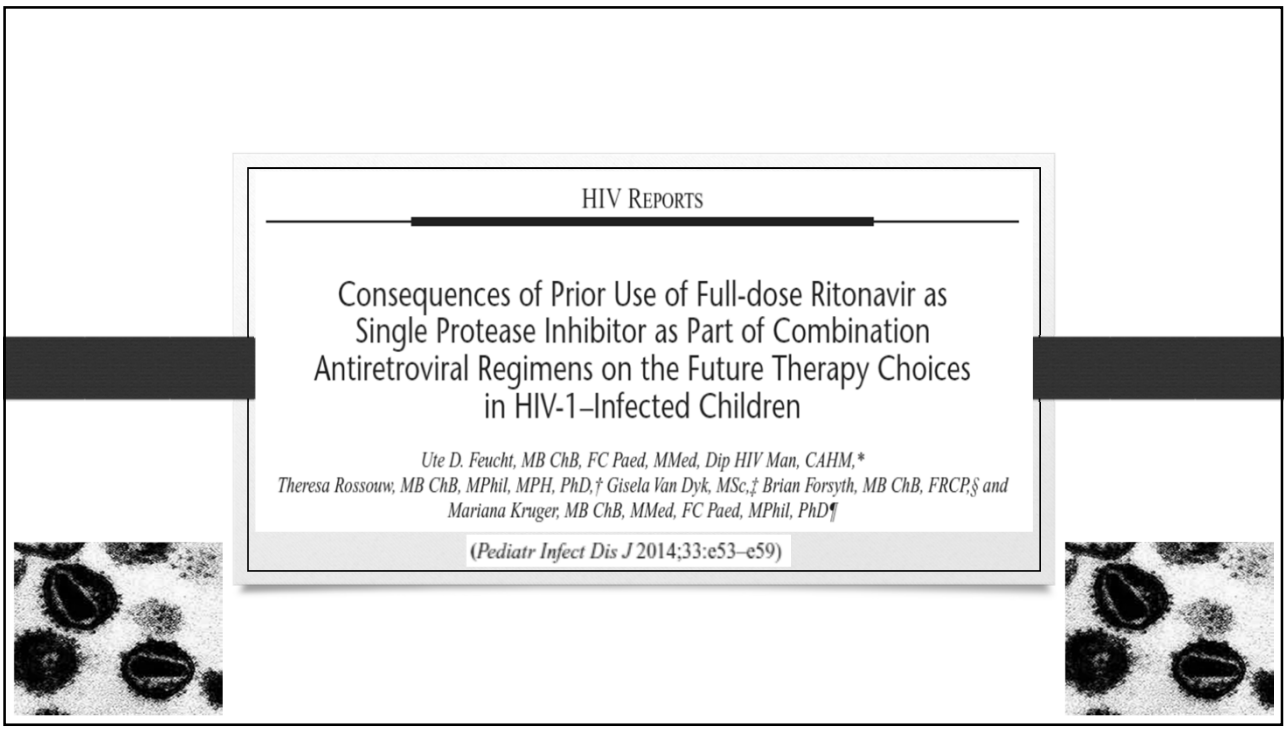
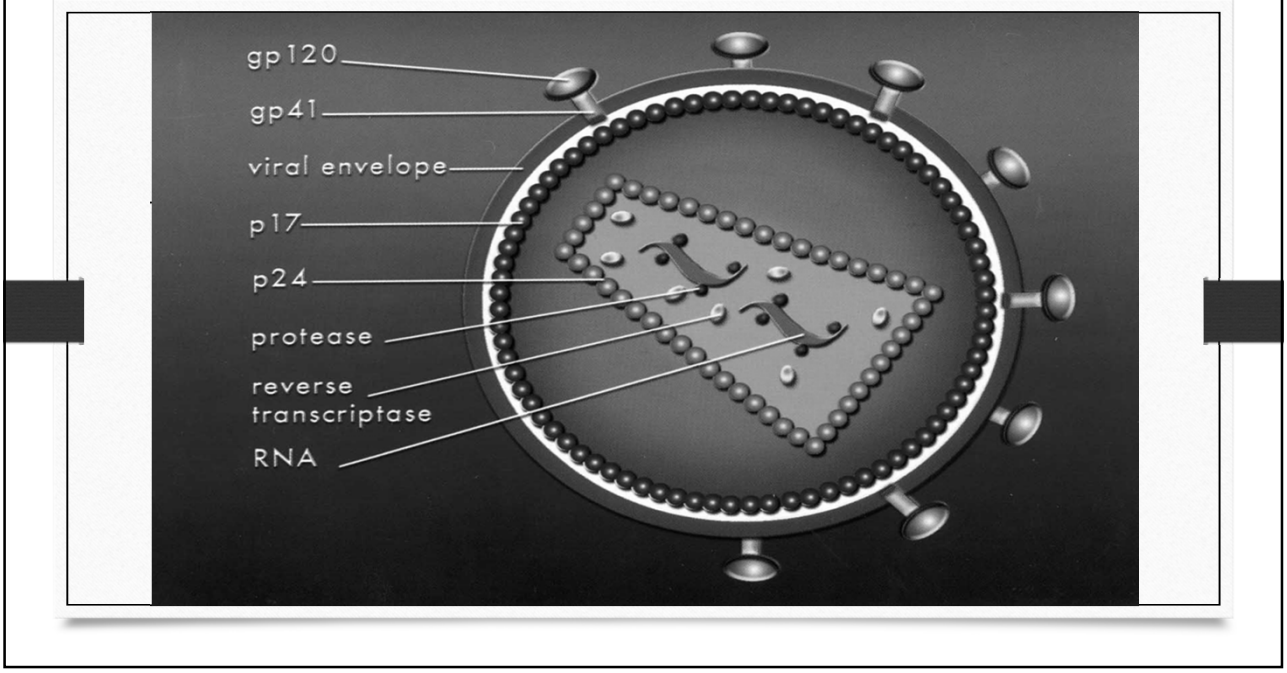


