HIV TREATMENT

IAS 2015 vancouver, canada

New Directions in the 2015 Consolidated ARV Guidelines Update

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19 July 2015
WHO Satellite
Vancouver – IAS 2015

World Health Organization

Objectives of Presentation

- 2015 ARV Guidelines update - why now?
- Overview of Evidence Base
- New directions in guidance

Why do we need 2015 ARV guidelines?

New Science

- Early treatment trials starting to report (TEMPRANO, START)
- Data on safety of key ARVs in specific populations

New Commodities

- New ARVs at new doses & formulations (INI, low dose EFV, DVR/r FDC)
- Treatment optimisation for children and adolescents (pellets, new strategies)

New Technologies

- Balance of POC versus standard CD4, VL and EID platforms

Rethink Service Delivery Models

- Preparation for greater numbers on ARV; improve linkage, referral, adherence approaches; Enhance efficiency and maintain quality

2015 ARV : Timeline

Evidence retrieval:
Systematic reviews
Values and preferences
Community consultations
Modelling
Dec 2014 – May 2015

Key recommendations preview
July 19 2015

Launch Full Updated 2015 Consolidated ARV Guidelines
Dec 1 2015

Core group
July 23-24 2015

Supplement launch WAD
Dec 1 2014

Core group
Oct 20-21 2014

GDG Clinical/ Operational
June 1-5 2015
June 16-19 2015

Launch Interim Guidelines on when to start and pre-exposure prophylaxis
Sept -Oct 2015

Sep | Oct | Nov | Dec | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec | Ja n

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WHO Consolidated ARV Guidelines

WHAT TO DO?

- When to start
- What to use for children, adolescents, pregnant women
- How to monitor
- Co-infections
- HIV and MH & NCDs
- PrEP

Clinical

Operational & Service Delivery

Programmatic Prioritization

HOW TO DECIDE?

- Approaches to prioritization & sequencing
- Tool kits for country adaptation and implementation

HOW TO DO IT WELL?

- Care Packages (Differentiated /Adaptive Care)
- Linkages, Retention, Adherence
- Quality of care
- Diagnostics
- Supply chain

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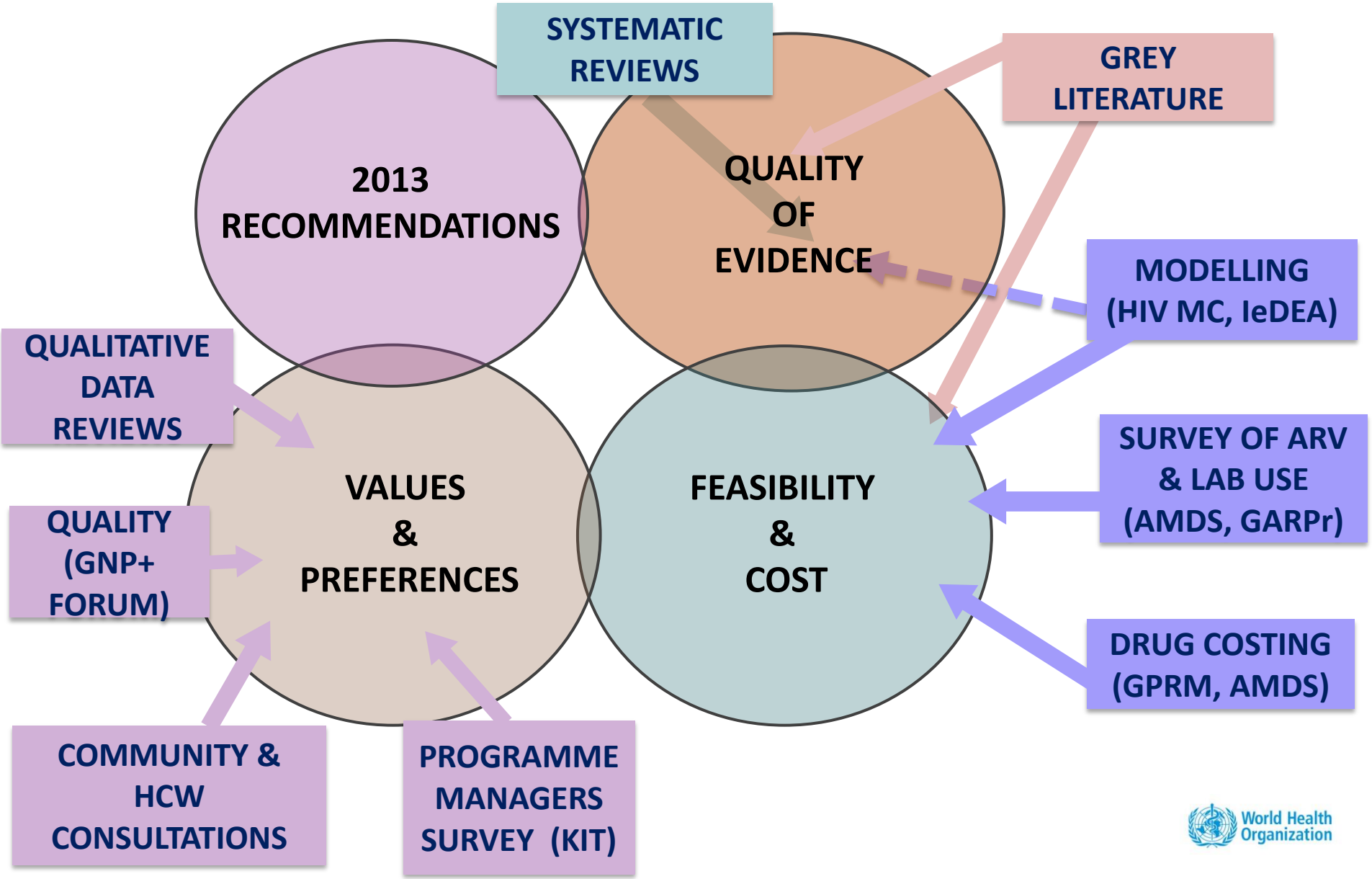
2015 ARV Guidelines Process

