When to start ART in Children and Adolescents
2015 ARV Interim Guidelines

IATT Webinar

October 13, 2015

World Health Organization

Background & rationale

- Only 32% of HIV infected children in Sub-Saharan Africa are receiving ART compared to 42% of adults[1].

- Only 50% of HIV exposed infant receive a virological test by their first 2 months of age[1].

- Despite progress in most low- and middle-income countries, many children continue to start cART with severe immunodeficiency[2].

- Overall retention is reported to be poorer prior to ART initiation[3]

- Access to CD4 is limited and reported to be around 50% in several high burden countries[4]

- Limited evidence exists to inform treatment initiation criteria[5]

- Simplification of treatment initiation criteria appears to be critical in enabling paediatric ART scale up[4].

1. *UNAIDS 2015 and GARPR 2015*
2. *Koller et al, JAIDS 2015*
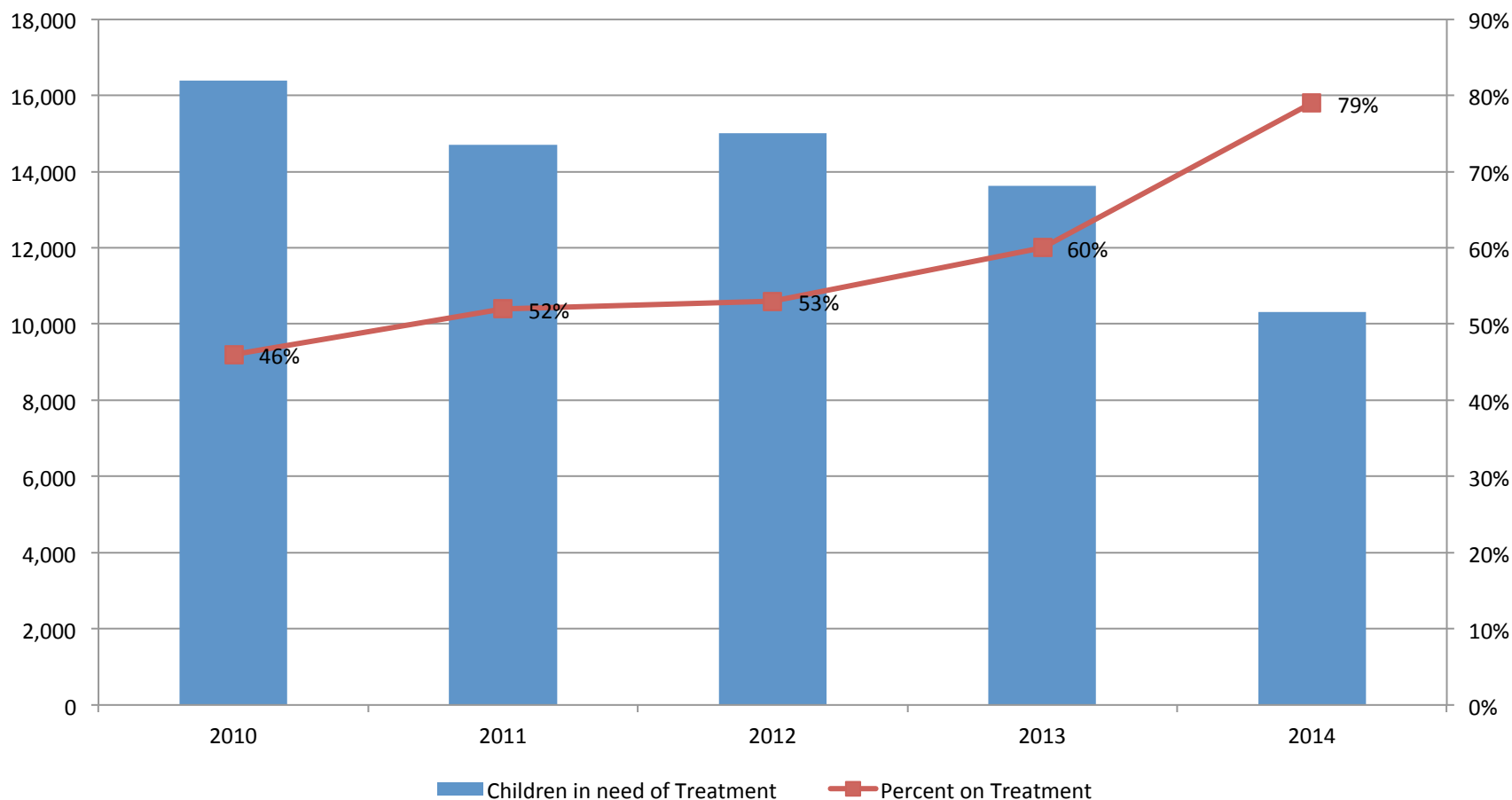3. *Kranzer et al, JIAS 2012*
4. *USAID survey 2015*
5. *Penazzato, AIDS 2014*

2013 Recommendations

AGE GROUP	2013 RECOMMENDATIONS
< 1 YEAR	Treat ALL Strong recommendation, moderate-quality evidence
1-5 YEARS	Treat ALL Priority: children < 2 years or WHO stage 3-4 or CD4 count ≤ 750 cells/ mm3 or < 25% Conditional recommendation, very-low-quality evidence
≥5 YEARS	CD4 ≤ 500 cells/mm3 Conditional recommendation, very-low-quality evidence CD4 ≤350 cells/mm³ as a priority (As in Adults) Strong recommendation, moderate-quality evidence

CHER trial

IeDea SA cohort
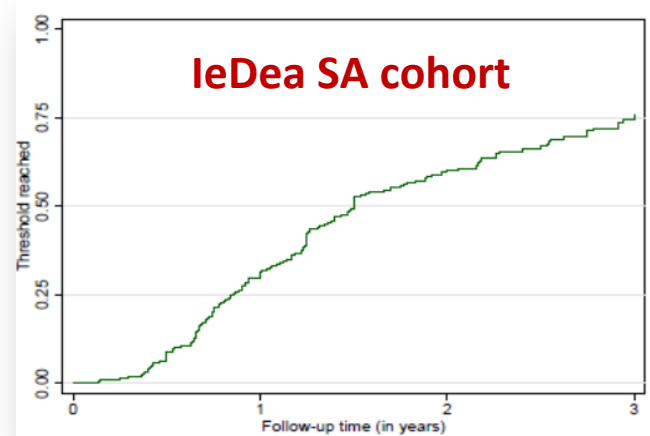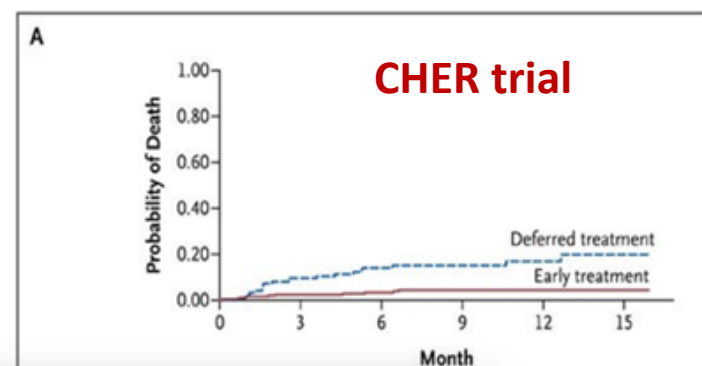
Treat ALL less than 5 years to reduce mortality and to remove barriers to ART initiation in children

