Decreased bone turnover in HIV-infected children on antiretroviral therapy

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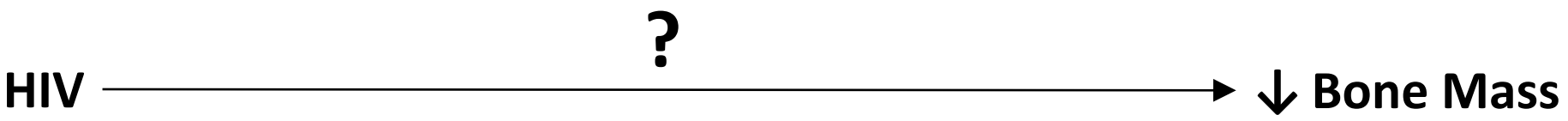
CHANGES Bone Study Team

HIV and Bone in Children

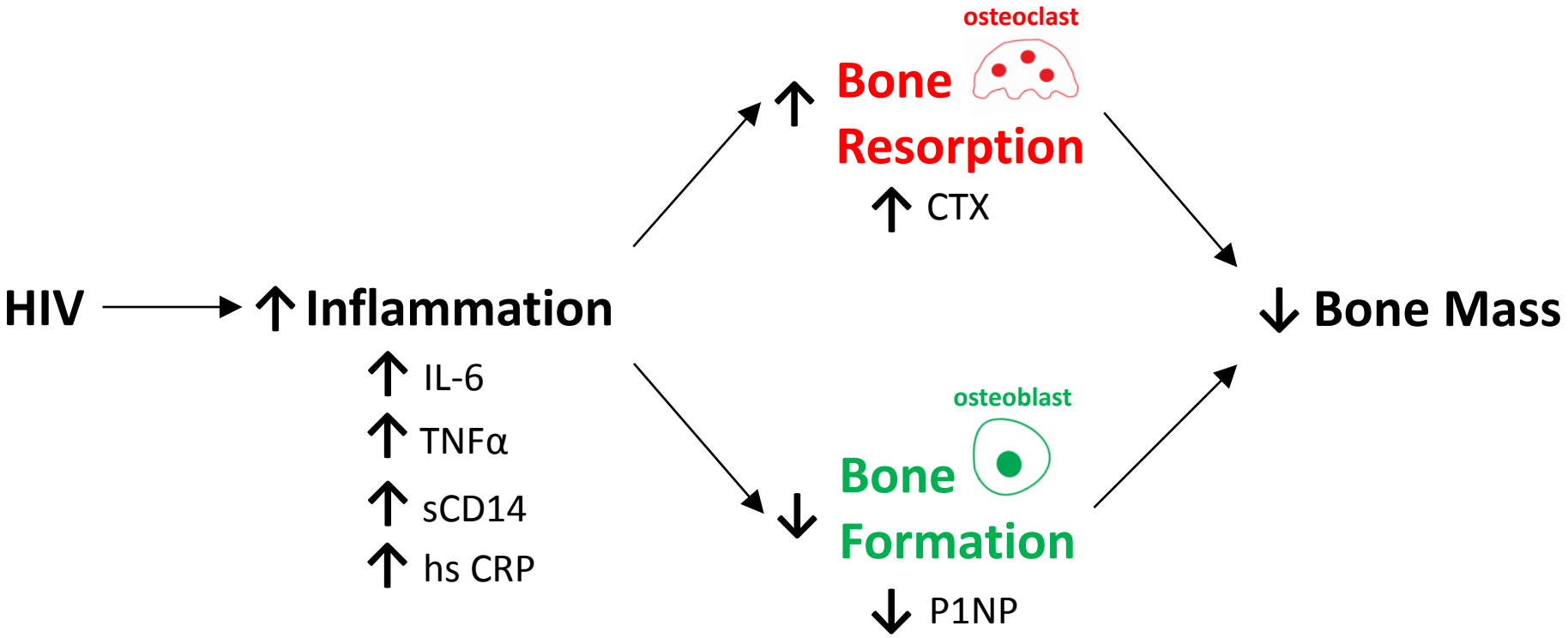
- HIV appears to be associated with deficits in childhood bone mass accrual[1,2]
- We previously reported lower bone mineral content (BMC) among South African HIV-infected children who[3]:
  - Initiated treatment early in life
  - Have excellent virologic control
- Disruption of bone accrual can compromise adult peak bone mass and increase the risk of later life osteoporosis and fracture