HIV/AIDS Department



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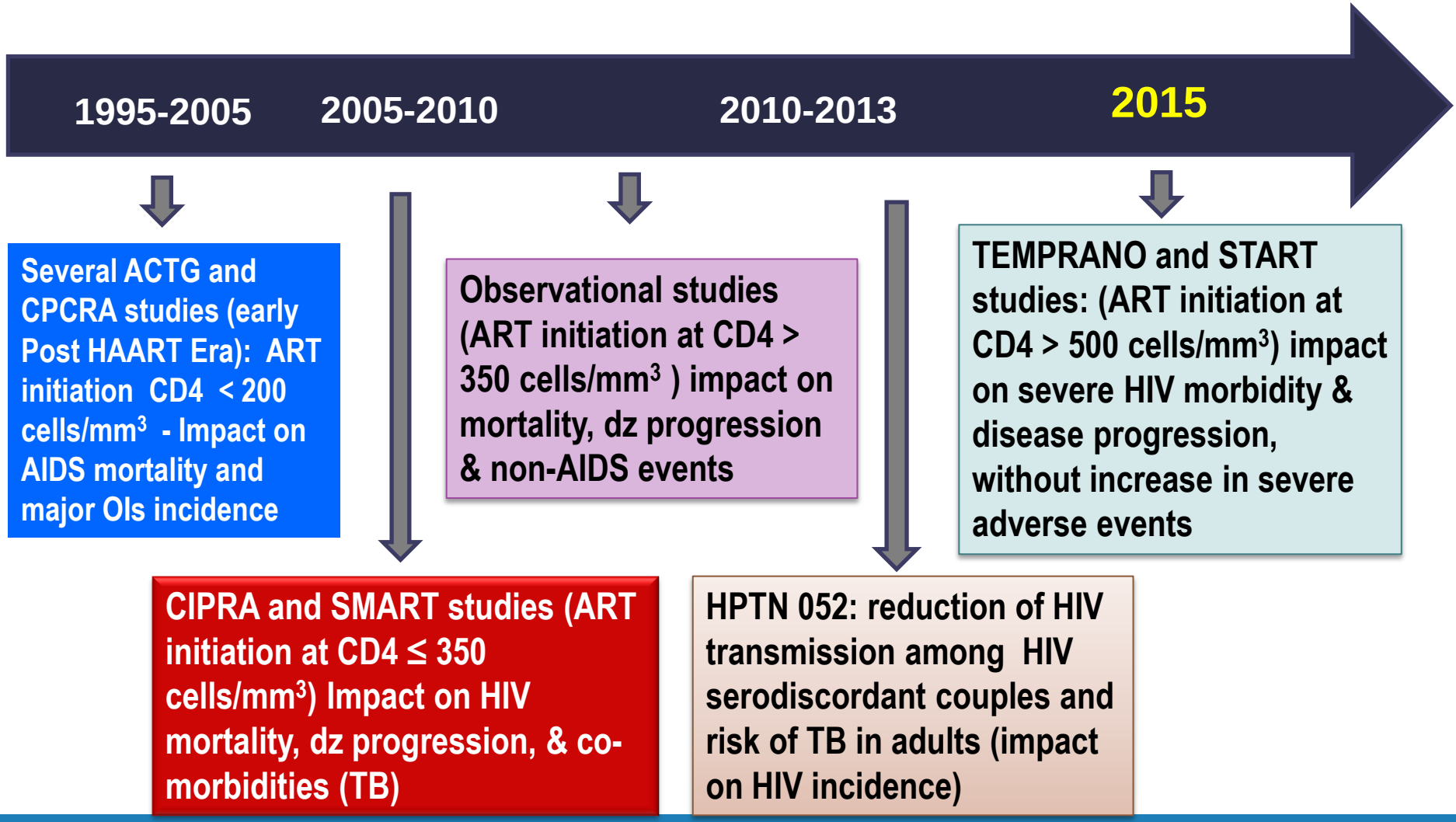
Overview of when to start ART studies



