HIV Treatment Initiation: the evidence

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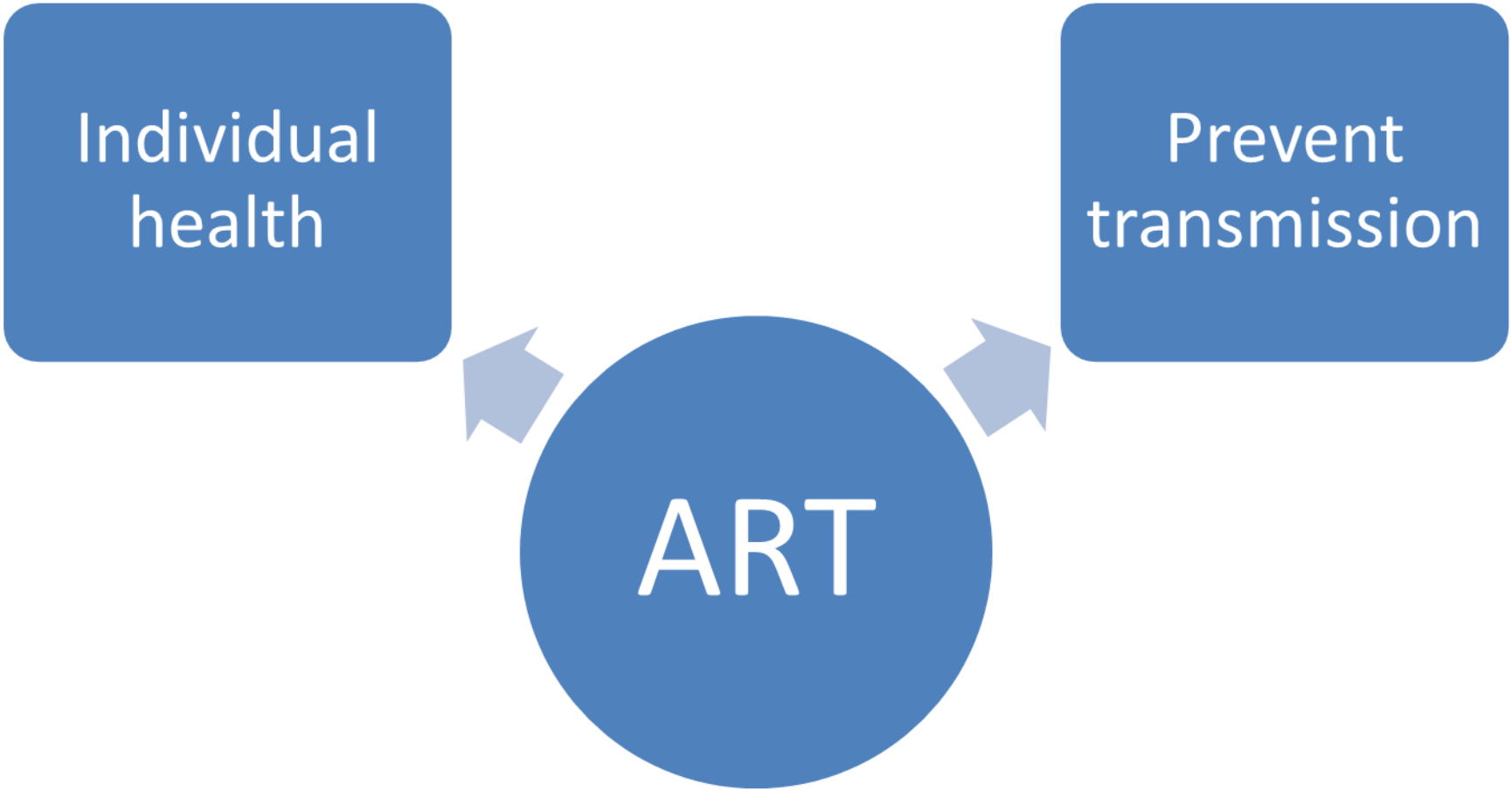