[1]Jacobson et al. *AIDS* 2010; [2]Mora et al. *J Clin Endocrinol Metab* 2004;
[3]Arpadi, Shiau, Strehlau et al. *AIDS* 2016 (in press)

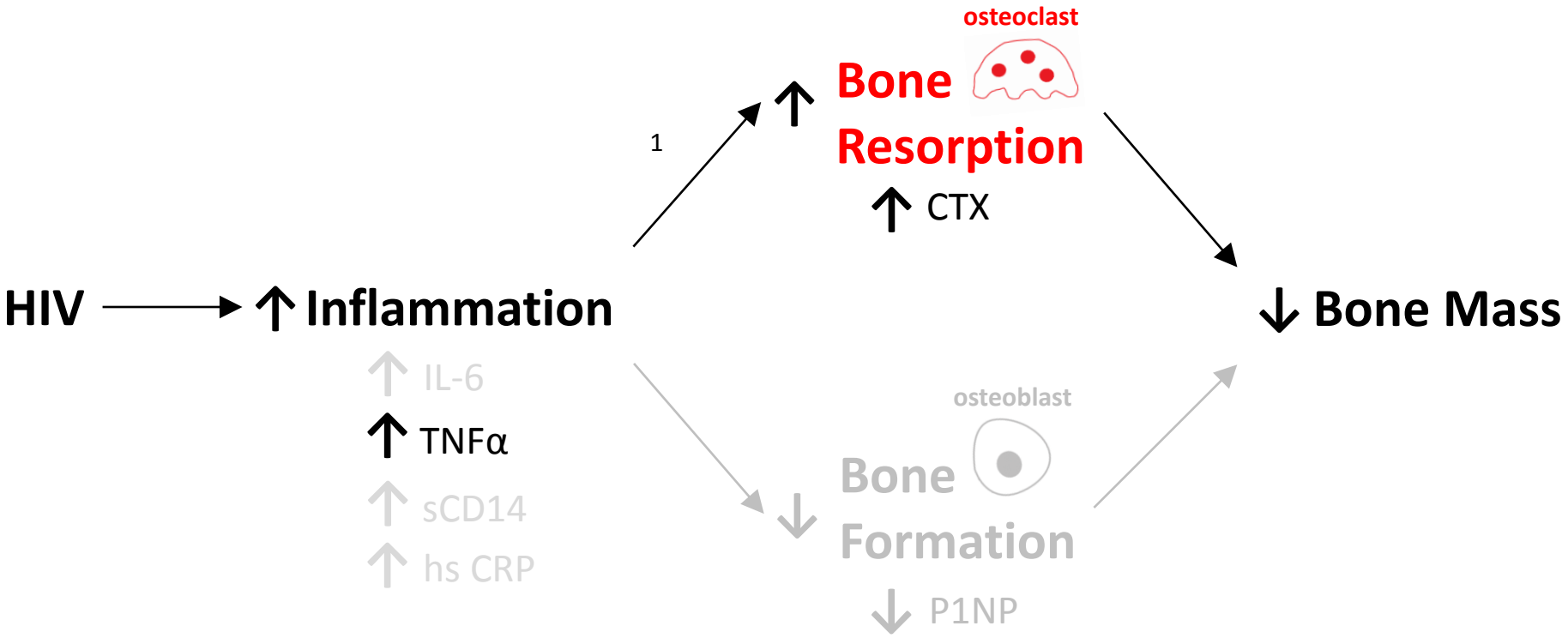
Mechanisms Unclear



Hypothesized Mechanisms



Previous Studies



Children?

[1]Yin *Clin Endocrinol Metab* 2010

Study Design

- CHANGES Bone Study
- ESRU, Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa
- 219 HIV-infected children
- 219 HIV-uninfected controls
  - 180 controls included in this analysis

Measurements

Inflammation

- IL-6
- TNF-α
- sCD14
- hs-CRP

Bone turnover markers

- Resorption: CTX
  (C-telopeptide)
- Formation: P1NP
  (procollagen type 1 N-terminal propeptide)

Bone mass

- Whole body BMC by DXA
- BMC Z-scores (adjusted for sex, age, and height)

