Infektsioonid langenud immuunsusega haigetel

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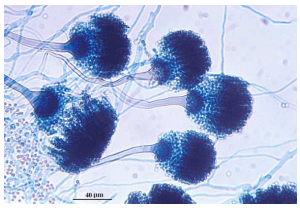
Tartu, 13.oktoober 2017

Langenud immuunsusega haige

- Kaasasündinud immuunsuse langus

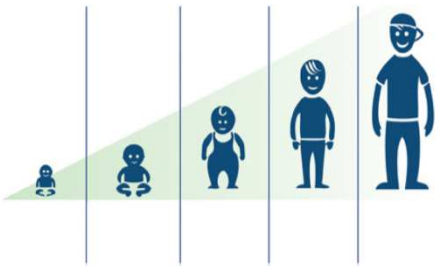
- Omandatud immuunsuse langus

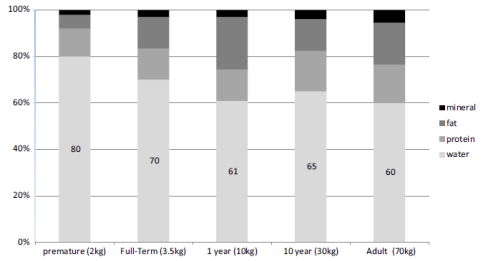


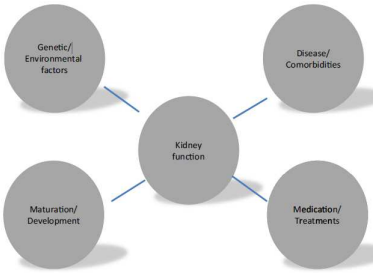
Probleem

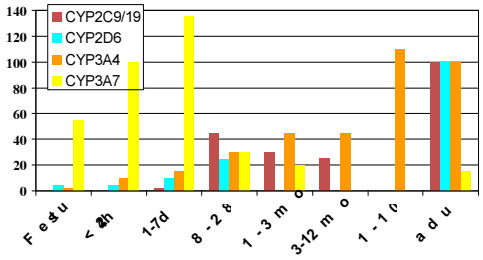
- Missugune on mikroobivastaste ainete optimaalne annustamine immuunsüsteemi häirega lastele?

Lapsed ei ole miniatuursed täiskasvanud vaid on täiesti omaette organismid (A.Jacobi >100 aastat tagasi)









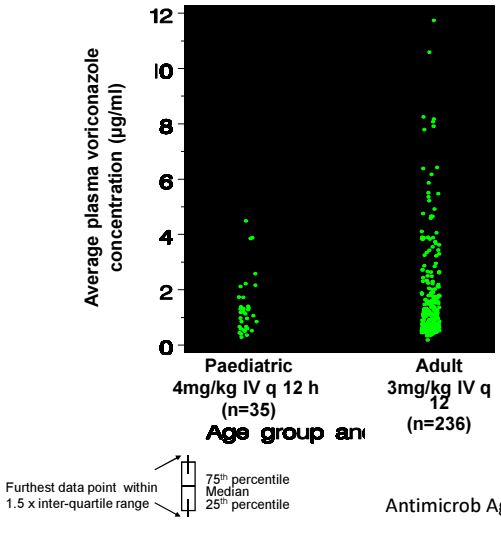
F Rodieux et al. Clin Pharmacokinet 2015; 54: 1183-1204

Vorikonasool

- Asooli tüüpi seenavastane aine
- CYP3A4, CYP2C19 ja CYP2C9 inhibiitor ja indutseerija
- Täiskasvanutel mittelineaarne farmakokineetika