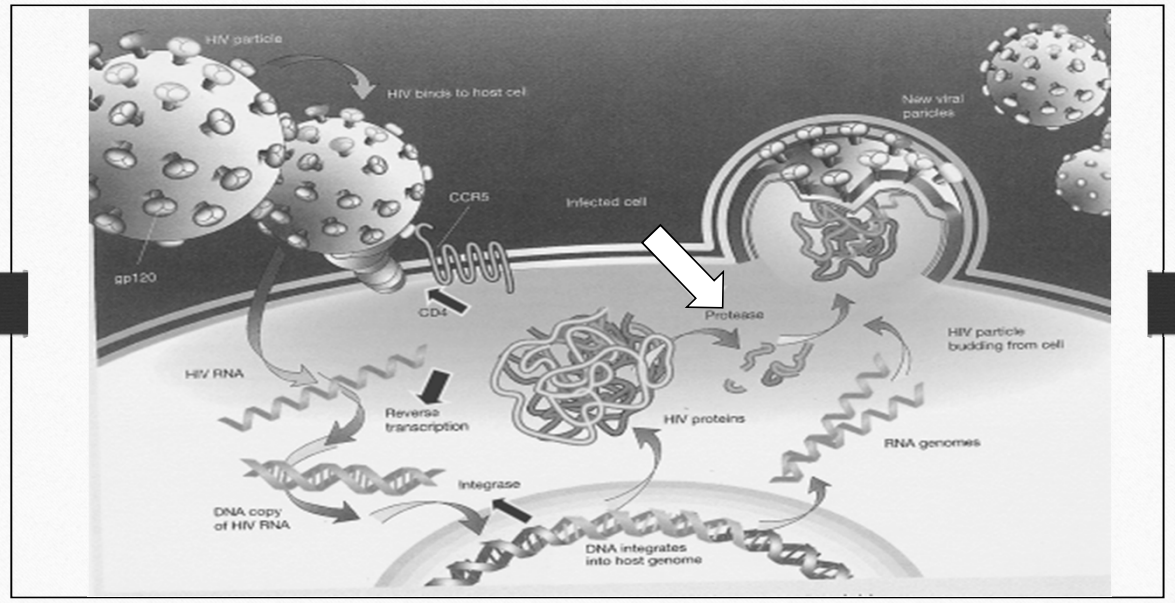
HIV REPORTS

Consequences of Prior Use of Full-dose Ritonavir as Single Protease Inhibitor as Part of Combination Antiretroviral Regimens on the Future Therapy Choices in HIV-1–Infected Children

*Ute D. Feucht, MB ChB, FC Paed, MMed, Dip HIV Man, CAHM,**
Theresa Rossouw, MB ChB, MPhil, MPH, PhD,† Gisela Van Dyk, MSc,‡ Brian Forsyth, MB ChB, FRCP,§ and Mariana Kruger, MB ChB, MMed, FC Paed, MPhil, PhD¶