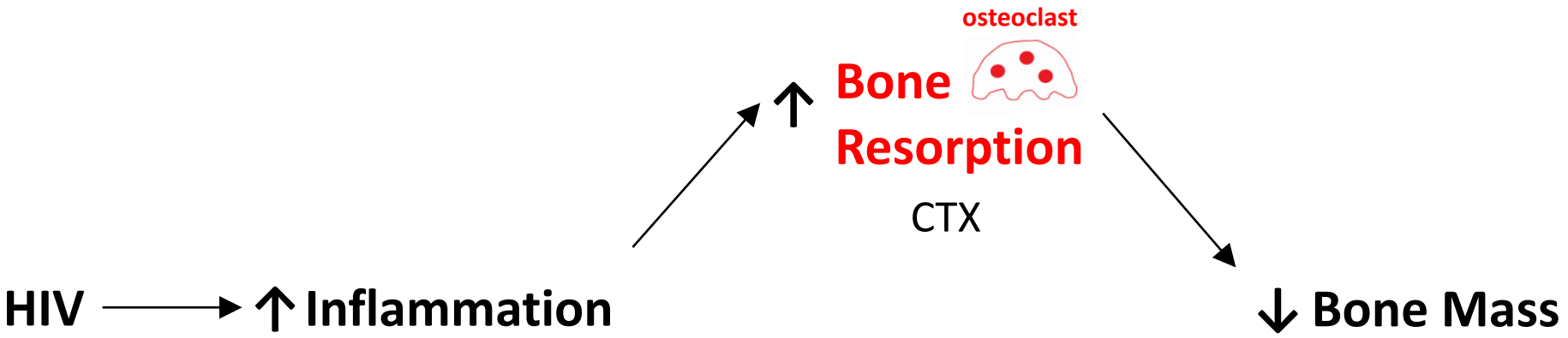
Results: Characteristics

	HIV+ (N=219)	HIV- (N=180)
Males	49%	55%
Mean Age	6.4 years	7.1 years
Tanner 1	98%	96%
Duration on ART	5.7 years	-
Mean CD4%	37%	-
HIV-1 RNA <400 copies	94%	-
Mean WB BMC Z-Score	-0.95	-0.79

Results: Inflammation

Marker		HIV+ (N=219)		HIV- (N=180)	
IL-6 (pg/mL)	Mean (SD)	1.72 (3.6)		1.73 (3.5)	–
≥ 9.96 pg/mL	N (%)	4 (1.8)		3 (1.7)	
TNFα (pg/mL)	Mean (SD)	2.2 (1.4)	*	2.6 (1.2)	–
≥ 4.71 pg/mL	N (%)	1 (0.5)		0 (0.0)	
sCD14 (ng/mL)	Mean (SD)	1453 (550)	*	1195 (437)	↑
≥2300 ng/mL	N (%)	18 (8.2)	*	4 (2.2)	
hs CRP (mg/dL)	Mean (SD)	4.71 (14.7)	*	1.81 (4.0)	↑
≥ 0.5 mg/dL	N (%)	128 (58.5)	*	77 (42.8)	