Pediatric ART coverage in Rwanda

Legend: Children in need of Treatment — Percent on Treatment

Data points: 2010: 46%; 2011: 52%; 2012: 53%; 2013: 60%; 2014: 79%

Source: Rwanda TRAC Net System - Spectrum estimates 2014

- ART **coverage** in children and adolescents below 15 years lags significantly behind

- After 5 years of age the risk of **mortality and disease progression** is similar to the one estimated for adults, but HIV has been reported as second cause of mortality in adolescents globally

- Increasing evidence that ART impact **non-AIDS morbidity** such as growth and neurodevelopmental delay.

- Treatment initiation criteria recommended by WHO has been wide **adopted** in the African region (~70%)

- Limited **access to CD4 and poor WHO clinical staging** prevent treatment initiation in children and adolescents who are already eligible.

- Some countries (i.e.Uganda, Zambia, Ethiopia, Kenya) are introducing **immediate ART for children < 10 or 15 years** on programmatic grounds.

Sources of evidence

Systematic review	Modelling and Indirect evidence
Programmatic assessment	
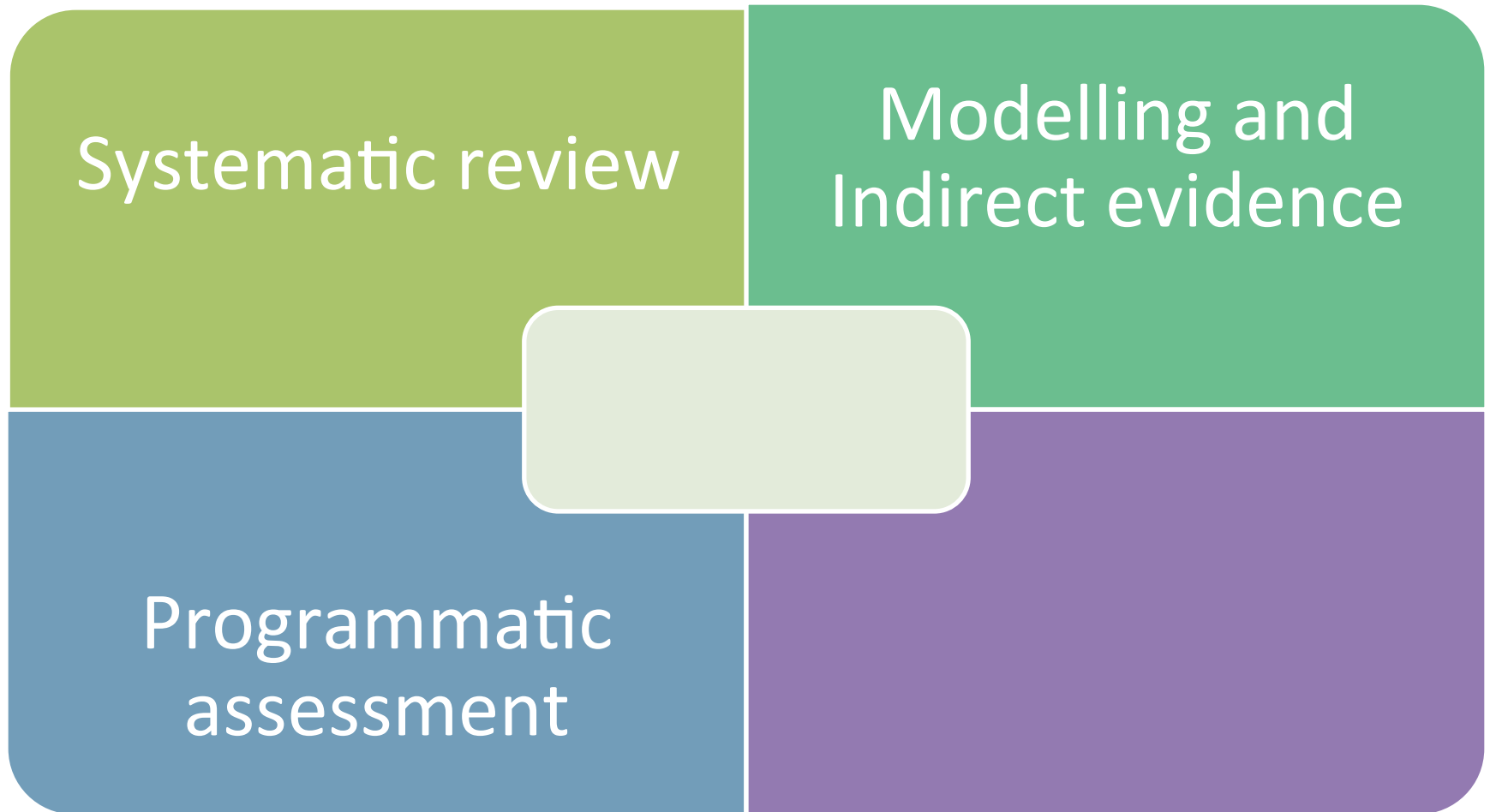
Early versus deferred antiretroviral therapy for children older than 1 year infected with HIV (PREDICT): a multicentre, randomised, open-label trial

Thanyawee Puthanakit, Vonthanak Saphonn, Jintanat Ananworanich, Pope Kosalaraksa, Rawiwan Hansudewechakul, Ung Vibol, Stephen J Kerr, Suparat Kanjanavanit, Chaiwat Ngampiyaskul, Jurai Wongsawat, Wicharn Luesomboon, Nicole Ngo-Giang-Huong, Kea Chettra, Theshinee Cheunyam, Tulathip Suwarnlerk, Sasiwimol Ubolyam, William T Shearer, Robert Paul, Lynne M Mofenson, Lawrence Fox, Matthew G Law, David A Cooper, Praphan Phanuphak, Mean Chhi Vun, Kiat Ruxrungtham, on behalf of the PREDICT Study Group

- No statistically significant difference in critical outcomes

- In PREDICT trial, small but statistically significant differences in terms of changes in weight-for age and height favouring immediate over deferred treatment

- In PREDICT, a subset of children were assessed for neurodevelopmental outcomes: children in immediate group scored better than deferred