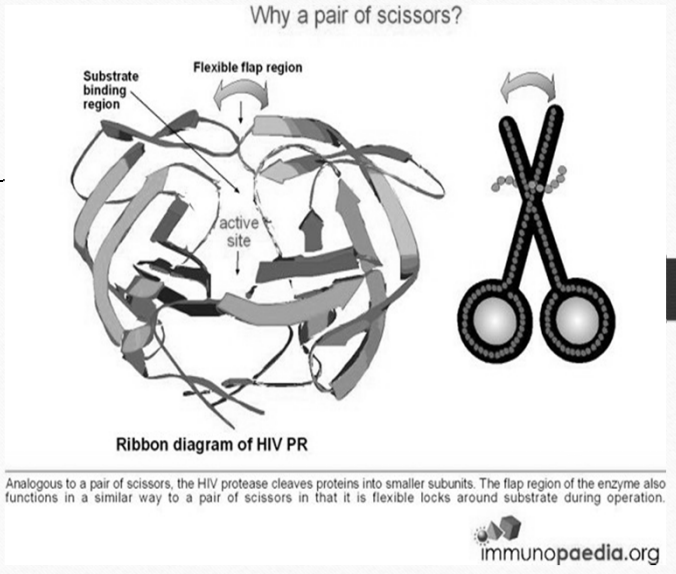
(*Pediatr Infect Dis J* 2014;33:e53–e59)





HIV-1 Protease

- Essential for HIV life-cycle
- Cleaves newly synthesized polyproteins to create mature protein components of infectious HIV
- Mutation of active site disrupts HIV's ability to replicate & infect cells



ART drugs:

NRTI	AZT	Zidovudine	Retrovir ®
	d4T	Stavudine	Zerit ®
	3TC	Lamivudine	3TC ®
	FTC	Emtricitabine	Emtriva ®
	ddI	Didanosine	Videx ®
	ABC	Abacavir	Ziagen ®
	TDF	Tenofovir	Viread ®
NNRTI	EFV	Efavirenz	Stocrin ®
	NVP	Nevirapine	Viramune ®
PI	LPV/r	Lopinavir/ritonavir	Kaletra ®; Aluvia ®
	RTV	Ritonavir	Norvir ®

Background to the study

- RTV-sPI (+2 NRTI) in SA National Guidelines from 2004 to 2008
  - Younger than 6m at ART initiation
  - Concomitant anti-TB Rx
- Use of RTV-sPI is now known as a risk factor for PI drug resistance
  - BUT: Extent of resistance not fully understood

Aim of study

- Cohort of children who received RTV-sPI
  - Large SA ART site
  - High TB burden setting

→Clinical Outcome

→Virological Outcome

→Resistance mutations if ART failure

Study Methods

- Patient inclusion:
  - ART initiation before Dec 2008 at Kalafong Hospital
  - All children ever on RTV-sPI-based regimens
- Assessment in terms of:
  - Patient outcome
  - Virological failure
  - Drug resistance
- HIV VLs done 6-monthly and HIV genotyping since 2009

Study Results

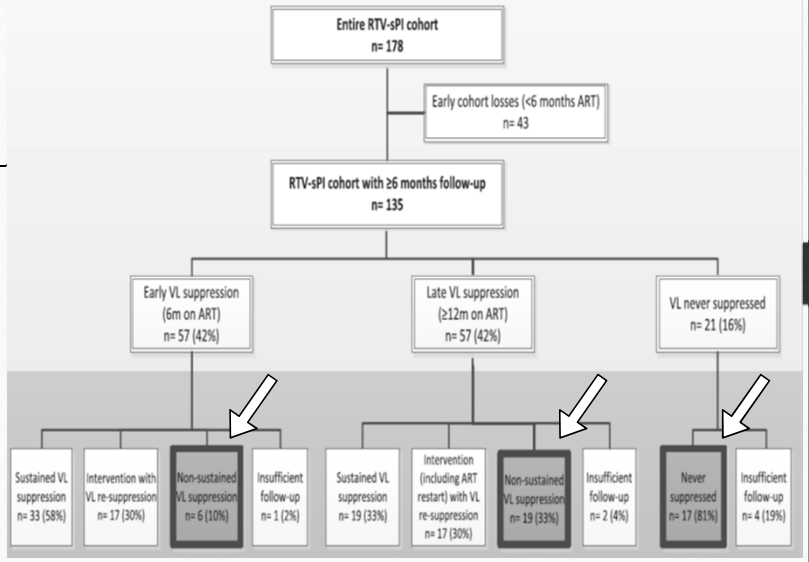
- 416 children started on PI-based ART before Dec 2008
- RTV-sPI= 178 (43%); mean age (ART initiation) = 1.4 yrs
- Reason for RTV-sPI:
  - TB= 157 (88%)
  - ART initiation <6m= 5 (3%)
  - Both= 16 (9%)
- Follow-up: 44 m (0 – 94m)
  - On RTV-sPI: 8m (0 – 28m)
  - On additional LPV/r regimens: 23m (0-91m)