Comparison of Voriconazole Exposure in Adult and Paediatric Subjects

Inappropriate study design → wrong dosing



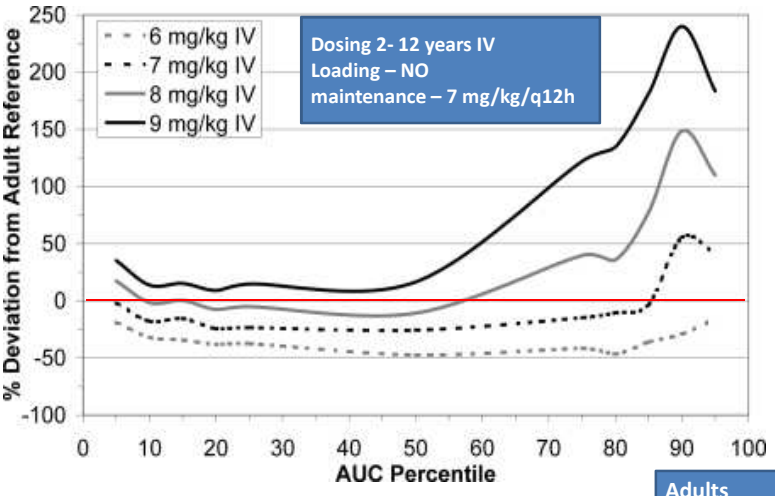
Dosing:
6 mg/kg/q12h loading
4 mg/kg/q12h maintenance

Antimicrob Agents Chemother. 2004; 48: 2166-72

Vorikonasooli farmakokineetiline uuring

- Kaks uuringugruppi
- *Rich* sampling
- Vaheanalüüs
- Klassikaline farmakokineetiline analüüs
- Populatsiooni kineetika
- Kokku osales 48 last 2-11 aasta vanust last

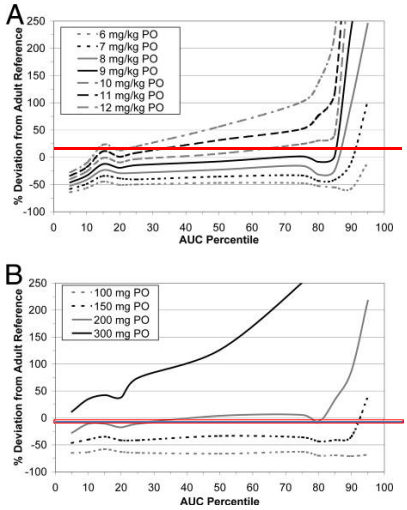
Percent deviations from the reference adult population AUC distribution



Antimicrob Agents Chemother. 2009 March; 53(3): 935–944

Adult reference: 4 mg/kg bid IV or 200 mg bid

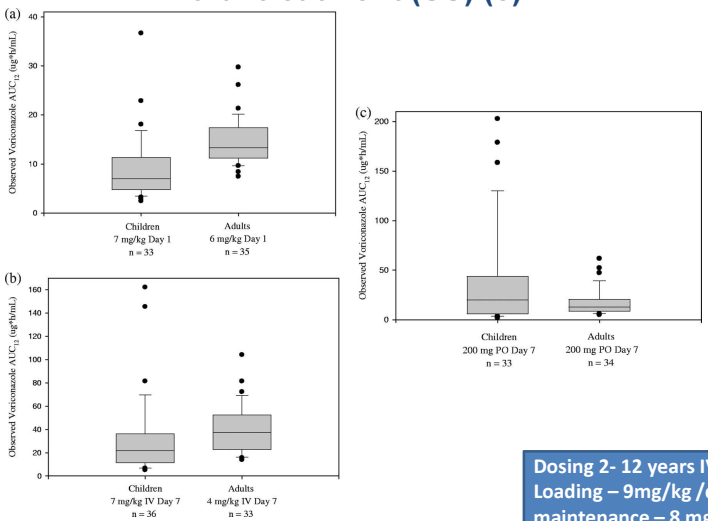
Deviations (%) from the adult AUC distribution (200 mg BID p.o.) for a range of weight adjusted (A) and fixed (B) oral doses in children



Dosing 2- 12 years
IV – 7 mg/kg /q12h
PO – 200 mg bid

Antimicrob Agents Chemother. 2010; 54: 4116-23

Voriconazole AUC_{0-12} in children and adults on Day 1 of IV treatment (a), Day 7 of IV treatment (SS) (b), and Day 7 of oral treatment (SS) (c)