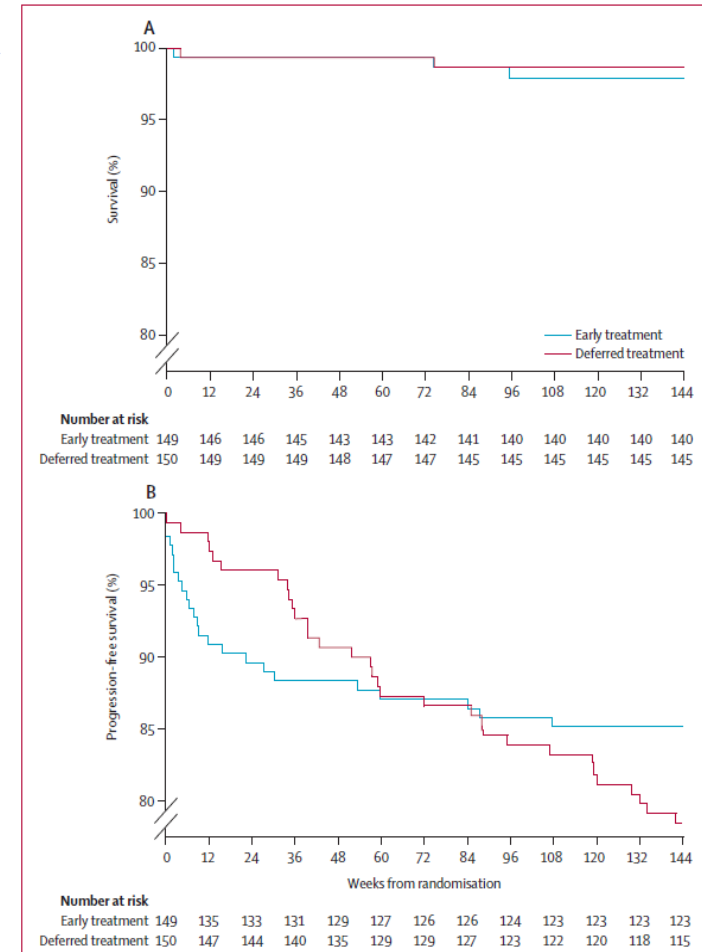- Greater % ART-related adverse events in immediate versus deferred

Figure 2: Kaplan-Meier estimates of the probability of AIDS-free survival (A) and time to the first Centers for Disease Control and Prevention category B or category C event or death (B)

QUALITY OF EVIDENCE: LOW

Causal modelling

To use observational data from children aged 5-16 years in the IeDEA-WA, IeDEA-SA and COHERE collaborations to compare

- cumulative mortality and
- growth

- We included ART naive children from 19 cohorts from West and Southern Africa and Europe

- 7,358 children aged 5-10
  (SA: 5753; WA: 1249; Europe: 356)

- 4,553 children aged 10-16
  (SA: 3729; WA: 589; Europe: 235)