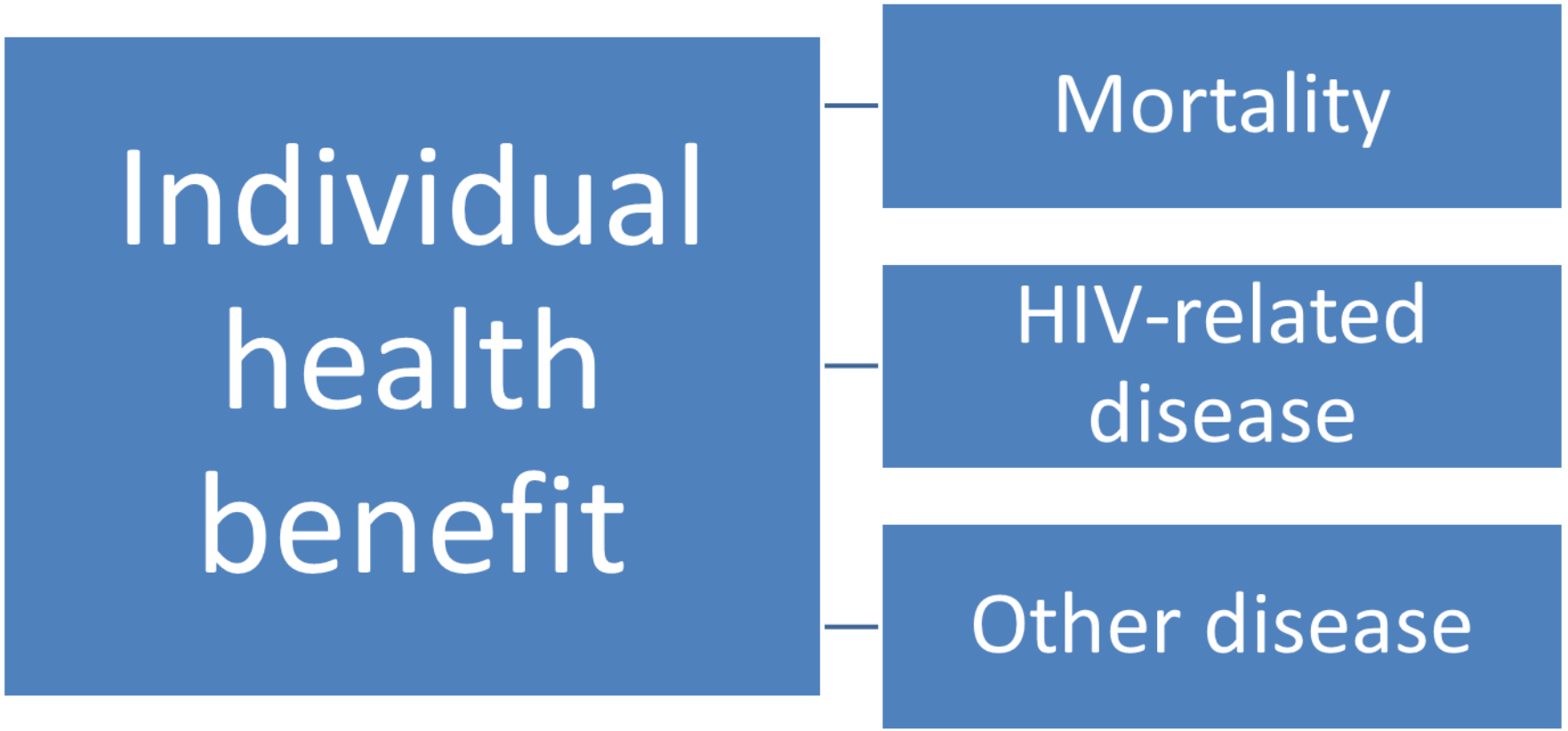
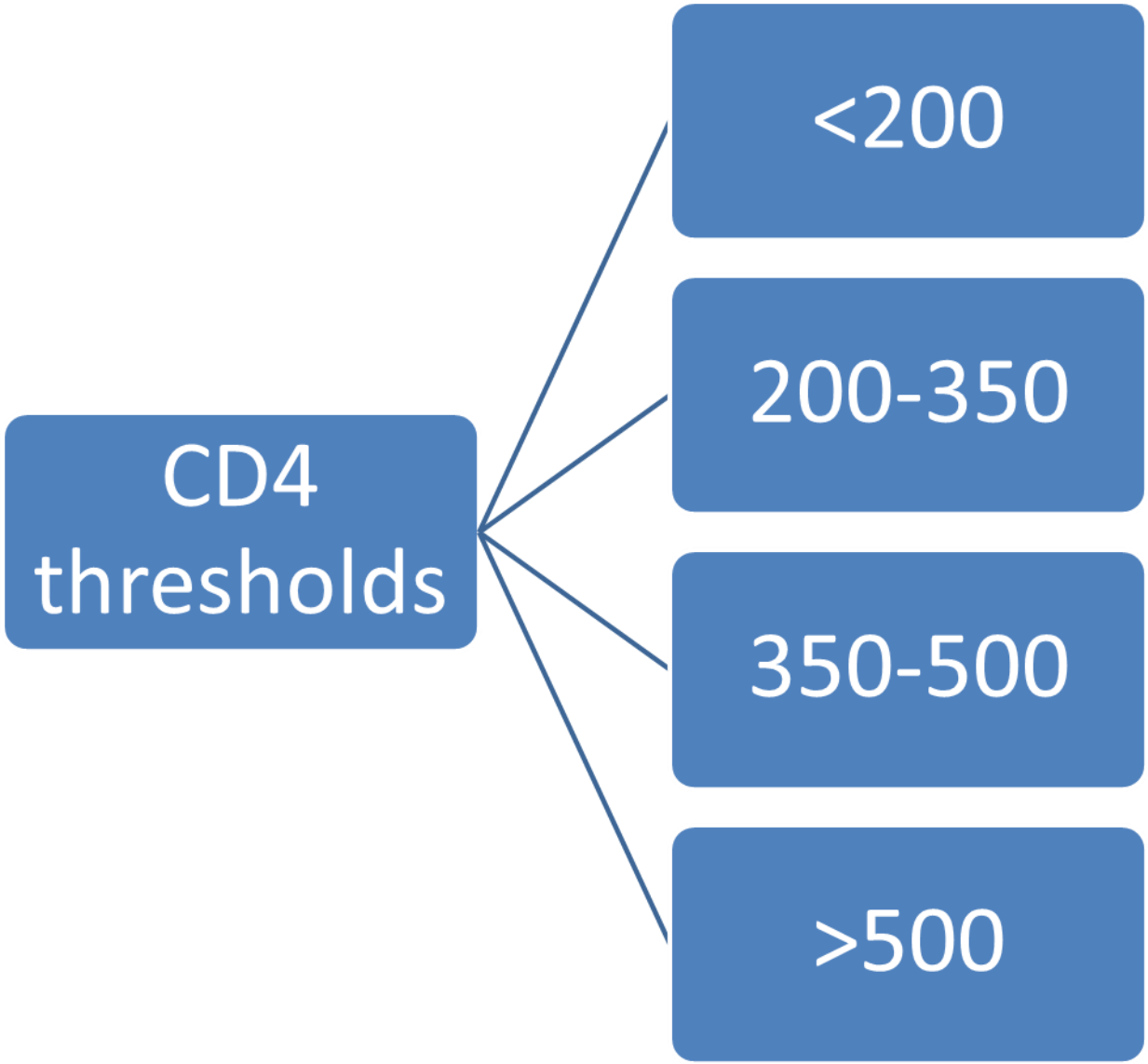
Treatment goals