Driscoll T A et al. Antimicrob. Agents Chemother. 2011;55:5770-5779

Dosing 2- 12 years IV
Loading – 9mg/kg /q12h
maintenance – 8 mg/kg /q12h

Vorikonasooli farmakokineetiliste uuringute tähtsus

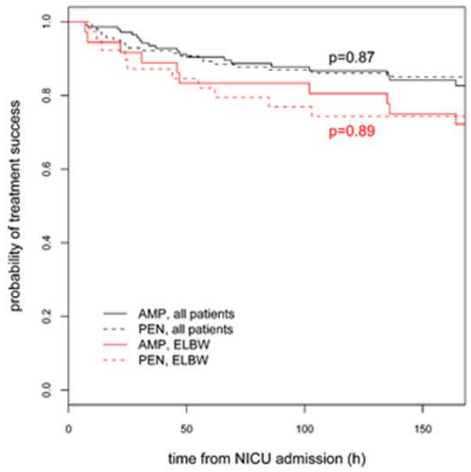
	Täiskasvanud	Lapsed vanuses 2 – 12 aasatat		
		-2005	2005-2012	2013 -
	Intravenoosne			
Küllastusannus	6 mg/kg/q12h		ei	9 mg/kg/q12h
Säilitusannus	4mg/kg/q12h		7 mg/kg/q12h	8 mg/kg/q12h
	Suukaudne			
Küllastusannus	400 mg/BID	Sama mis IV	400 mg/BID	ei
Säilitusannus	200 mg/BID		200 mg/BID	9 mg/kg BID

PK parameters of penicillin G in neonates (<7days) and adults at steady state

PK Parameter	GA<28 w (n=16)	GA 32-35 w (n=7)	GA≥35 w (n=9)	Adults* (n=15)
C_{max} (mg/L) – 15 mg/kg	65	51	71	67
$T_{1/2}$(h)	4.6	3.5	4.5	0.2
Vd (L/kg)	0.6	0.5	0.5	0.3
CL (L/h/kg)	0.1	0.1	0.1	0.3
AUC (h*mg/L) Dose 15 mg/kg 30 mg/kg	160 383	148 225	218 339	34

*Pregnant women received single dose of 1 MU penicillin G
Johnson *et al*. Am J Obstet Gynecol. 2001 Oct;185(4):850-3
Metsvaht *et al*. 2007; Padari *et al*. 2014

Ampicillin + gentamicin vs penicillin + gentamicin in empiric treatment of EOS



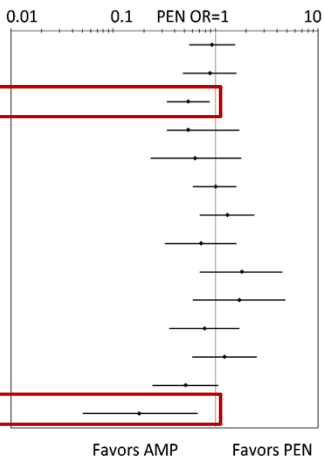
Treatment failure: death and/or change of initial antibiotics with 7 days

Metsvaht *et al*. Acta Paediatr. 2010; 99: 665-72

5% of patients had culture proven sepsis

Secondary endpoints

	AMP N=142	PEN N=141
Early AB >72h	64	66
Need for vasoactive drugs (N of pt)	61	65
Need for late AB (N of pt)	43	63
Proven LOS (N of pt)	26	29
Proven LOS (N of episodes)	32	40
Colonization with AMP-R Gram-neg. bacteria (N of pt)	44	44
Colonization with *Candida* spp (N of pt)	26	21
PDA requiring surgery (N of pt)	12	16
Threshold ROP (N of pt)	14	8
NEC II-III (N of pt)	10	8
IVH III-IV (N of pt)	13	16
BPD (N of pt)	18	15
NICU mortality (N of pt)	13	23
NICU mortality <26 wk GA (N of pt)	6/24	13/21