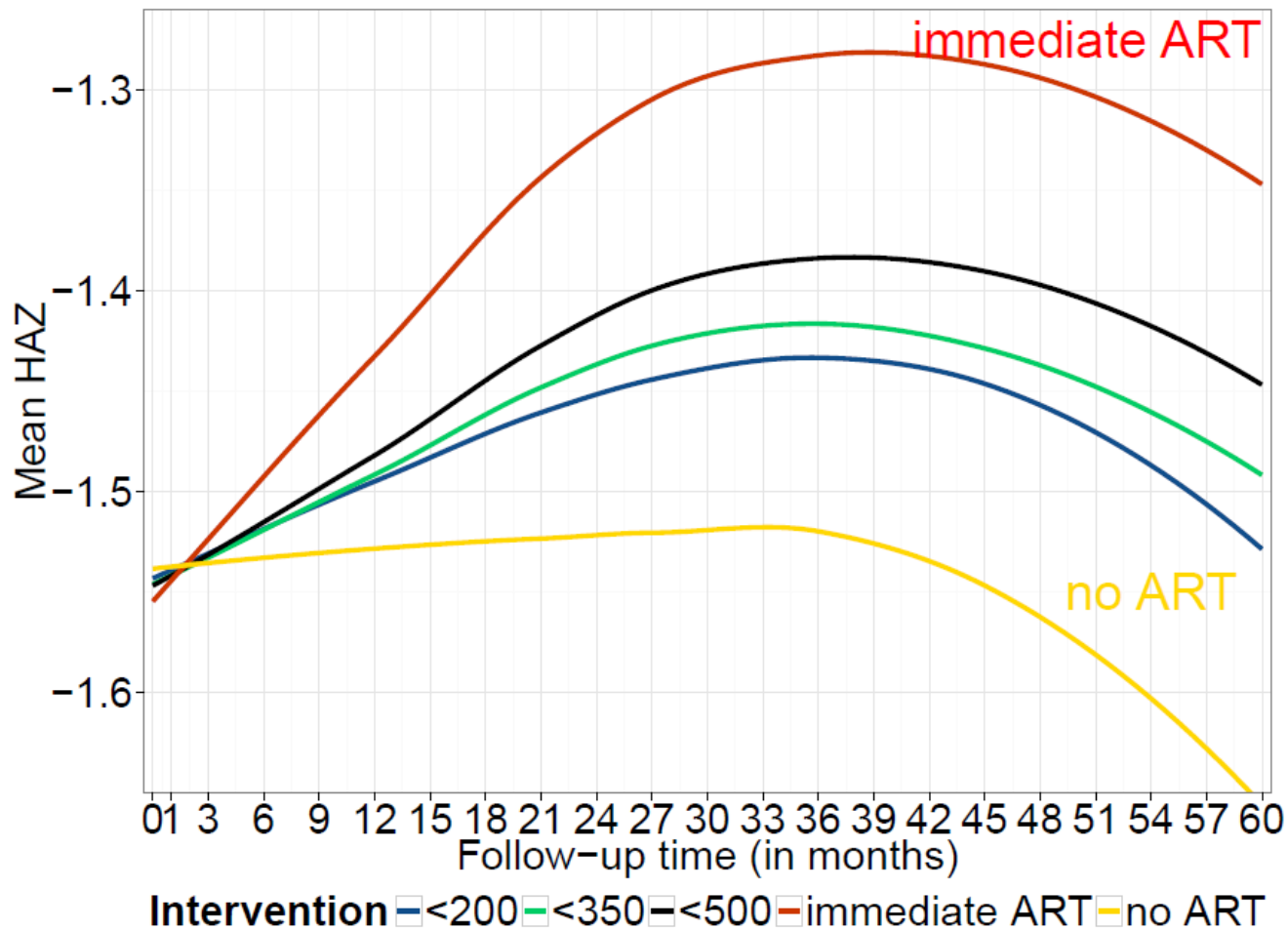# Mortality – age 5-10 – present with CD4> 500
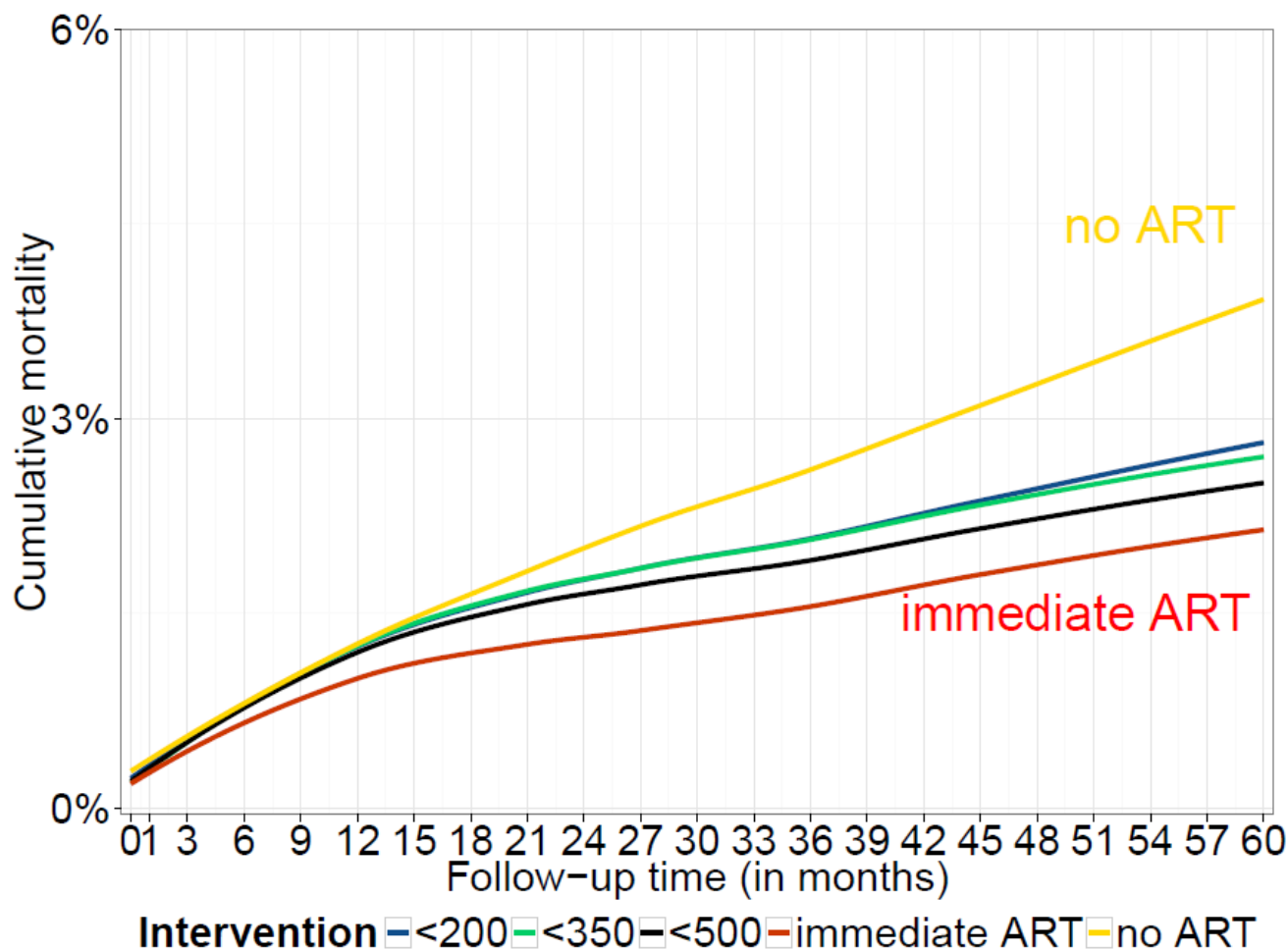
Difference 'immediate ART' to '< 500':
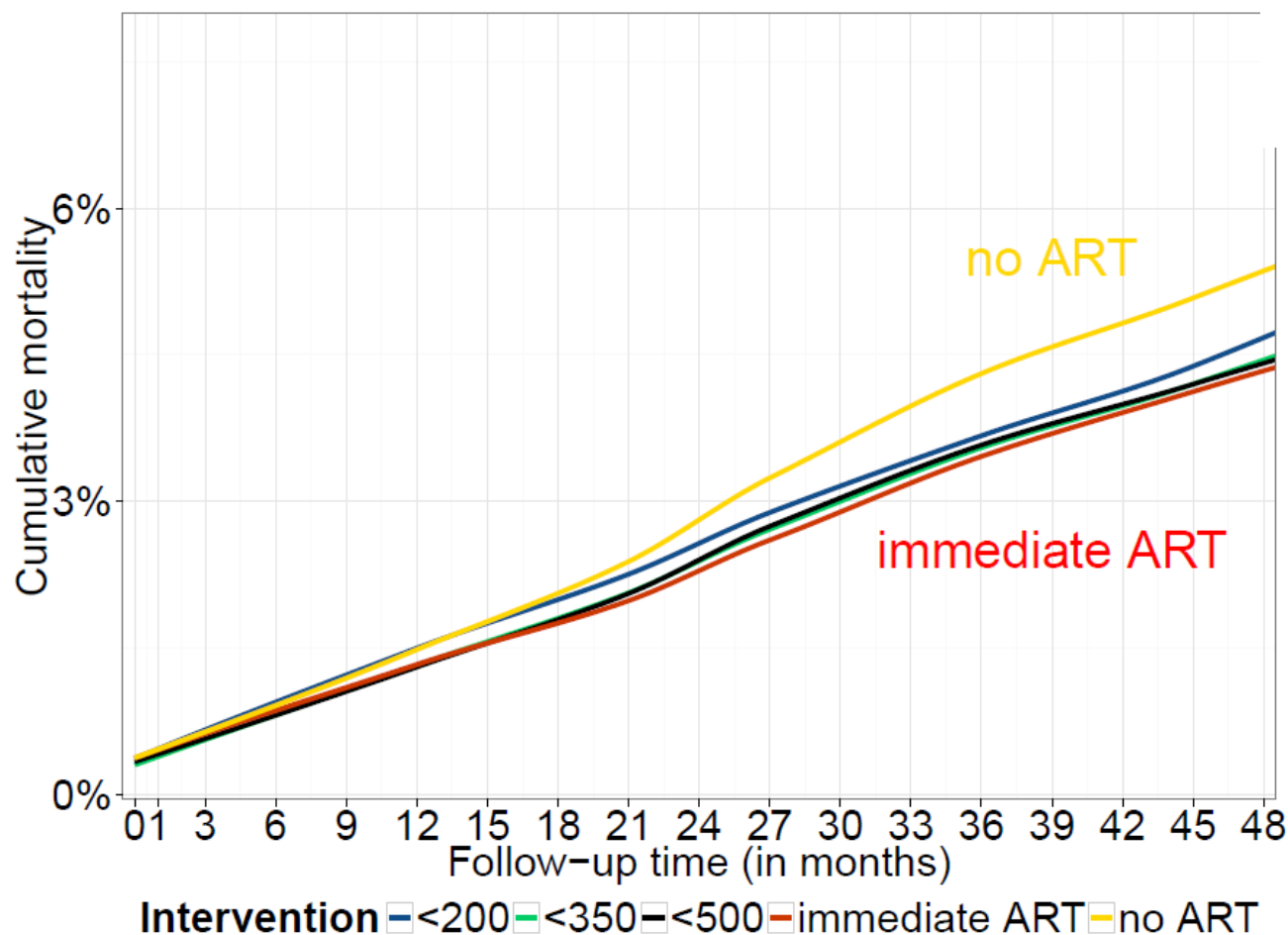   0.4% (0.02%; 0.6%)