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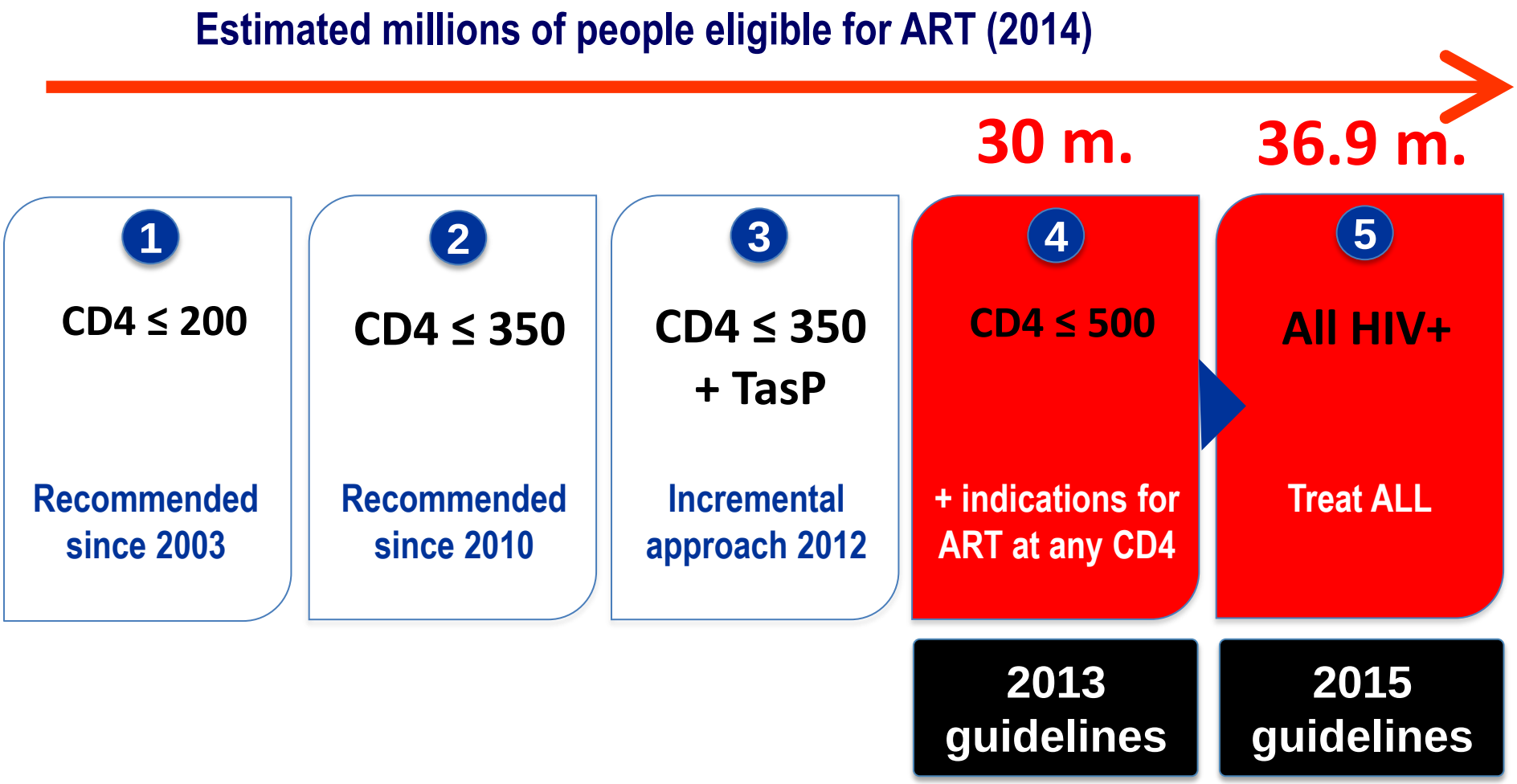
ART eligibility: 5 policy scenarios