Results: Bone Resorption

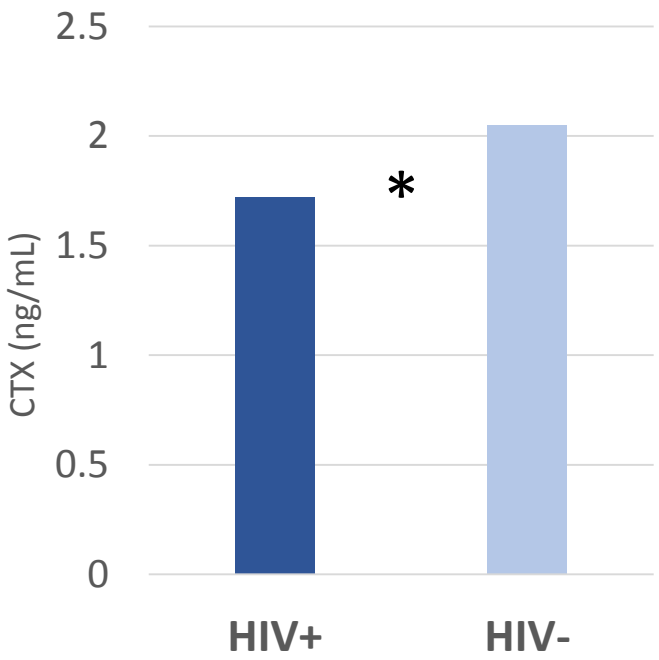


Results: Bone Resorption

osteoclast

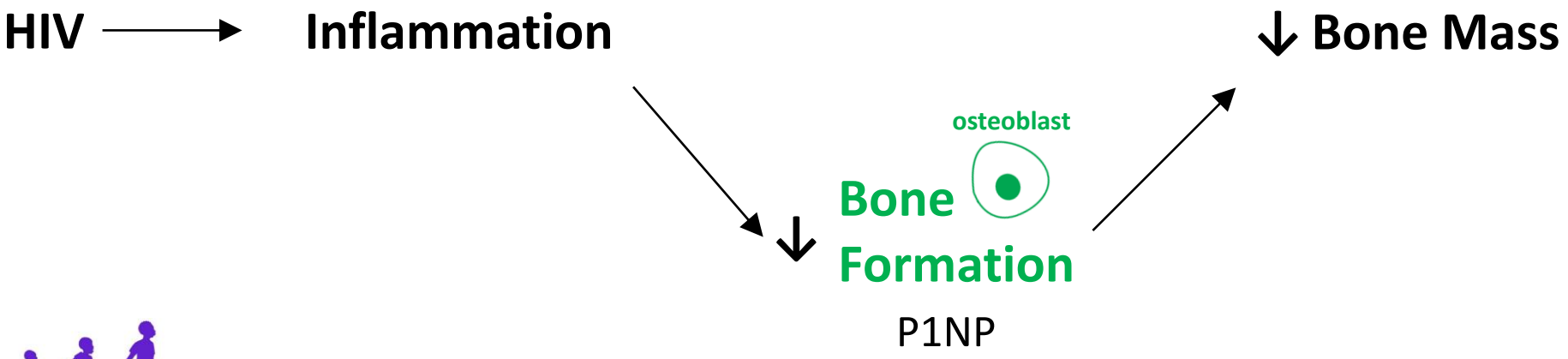
↑ Bone Resorption

HIV → ↑ Inflammation → ↓ CTX → ↓ Bone Mass



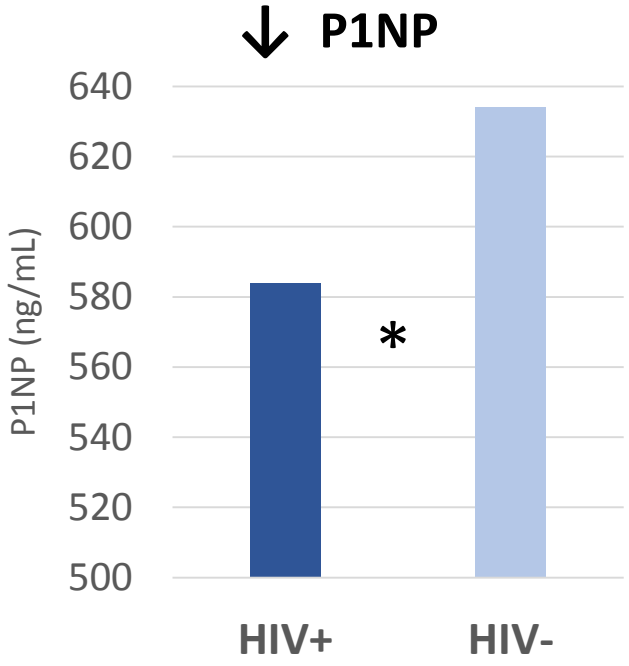
*p<0.05

Results: Bone Formation



*p<0.05

Results: Bone Formation



HIV → Inflammation → ↓ Bone Mass

osteoblast

↓ Bone Formation

*p<0.05

Results: Correlations

	Inflammation				Bone Mass
	IL-6	**TNFα**	**sCD14**	**hs CRP**	**WB BMC Z**
CTX Resorption	0.01	0.04	-0.06	-0.08	0.05
P1NP Formation	-0.11*	0.01	-0.05	-0.19*	0.09

*p<0.05

Summary

- Compared to HIV-uninfected controls, HIV-infected children had:
  - Lower BMC
  - Similar IL-6 and TNF-a
  - Higher sCD14 and hsCRP
  - Lower bone resorption (CTX) and bone formation (P1NP)
- Bone turnover markers were not strongly correlated with markers of inflammation or BMC
- In summary, HIV-infected children with virologic suppression on antiretrovirals had lower BMC and lower bone formation

Implications

- In HIV-infected children with viral suppression, decreases in bone accrual may occur independently of immune activation
  - HIV viral proteins and/or ART may have a direct effect on osteoblasts resulting in decreased bone formation[1-3]
- Longitudinal studies that include bone turnover markers are needed to understand the dynamics of bone remodeling in growing children

[1]Fakruddin *Arch Virol* 2005; [2]Butler *J Orthop Res* 2013; [3]Malizia *AIDS Res Hum Retro* 2007

Acknowledgements

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