Growth - age 5-10 – present with CD4> 500

Difference 'immediate ART' to '< 500':

0.10 (0.07; 0.12)

Mortality – age 10-16 – present with CD4> 500

Difference 'immediate ART' to '< 500':
0.1% (-0.6%; 0.9%)

Growth – age 10-16 – present with CD4> 500
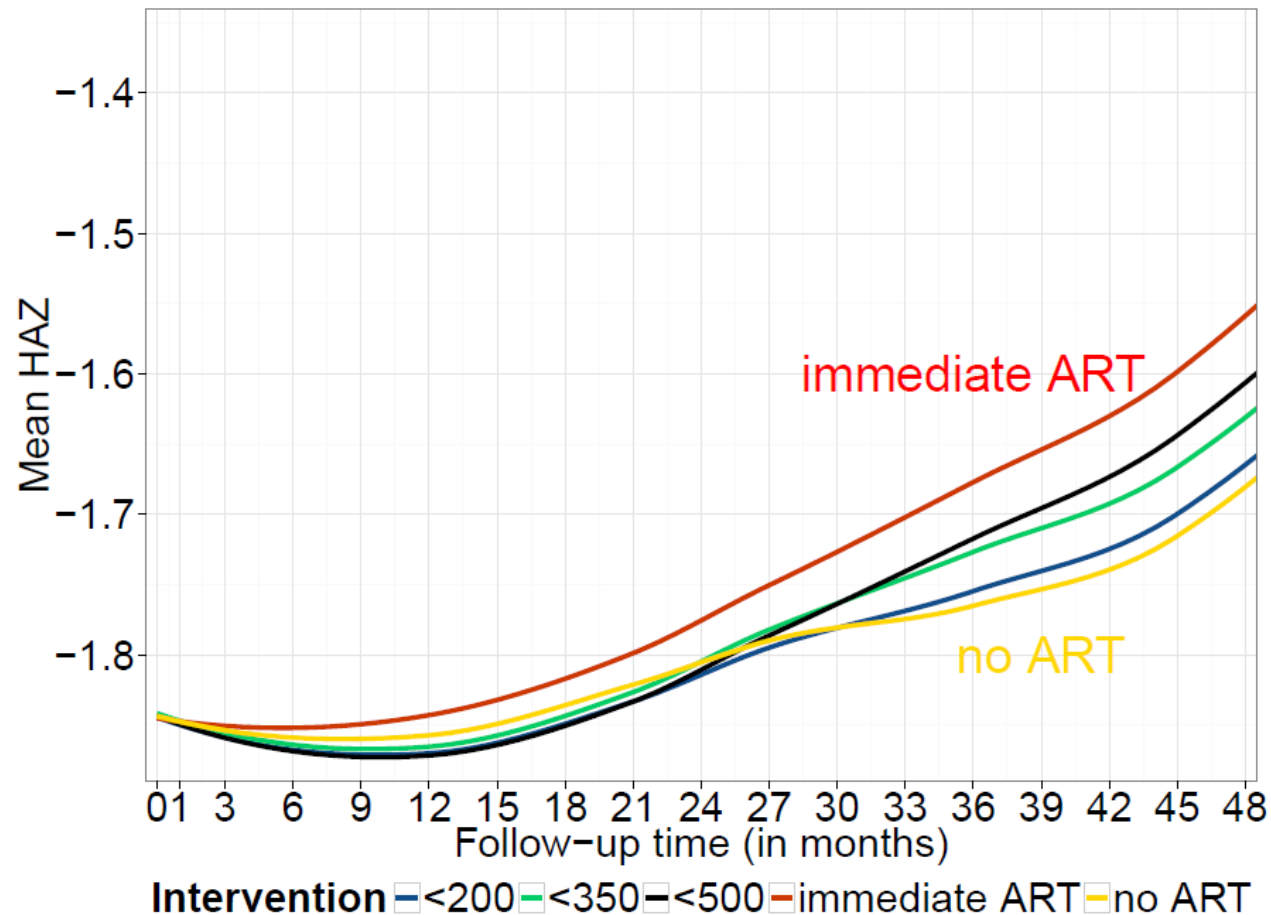
Difference 'immediate ART' to '< 500':

0.05 (-0.002; 0.10)

Conclusions

- Age 5-10: better growth response with earlier treatment initiation, possible mortality benefit for patients presenting with CD4 > 500

- Age 10-16: differences are not so clear, but also smaller sample and wider confidence intervals
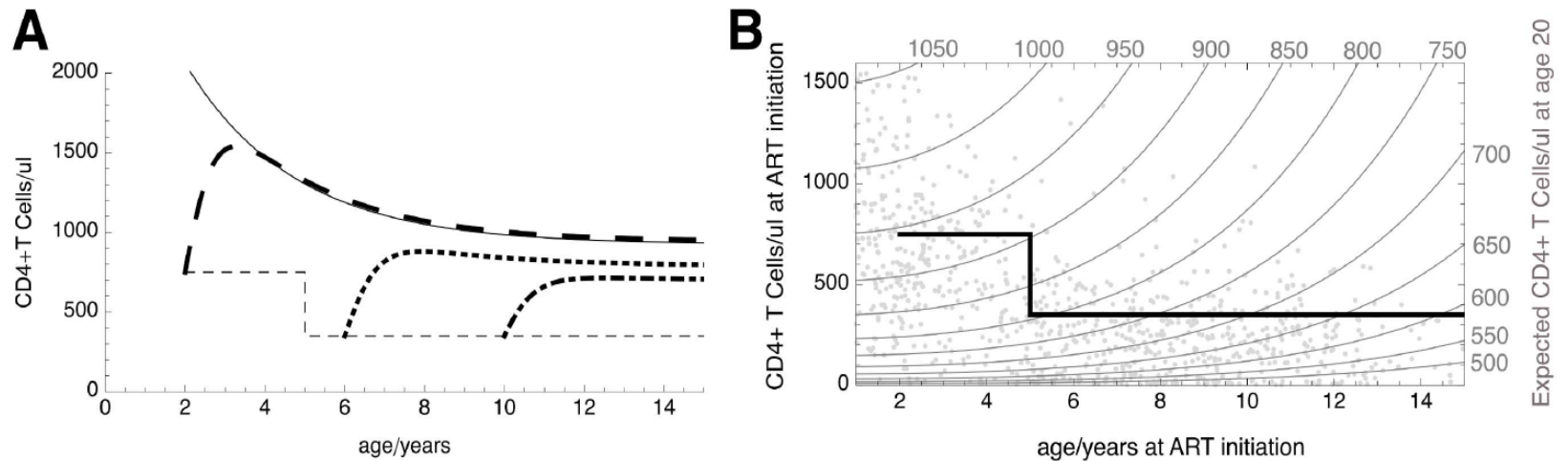
Immune Reconstitution

