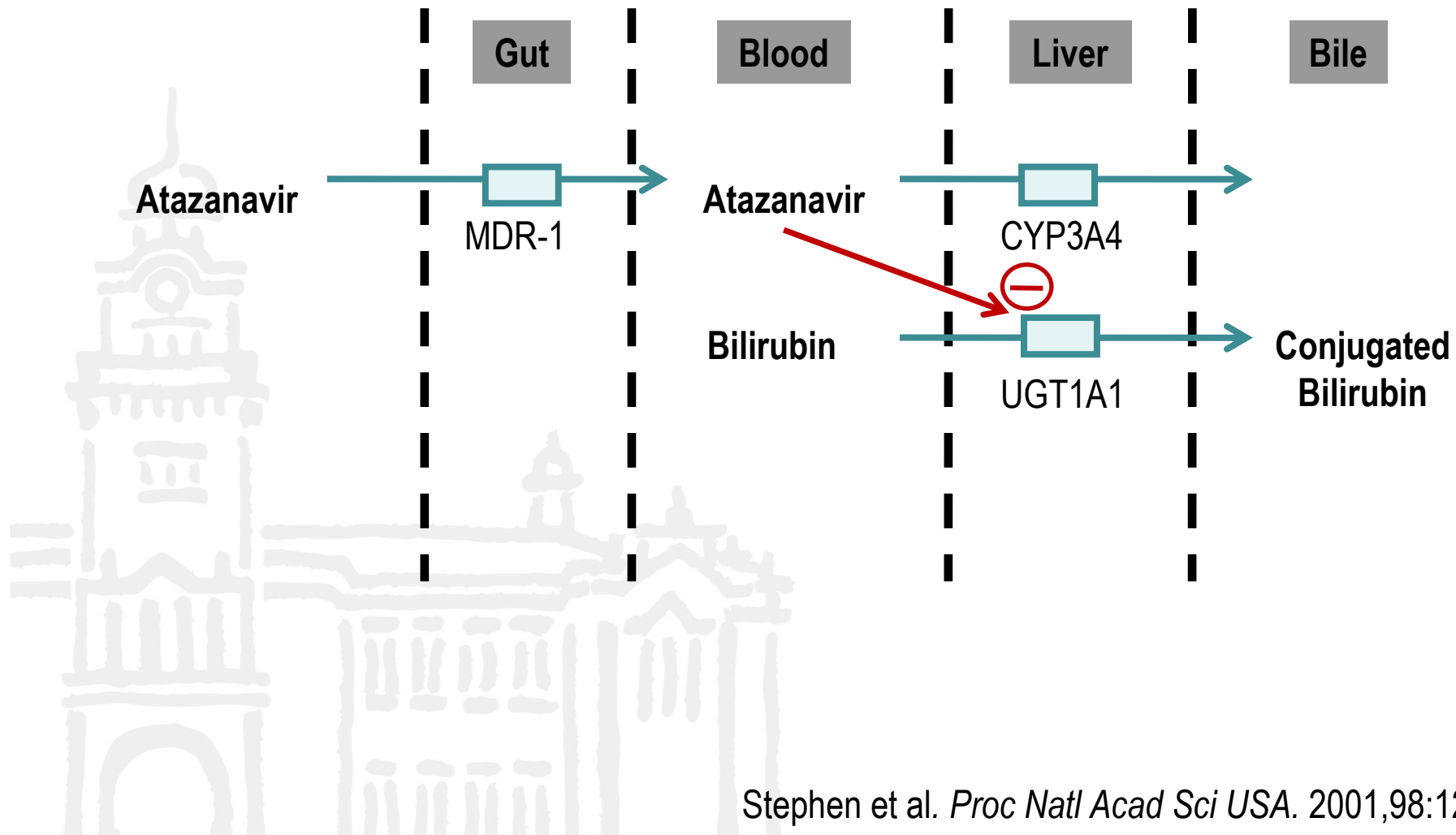
Back up slides for Questions



Dose-response Relationship



Mechanism of Hyperbilirubinemia

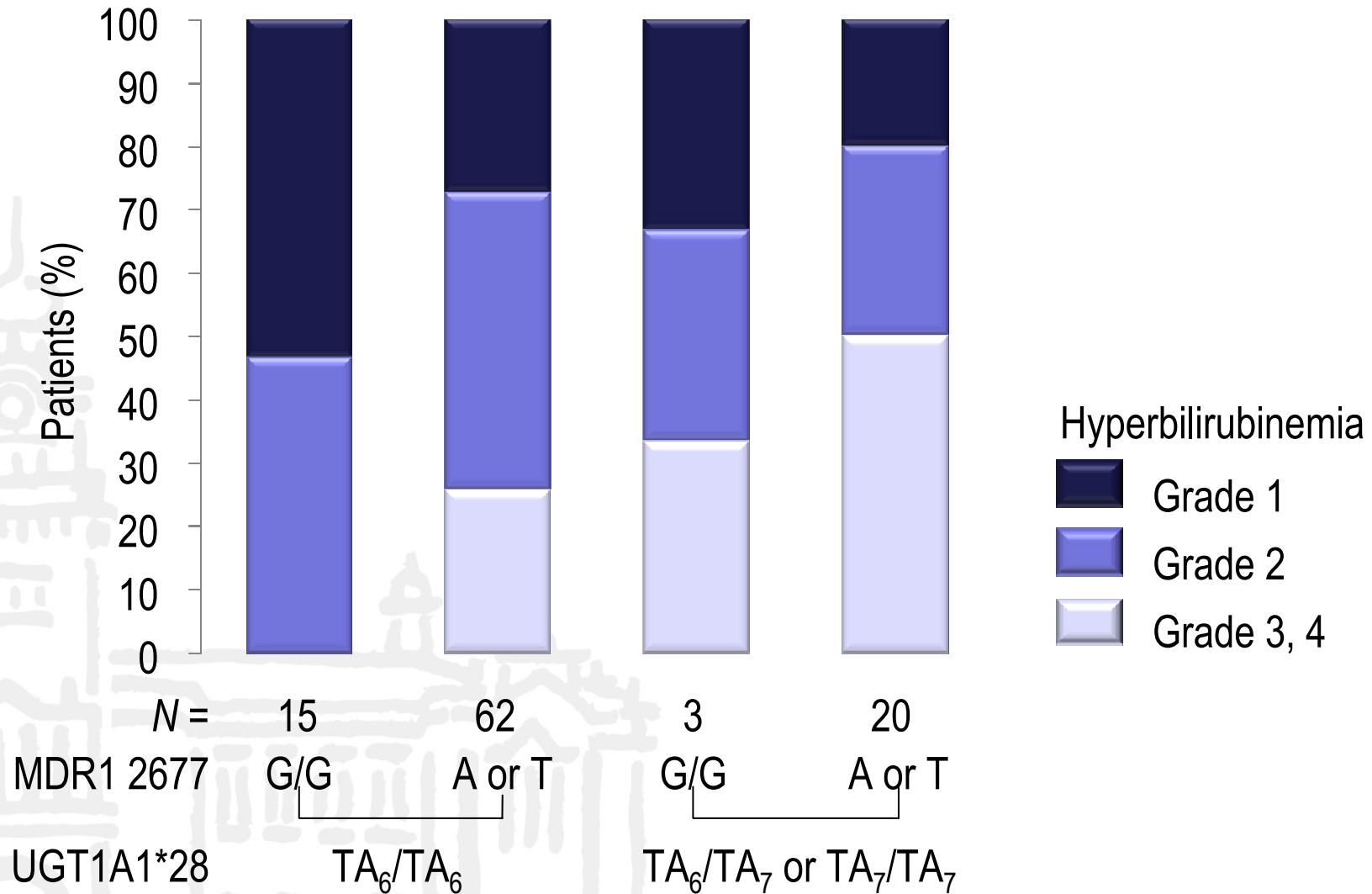




Risk Factors for ATV-associated HB

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P	aOR (95%CI)	P
Age (per year)	0.95(0.91-0.99)	0.014	0.96(0.92-1.01)	0.089
Hepatitis B or C	0.29 (0.04-2.32)	0.243	-	
Baseline CD4	0.97 (0.94-1.00)	0.028	0.97 (0.94-0.99)	0.036
At least one UGT1A1*6 allele	0.93 (0.37-2.36)	0.877	-	
At least one UGT1A1*28 allele	3.99 (1.55-10.24)	0.004	4.15 (1.46-11.84)	0.008
At least one 2677 at MDR1	6.74 (0.86-52.58)	0.069	9.65(1.09-85.61)	0.042
At least one 3435 at MDR1	1.77 (0.74-4.24)	0.200	-	

2677 G→T/A Polymorphism at MDR-1



(Park WB et al. submitted in CID)