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DIRECTIONS IN WHEN TO START

Target population	WHAT IS EXPECTED IN 2015 ART GUIDELINES?
Adults	ART initiation at any CD4 **NEW**
	As a priority, ART initiation if WHO clinical stage III/IV or CD4 ≤ 350
Pregnant/BF women	ARV initiation at any CD4 and continued lifelong (Option B+) **REVISED**
Adolescents (10-19 year old)	ART initiation at any CD4 **NEW**
	As a priority, ART initiation if WHO clinical stage III/IV or CD4 ≤ 350
Children	ART initiation at any CD4 if 1-10 years-old **NEW**
	ART initiation at any CD4 if < 1 year-old
	As a priority, ART initiation if < 2 years-old or WHO clinical stage III/IV or CD4 < 25% (< 5 years) or ≤ 350 (>5 years)

Evidence Summary: When to Start in Adults

- **Systematic Review of 18 eligible studies** (1 RCT and 17 observational cohorts)
- Some observational studies reported **results from a single cohort** (6 studies)
- **Outcomes reported:**

✓ **Mortality**

✓ **Severe HIV disease**

✓ **HIV disease progression**

✓ **AIDS events**

✓ **Non-AIDS events**

✓ **Malignancy (AIDS and non AIDS)**

✓ **Tuberculosis**

✓ **HIV transmission**

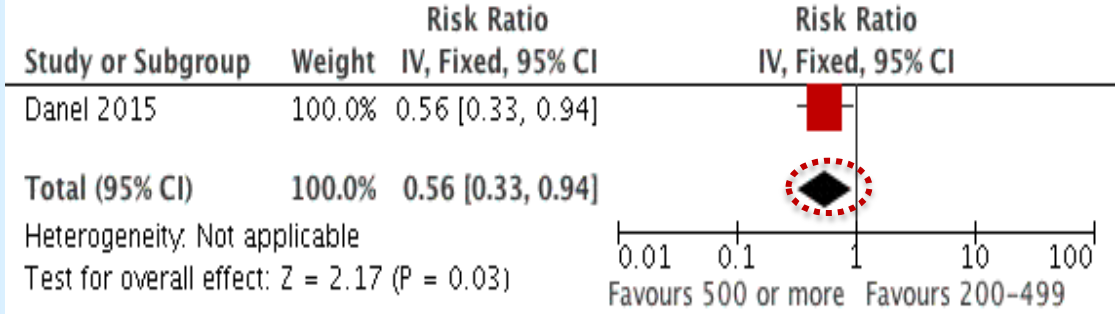
✓ **SAE and lab abnormalities**

✓ **Severe HIV disease or malignancy or mortality (combined outcome)**

Evidence Summary: Risk of death, severe HIV disease or HIV disease progression

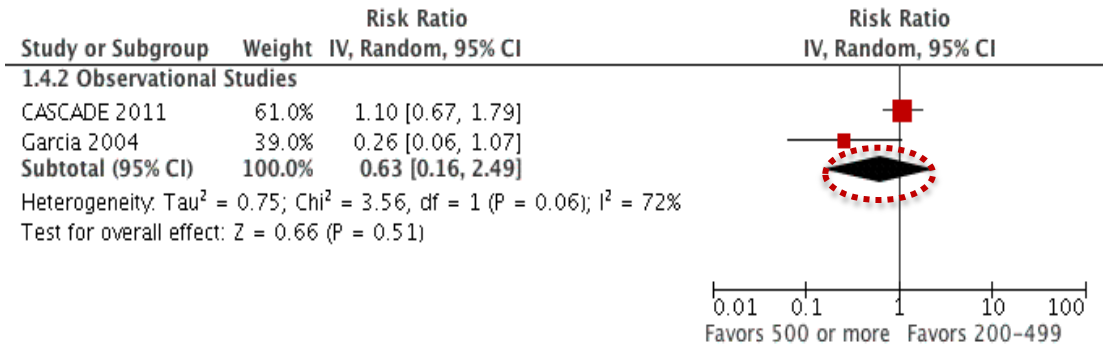
Clinical trials

Evidence for lower risk **of death, severe HIV disease or malignancy** compared to those deferring treatment **(1 study TEMPRANO)**



Observational studies

Evidence for lower risk of **death or progression to AIDS** compared to those deferring treatment **(2 studies)**



CI confidence interval; df, degrees of freedom; IV, inverse variance; RCT, randomised controlled trial

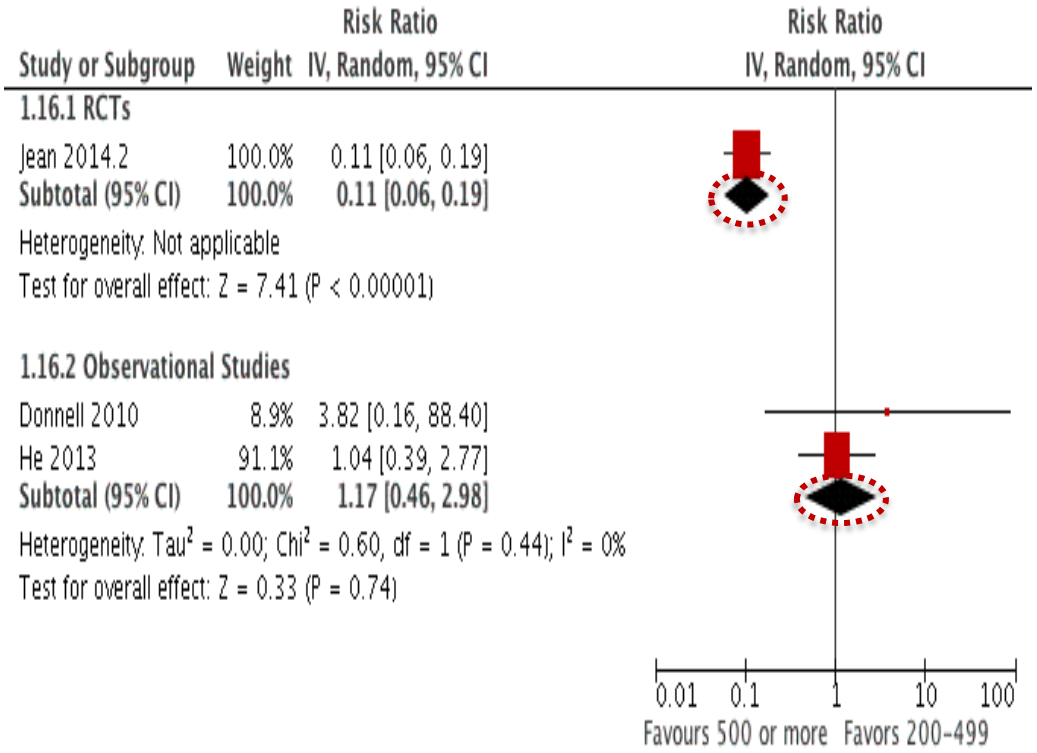
Evidence Summary: Risk of HIV transmission