No drug-related adverse events in either group

Metsvaht *et al*. Acta Paediatr. 2010; 99: 665-72

14

Empiric AB regimen and mucosal colonisation

- Penicillin and ampicillin have similar effect on gut colonisation with Gram-negatives
- Ampicillin promotes colonisation with *S. haemolyticus, S. hominis*
- Penicillin promotes colonisation with *Enterococcus* spp, *S. aureus*

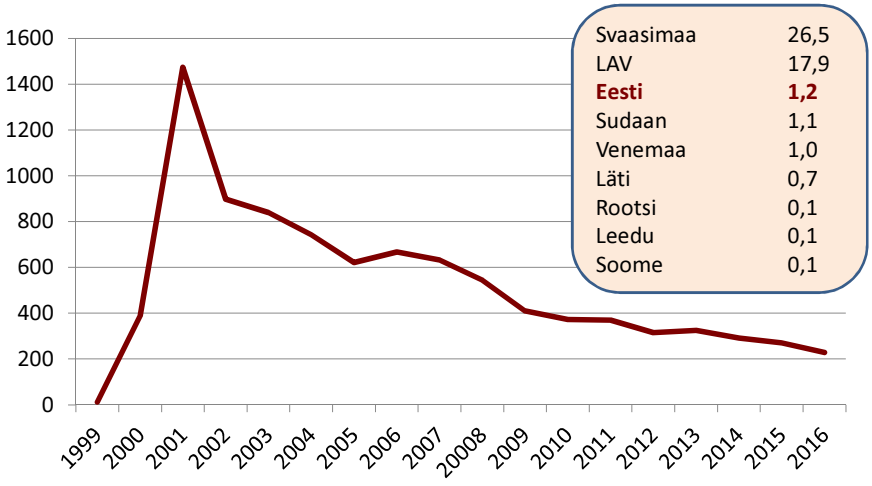
	Multifactorial mixed effect model analyses			
	Per subject	p=	CD	p=
Ampicillin treatment associated with increased colonisation			*K. pneumoniae*	0.012
			AR *Serratia* spp	0.012
	S. haemolyticus	0.039	*S. haemolyticus*	0.001
	S. hominis	0.009	*S. hominis*	0.001
			Candida spp	0.02
Penicillin treatment associated with increased colonisation			AR *Acinetobacter*	0.001
	Enterococcus spp	<0.001	*Enterococcus* spp	0.001
	S. aureus	0.006	*S. aureus*	0.052

Eur J Clin Microbiol Infect Dis. 2010; 29: 807-16

HIV infektsiooni probleem

- Vähendada HIV haigestumist ja likviderida epideemia
- Kes haigestuvad HIV infektsiooni?
- Eesti epideemia ja muu maailma epideemia erinevused
  - Viiruse tüüp
  - Ravimresistentsus
  - Haigestunute populatsioon

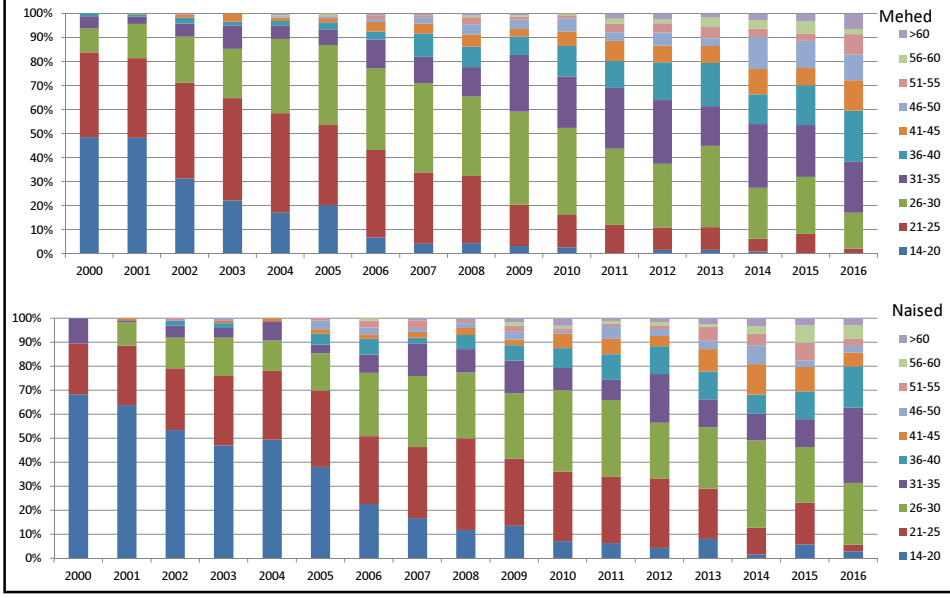
Uued HIV juhud (n) ja prevalents 2012 aastal 100, 000 15-49 aastase isiku kohta