Figure 3. Predicted long-term CD4 counts in children starting ART at different ages and CD4 levels. (A) CD4 trajectories predicted for children starting ART having reached WHO CD4 count thresholds at age 2 (dashed line), 6 (dotted line), or 10 (dot-dashed line) y. The thin dashed line indicates WHO thresholds for ART initiation, and the thin solid line the trajectory in CD4 count with age expected in a healthy child. (B) Expected CD4 count on immunological maturity (estimated at age 20 y) for different ages and CD4 counts at ART initiation. Values at the ends of the grey contour lines indicate expected adult CD4 count in children starting ART at the ages and CD4 counts given on the horizontal and vertical axes. The black line indicates the current WHO CD4 thresholds for ART initiation. Grey point markers show the age and fitted CD4 count at ART initiation of the 914 children on whom the model is based. They indicate at which ages/CD4 counts the model has substantial evidence, and where it represents an extrapolation from the available data.
doi:10.1371/journal.pmed.1001542.g003

ARROW trial n=1206 (0.4 –17) Initiating ART in children >5 years based on current WHO criteria results in lower CD4 counts in adulthood. HIV-infected children who remain ART-naïve beyond 10 years are unlikely to normalize CD4 count

Picat, et al PLOS 2013

BENEFITS & HARMS

Growth

Growth delays among HIV infected African children (n=582) enrolled in the Arrow Trial (Szubert, AIDS 2015)

BENEFITS & HARMS
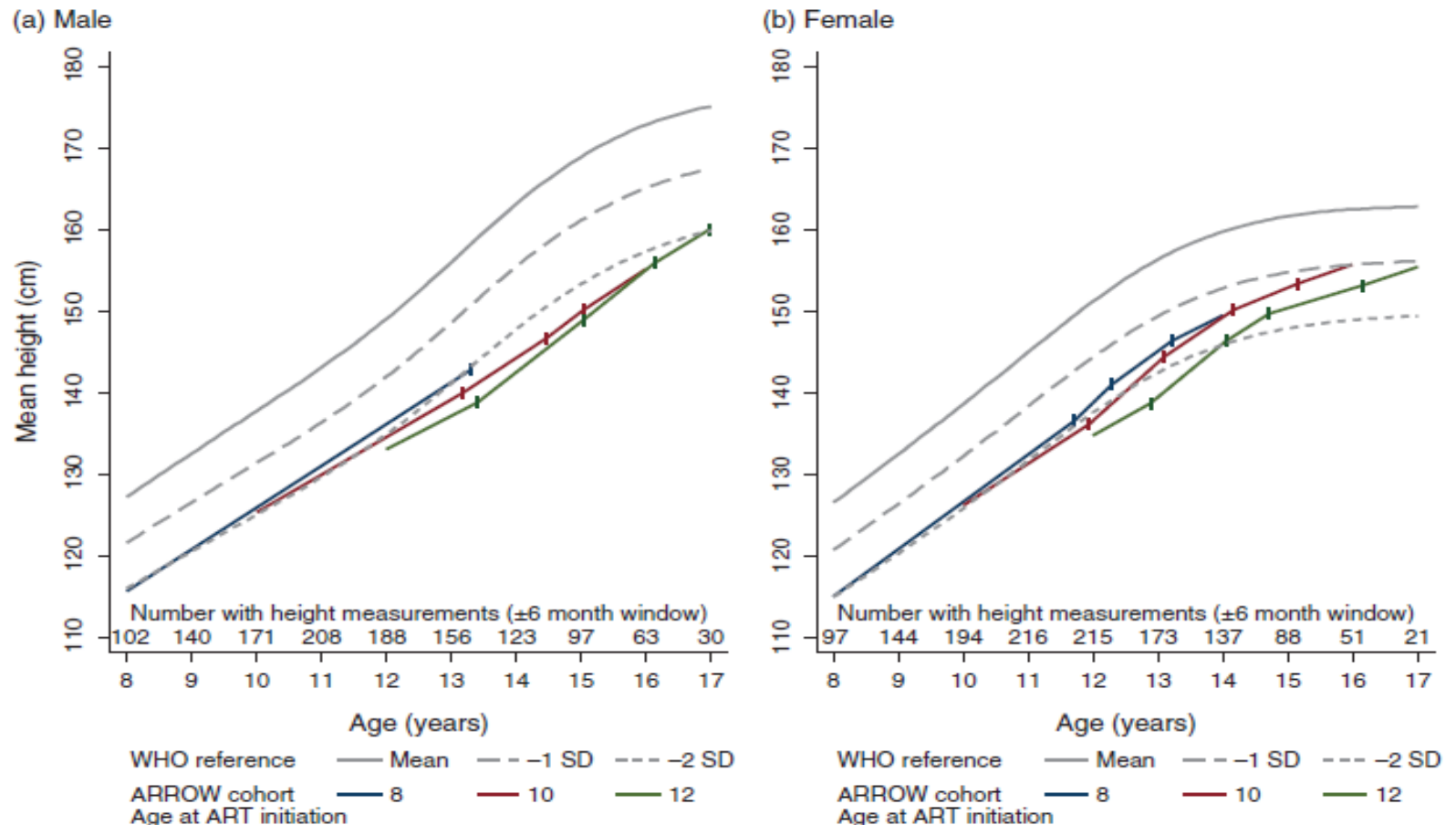
Neurodevelopment

- Early ART initiation of HIV infected children improves mortality and neurodevelopmental (ND)outcomes . (Violari A, NEJM 2008)

- HIV-infected children have worse ND outcomes compared to HIV-uninfected controls . (Ruel TD, CID 2012; Lowick S, Pscy Health Med 2012)