Cohort description

		Entire RTV-sPI Cohort (n = 178)
Age at ART initiation (in yr):	Mean (median) (SD)	1.4 (1.3) (0.8)
Anthropometry:	Mean (median) (SD)	
Weight-for-age Z score		−3.4 (−3.3) (1.8)
Height-for-age Z score		−3.2 (−3.0) (1.6)
BMI-for-age Z score		−1.2 (−1.0) (2.0)
HIV staging:	WHO stage 1:	0
	WHO stage 2:	2 (1.1%)
	WHO stage 3:	49 (27.5%)
	WHO stage 4:	127 (71.4%)
CD4 absolute count:	Mean (median) (SD)	680 (573) (544)
CD4 percentage:		15.9% (14.0%) (9.3)
	Categories:	
	CD4% <15%	97 (54.5%)
	CD4% 15%–25%	59 (33.1%)
	CD4% >25%	21 (11.8%)
	Not recorded	1 (0.6%)
HIV VL (log_{10} copies/mL):	Mean (median) (SD)	5.7 (5.9) (0.8)
	Categories:	
	VL <log_{10} 5	28 (15.7%)
	VL ≥log_{10} 5; <log_{10} 6	62 (34.8%)
	VL ≥log_{10} 6	74 (41.6%)
	Not recorded	14 (7.9%)

Viral suppression

- 135 (76%) >6m F/U
  - 25 (18%) virologic failure after initial suppression
  - 17 (13%) no viral suppression ever

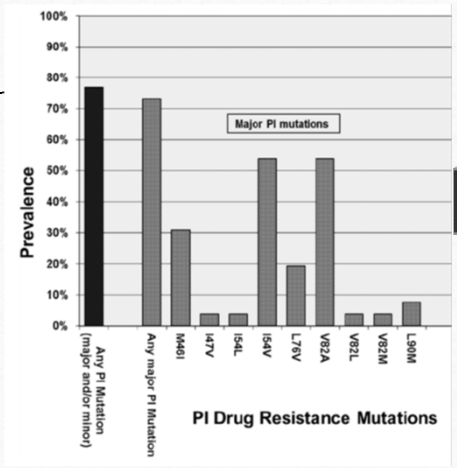


Study Results

- Study endpoint at January 2012: 95 (54%)
  - 69 on active treatment with viral suppression
  - 26 with virologic failure → genotype
    - NRTI mutations: 100%
    - Major PI mutations: 73%
      - I54V (54%), V82A (54%), M46I (31%), L76V (19%)
    - NNRTI mutations: 58%

→88% dual class mutations

→42% triple class mutations



Resistance patterns

- **Only ever on PIs:**
  - PI mutations +++
  - No TAMs
- **Switch to NNRTI:**
  - Fewer PI mutations +
  - NNRTI mutations +++
  - TAMs +++

		PI regimens Only (n=12)	Switch to NNRTI (n=10)	p value
Genotypes with mutations (Nr (%)	Major PI mutations: ≥3	67%	0%	0.002
	NNRTI mutations: ≥1	8%	100%	0.000
	NRTI mutations: ≥1 TAM	0%	60%	0.003
Mutations per genotype (Mean (SD))	Any	3.8 (1.9)	5.6 (1.7)	0.026
	Major PI mutations	2.5 (1.7)	0.6 (0.5)	0.002
	NNRTI mutations	0.1 (0.3)	2.3 (0.7)	0.000
	NRTI: Nr of TAMS	0 (0)	1.6 (1.6)	0.011

What does this mean for future ART?

PI resistance	Lopinavir	19 (73%)
	Darunavir	6 (23%)
	Atazanavir	19 (73%)
	Tipranavir	14 (54%)
NNRTI resistance	Efavirenz	15 (58%)
	Nevirapine	15 (58%)
	Etravirine	11 (42%)

Study Conclusions

- ART failure is not universal feature with prior RTV-sPI regimens
  - BUT: Significant proportion (31%) with virological failure
  - Concern due to high prevalence of major PI- and multiclass mutations
- Urgent need for a 'third-line' regimens for affected children

Relevance

- Advancement in ART is potentially threatened by viral resistance
  - ➢ Partly due to suboptimal ART regimens (in hindsight!)
- Most HIV resistance data is from HIV-1 subtype B (not subtype C as in SA)
- High burden of TB in SA complicates ART management
- Large % of SA children during initial ART roll-out were on RTV-sPI (43%)
- Predictable ART resistance patterns
- Urgent need for 3rd line drugs for selected children

Thank you!