Individual health benefit
Mortality
HIV-related disease
Other disease


CD4 thresholds
<200
200-350
350-500
>500

<200

- RCT and meta-analysis showing reduction in death and morbidity with combination ART

- CLEAR EVIDENCE

HIV Trialists' Collaborative Group. *Lancet*. 1999.
AIDS Clinical Trials Group 320 Study Team. *N Engl J Med.* 1997.
Zolopa A, Andersen J, Powderly W, et al. *PLoS One*. 2009.

200-350

- One RCT – CIPRA HT 001
  - Conducted in Haiti – randomized to start between 200-350 or wait to <200
  - Delay led to increased death and TB

- CLEAR EVIDENCE

Severe P, Juste MA, Ambroise A, et al. *N Engl J Med.* 2010

350-500

- Observational cohort studies
- Secondary analysis of RCTs

350-500

- Large observational **cohort studies**
- Inherently non-randomized
- Use of advanced statistical techniques to reduce the effect of bias and confounding
- Question of unmeasured confounders

		Benefit for earlier cART?	
Study	**Participants**	**Mortality**	**Mortality/AIDS**
ART-Cohort Collaboration	45691	No difference	28% reduction
NA-ACCORD	6278	41% reduction	Not measured
HIV-CAUSAL	8392	No difference	38% reduction
CASCADE	5527	49% reduction	No difference

350-500

- Secondary analysis of RCTs
- SMART
  - 249 participants naïve to ART randomized to start or wait
  - no significant difference between groups with respect to death, opportunistic disease or composite (numerically fewer, p=0.06)
- HPTN 052
  - 1763 participants – randomized to treatment
  - no significant difference in mortality (p=0.43); fewer AIDS events (p=0.031) but not “any serious event” (p=0.074)

>500

		Mortality	Morbidity/Mortality
NA-ACCORD	6278	49% reduction	Not measured
ART-Cohort Collaboration	45691	No difference	No difference
CASCADE	5527	No difference	No difference

- 2 RCT of treatment at high CD4 count – SETPOINT and Le et al (NEJM, 2013)
  - Increase in CD4 count in comparison with deferral

Hogan CM, Degruttola V, Sun X, et al. *J Infect Dis.* 2012

Summary of evidence for individual benefit from early treatment

- Strong evidence for treatment of patients with CD4<350
- Supportive evidence for patients with CD4 350-500
- No good evidence for patients with CD4>500

Are there other reasons for individual benefit for early treatment?

- Viraemia predicts clinical progression
- Failure to suppress VL when on ART predicts progression of clinical disease

- EuroSIDA collaboration looking at CD4>500 found non-AIDS events more likely to occur in high and middle strata of VL than low[1]

1 Reekie J, Gatell JM, Yust I, et al. *AIDS*. 2011

Other reasons

- Viraemia and inflammation
  - Vascular disease, malignancies, neurological disease
- Immune preservation

Treatment to prevent transmission

- Prevention of mother to child transmission
  - Very strong evidence from RCT
- Prevention of transmission to sexual partners
  - Also strong evidence from RCT - HPTN 052 (mostly heterosexuals)
  - Conference presentation from PARTNERS study - similar high rate of prevention

Pitfalls of early therapy

- Drug toxicity
- Less time to work on barriers to excellent drug adherence
- Drug resistance and impact on future therapeutic options
- Cost

Where to from here?

- Strong momentum for early treatment
- Prevention of transmission is compelling
- Safety of drugs continues to improve
- Need to pay attention to the basics of preparing the patient for the long journey

- Need to bring colleagues along