- Difference in ND outcomes among HIV subtypes (A < D) (Boivin et al, JAIDS 2014)

- HIV-positive children, longer duration on ARTs was associated with a reduced risk of impairment in fine motor, receptive language, expressive language and overall global Early Learning Composite score. (Brahmbhatt, JAIDS, 2014)

- Prevent premature death or loss to follow-up
- Enable better immune reconstitution
- Prevent growth delay
- Prevent puberty delay
- Improve neurocognitive outcomes
- Potentially improve school performance
- Avoid future burden to health care system with complications from untreated HIV-related complications
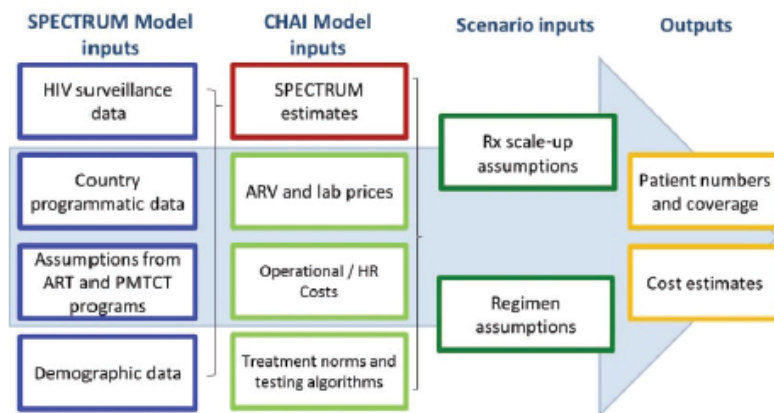
Benefits

- HIVDR
- Toxicity
- Burden on programmes

Risks
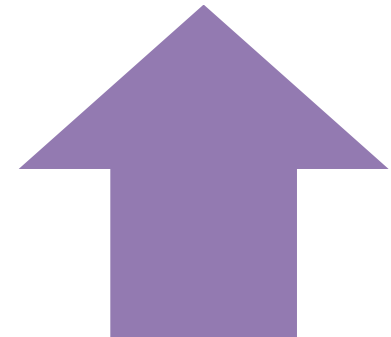
Driver of costs is ARVs

FIGURE 2: Methods overview: inputs, assumptions and outputs

FIGURE 3: Treatment scenarios

Scenario	Guidelines	Eligibility	Coverage Rate
Scenario 1	2010 Zambian Guidelines	<2 yrs or CD4 <25% / <350	No change in coverage
Scenario 2	2010 Zambian Guidelines	<2 yrs or CD4 <25% / <350	UA by 2018
Scenario 3	2013 WHO Guidelines	<5 yrs or CD4 <500	UA by 2018
Scenario 4	2013 Zambian Guidelines	<15 yrs	UA by 2015
Scenario 5	2013 Zambian Guidelines	<15 yrs	UA by 2018
Scenario 6	2013 Zambian Guidelines w/WHO	<15 yrs	UA by 2015

TABLE 3: Average Cost Per Patient Per Year (US$)

	2014	2015	2016	2017	2018	Average
0-9	480.7	495.7	507.3	519.2	530.7	506.7
10-14	337.3	342.0	345.5	350.0	351.5	345.3
15-19	236.4	242.9	248.3	255.1	261.9	248.9
0-14	440.0	448.9	455.0	460.9	464.7	453.9
0-19	402.9	411.7	415.2	418.5	419.6	413.6

TABLE 4: Costs 0-14 (US$ Millions)

	2014	2015	2016	2017	2018	Total
ARVs	39.3	50.2	50.6	50.5	49.9	240.5
CTX	1.2	1.5	1.5	1.4	1.4	7.0
Direct HR	2.4	3.0	2.8	2.8	2.7	13.8
Lab Commodities	5.9	7.5	7.5	7.5	7.3	35.7
Total	48.8	62.2	62.5	62.3	61.3	297.0

Paediatric and Adolescent Antiretroviral Treatment in Zambia: Estimating the Cost of Universal Access 2014-2018

September 2014

World Health Organization   IATT   unicef

Community Consultations
-Parents and caregivers

ACCEPTABILITY

- While motivating PLHIV to start treatment may be relatively "easy" to do, staying on and **adhering to treatment over the long terms is challenging**, particularly for children and adolescent.

- Facilities had **insufficient numbers of and trained staff** to adequately provide the care and support the treatment needs of their children.

- Services were not perceived as being "child-friendly"; service providers were sometimes **unable to deal with side-effects**; and they did not understand issues of care-giver consent.

- **Psychosocial support for parents and caregivers** is required especially to support disclosure to the child.

"I am always crying because I see my child's health deteriorating" (Parents/Caregivers, Zimbabwe)

Community Consultations
- Adolescents and Young People

ACCEPTABILITY

- Adolescents and young people voiced **being left out of decisions about treatment altogether**, often being made without their knowledge of their own status or what the treatment is for.

  - This was highlighted as a **major barrier for adherence**.

  "Most of the time I did not take my medication because I had no understanding of what I was drinking." (Adolescent, Zimbabwe)

- **Supportive and sensitive health providers, peer support** and sharing experiences especially during transition to adult services is critical for adherence for adolescents.

"Knowing that my peer became a doctor makes me feel that I can also become one." (Adolescent, Zimbabwe)

Additional unpublished literature
- Adolescent treatment and care

- Y+ global consultation, PATA facility analysis and two multi-country longitudinal qualitative studies (ARROW, BREATHER)

Key themes
- **Adherence is an ongoing challenge for adolescents**
- Forgetting and being busy are key barriers however many **complicated psychosocial issues** impact their adherence at different intensities at different times.
- There are **limited opportunity for adolescents to discuss their concerns** including those beyond ART.
- Poor adherence increases stress: worry, guilt and fear about the impact on their health and also **reaction of clinicians**.
- **Ongoing effective support is critical for adherence** –support and environments that provide opportunities for open discussion – through peers and improved attitudes of service providers.

ACCEPTABILITY

- This intervention is **expected to be feasible** since the number of children and adolescents less than 15 years that are not already eligible based on existing guidance, and current practice is expected to small.

However…

- It will likely put increased demands on supply chain systems and **increased workload** to the human resources.
- **Stock outs** have been observed in several priority countries, including Malawi, Tanzania, Uganda and Zimbabwe.
- Need to strengthen **laboratory monitoring**, particularly virological monitoring given that several children will have initiated ART without baseline CD4 testing and without clinical features of advanced disease.
- Early treatment would mean **more second and third line regimens** being used however options are still limited for children.

The experience of the Ugandan National Programme has highlighted that **despite the efforts made in planning for scale up some key challenges** were encountered. This included ensuring that commodities were available, conducting wide training and ensuring financial support to sustain the effort.