Clinical Trial (1 RCT)

Evidence for lower risk of HIV transmission compared to those deferring treatment

Observational studies

Evidence for no significant difference in the risk of HIV transmission between early vs deferred treatment (**2 studies**)



CI confidence interval; IV, inverse variance; RCT, randomised controlled trial

WHEN TO START EVIDENCE

Evidence Summary: Risk of Hepatic & Renal SAE or any grade III/IV SAE

Clinical trial

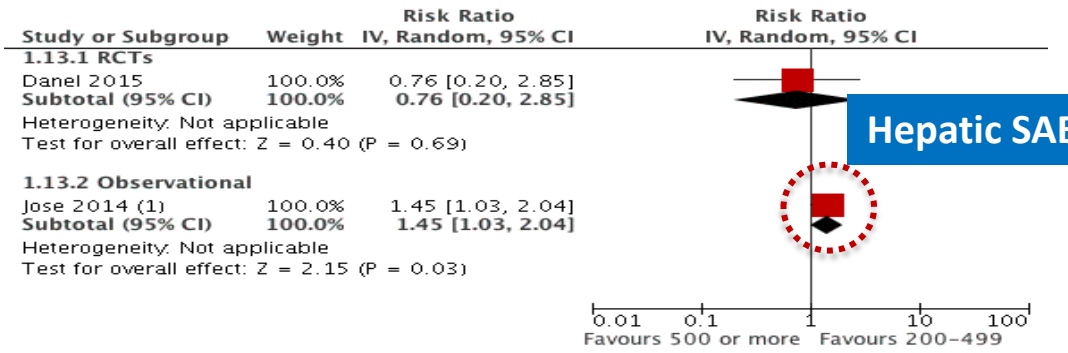
no increased risk of hepatic and renal SAE between early vs deferred treatment **(1 study)**

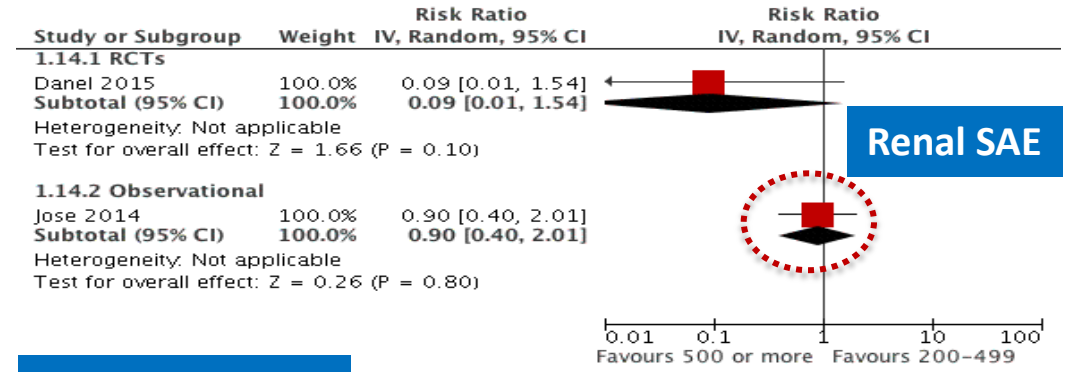
Observational studies

increased risk of hepatic SAE compared to those deferring treatment but no increased risk for renal SAE **(1 study)**