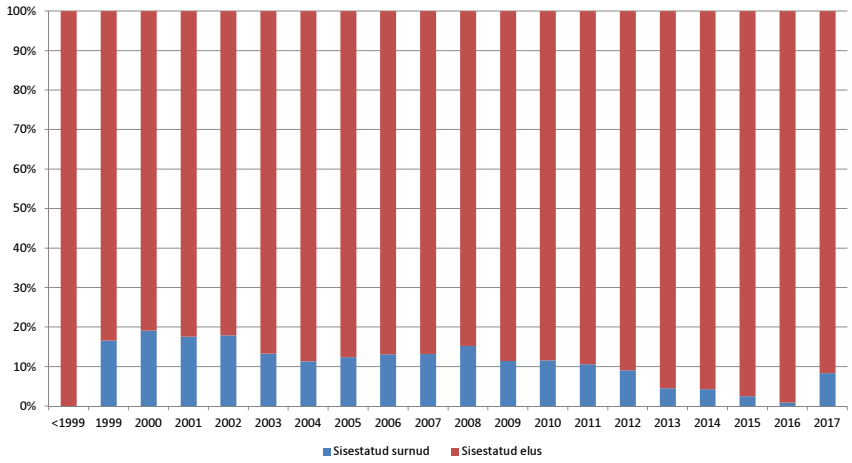
Svaasimaa	26,5
LAV	17,9
Eesti	**1,2**
Sudaan	1,1
Venemaa	1,0
Läti	0,7
Rootsi	0,1
Leedu	0,1
Soome	0,1

www.terviseamet.ee

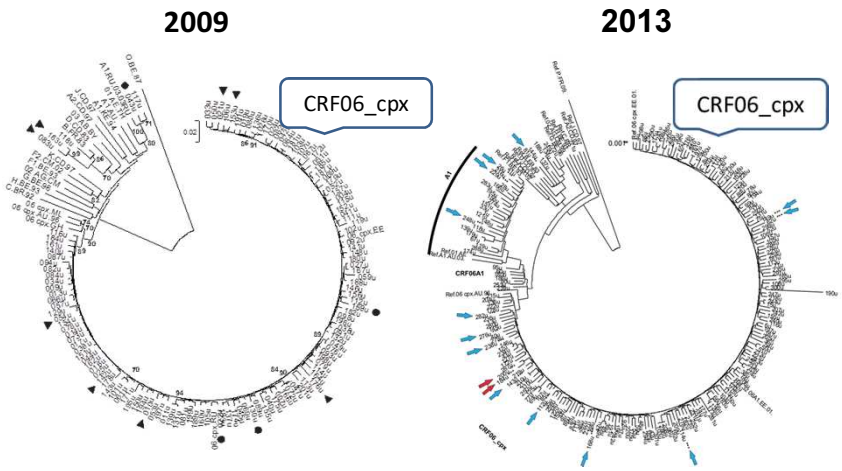
HIV positiivne patsient: vanus diagnoosimisel ja sugu



Üldine suremus HIV andmekogu põhjal (10.03.2017)