- Expanding ART services will require ensuring retention in care and should be matched with concomitant expansion of interventions to support adherence.
- Ensuring retention in care and adherence to ART , in order to maximize treatment response and minimize HIV drug resistance emergence and transmission.
- Ensuring access to services for adolescent and introducing interventions to support adolescents to remain in care and adhere to ART.
- Determining the baseline CD4 count, as a key monitoring tool to combine with clinical assessment when viral load is not available.
- Careful clinical monitoring remains an essential tool to assess the risk of failure, and lack of laboratory monitoring should therefore never be a barrier to initiating ART

IN SUMMARY….

Evidence

- **Lack of direct evidence** in support of earlier initiation (particularly for horizontally infected adolescents)[1]

- Indirect evidence suggests **reduction in mortality and improvement in growth** (particularly in children 5-10 years with CD4 >500)[2]

- A growing body of evidence demonstrates the **positive impact of ART** on growth[3], neurodevelopment[4], immunological recovery[5] and in preventing pubertal delays[6]

- Gains appear to be limited for vertically infected **adolescents**[2,5]

Mortality – age 5-10 – present with CD4 > 500

Difference 'immediate ART' to '< 500':
0.4% (0.02%; 0.6%)

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References:
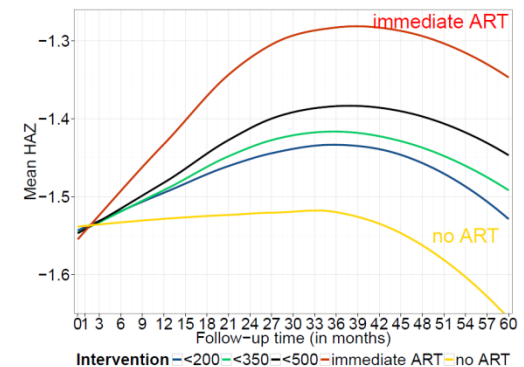1. Sigfried et al 2014   3. McGrath et al 2011   5. Picat et al 2013
2. IeDea network 2015   4. Laughton et al 2012   6. Szubert et al 2015
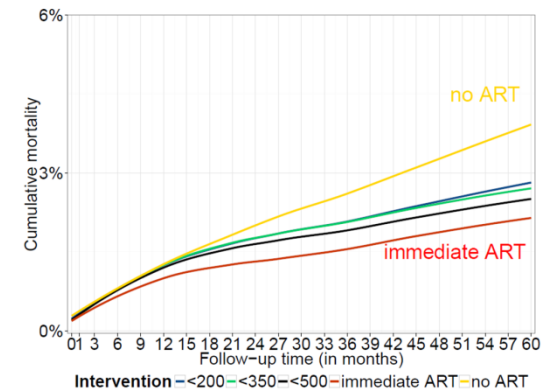
Rationale

Only ~20% are not eligible based on existing criteria

- **Eliminates the need** for determining CD4 count to initiate ART

- **Avoids delaying** ART in settings without access to CD4 testing.

- **Simplifies** paediatric treatment and facilitate expansion of paediatric ART (task-shifting and decentralization)

- Improves **retention** in care compared to pre-ART

However…need for support to adherence (particularly in adolescents), careful planning, strengthening laboratory services and improvement of procurements and supply of key commodities

Eligible for ART
146,535
83%

Not Eligible
for ART
30,413
17%

Number of Children newly initiated on ART

	Q1 2013	Q2 2013	Q3 2013	Q4 2013	Q1 2014	Q2 2014	Q3 2014	Q4 2014
5-14 yr	1158	1957	1167	983	2200	3306	4105	2719
2-4 yr	601	694	793	574	822	1048	1362	1125
<2 yr	819	979	1096	803	910	859	917	892
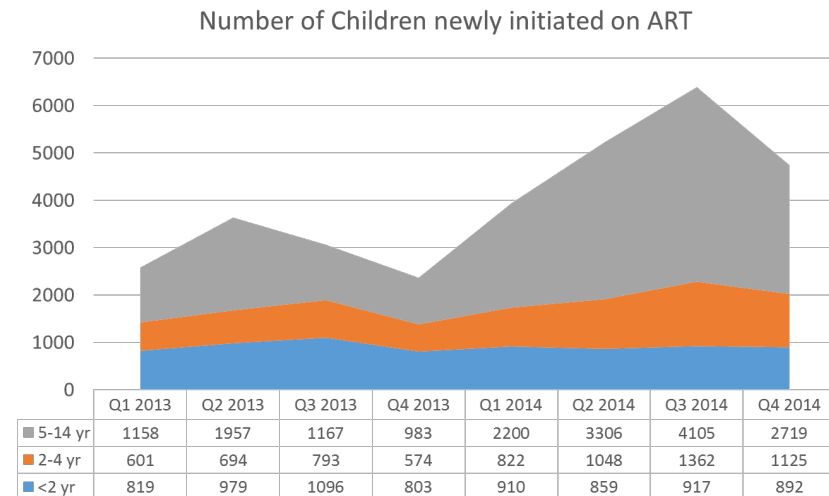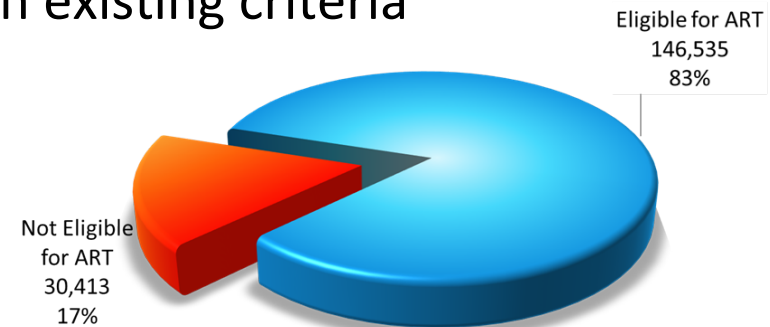
Source: Uganda National programme - Rapid assessment May 2015

Recommendations

- ART should be initiated in all adolescents with HIV regardless of WHO clinical stage and at any CD4 cell count *(conditional recommendation, low-quality evidence).*

- ART should be initiated in all children infected with HIV, regardless of WHO clinical stage or CD4 cell count
  - Infants diagnosed in the first year of life *(strong recommendation, moderate-quality evidence)*
  - Children infected with HIV one year to less than 10 years of age *(conditional recommendation, low-quality evidence).*

Age	When you start
10 years to less than 19 years	**Treat all adolescents** individuals with WHO clinical stage 3 or 4 and with CD4 count ≤ 350 cells/mm3 as a priority
1 year to less than 10 years	**Treat all children** (children ≤2 years or with WHO stage 3 or 4 or CD4 count ≤750 cells/mm³ or <25% in younger than 5 years and CD4 count ≤350 cells/mm³ in 5 years and older as a priority)
Infants (<1 year)	**Treat all infants**