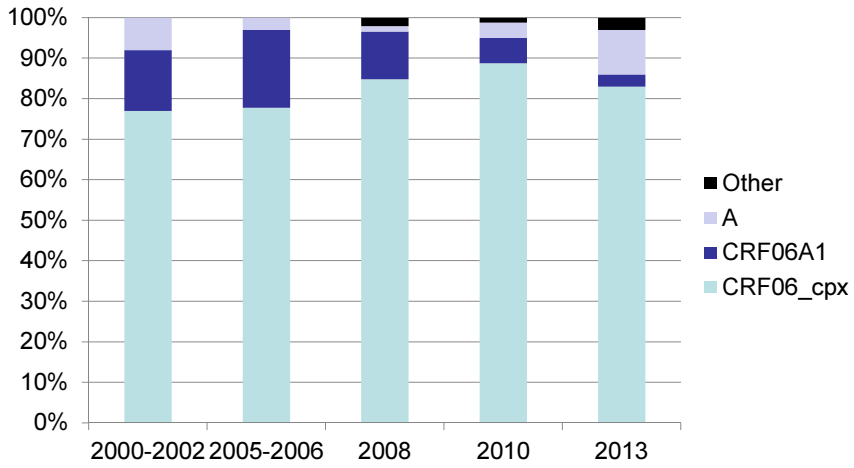


Eesti HIV fülogeneetiline puu



Avi *et al*. 2011
Soodla *et al*. (avaldamisel)

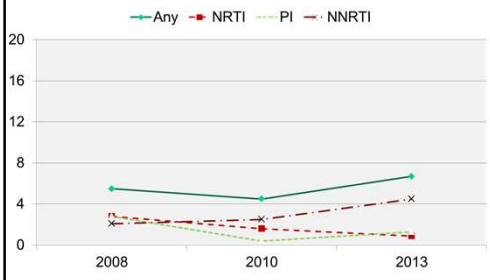
Enamus haigeid on nakatunud CRF06-cpx või tema rekombinandiga



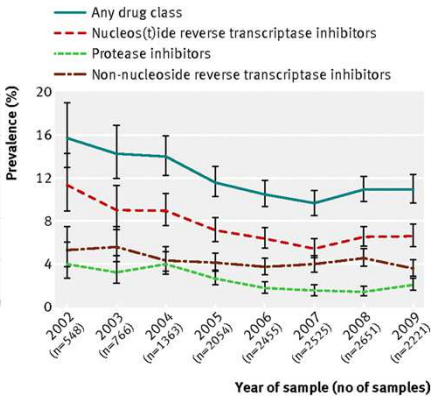
AIDS Res Hum Retroviruses. **2004**; 20: 1148-56
Scand J Infect Dis 2011; 43: 122-8
AIDS Res Hum Retroviruses 2014; 30: 278-83
J Med Virol. 2009; 81: 953-8
Soodla *et al.* (avaldamisel)

Transmitted drug resistance in Estonia and UK

Estonia



UK



BMJ 2012;345:bmj.e5253
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Soodla *et al.* (avaldamisel)

Eesti HIV positiivne patsient (E-HIV)

- ✓>90% räägib emakeelena vene keelt
- ✓>90% elab Põhja Eestis
- ✓63% on mehed
- ✓33% põeb lisaks C-hepatiiti
- ✓4% põeb lisaks tuberkuloosi
- ✓40% on nakatunud viimase 8 kuu jooksul
- ✓40% saab viirusvastast ravi

Teadustöö praktiline tähtsus

- Vorikonasooli annustamise skeem lastele
  - Ravimiomaduste kokkuvõte
  - Ravijuhised
- Penitsilliin G doseerimine vastsündinu sepsise empiirilises ravis
  - *NICE* ravijuhised
- Antiretroviirusvastaste ravimite resistentsus
  - *In house* resistentsuse määramine Eestis
  - ARV resistentsuse jälgimine
- 8 kaitstud doktoritööd + tugev rahvusvaheline koostöö

Ilma heade kolleegideta ma poleks mitte keegi!

HIV uuringute grupp (hiv.ut.ee)

Lasteuuringute grupp (www.elav.ee)

Lisaks paljud rahvusvahelised partnerid kogu maalimast