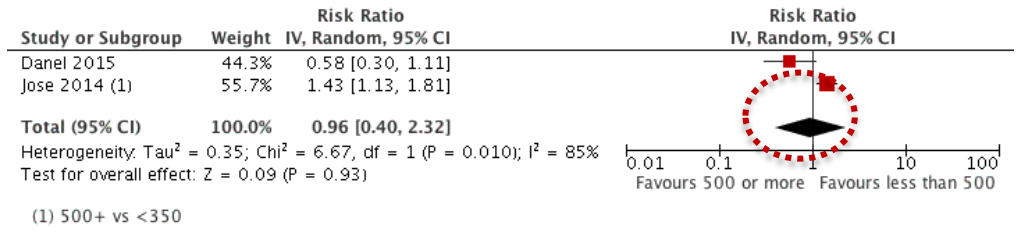
Combined

No increased risk of any grade 3 / 4 SAE between early and deferring treatment (**2 studies)**





Grade 3 / 4 SAEs



CI confidence interval; IV, inverse variance; RCT, randomised controlled trial

When to Start in Adults: Evidence Summary

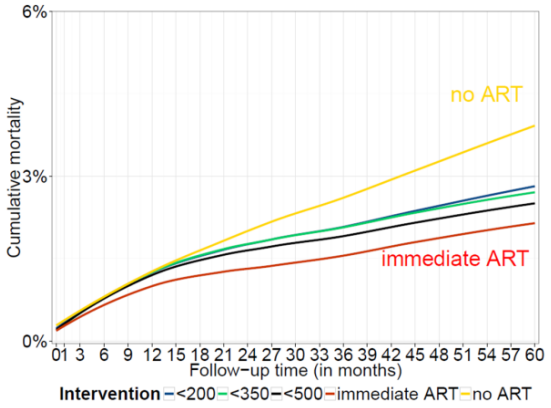
- Systematic review on when to start ART in asymptomatic PLHIV found 1 RCT and 17 cohorts or meta-analyses of cohorts reporting on 8 separate outcomes in patients with <500 CD4 and ≥500 CD4 cells/µL

- Clinical benefits of ART initiation over 500 CD4 to all PLHIV compared with < 500 CD4 initiation,
  - with reduction of severe HIV morbidity, HIV disease progression and HIV transmission,
  - without increase in grade III/IV adverse events.

Evidence for Children & Adolescents

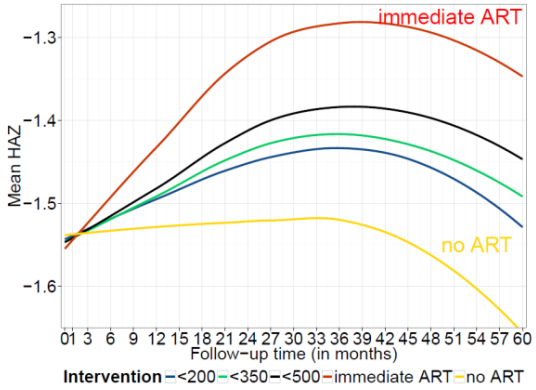
- **Lack of direct evidence** in support of earlier initiation (particularly for horizontally infected adolescents)[1]
- Indirect evidence suggests **reduction in mortality and improvement in growth** (particularly in children 5-10 years with CD4 >500)[2]
- A growing body of evidence demonstrates the **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%)

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



Difference 'immediate ART' to '< 500':
0.10 (0.07; 0.12)

References:

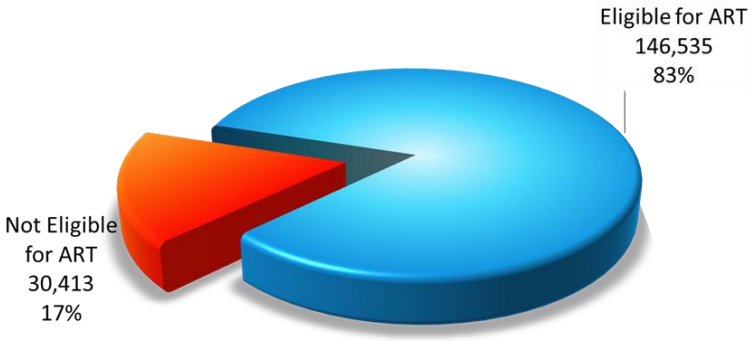
1. Sigfried et al 2014
2. IeDea network 2015
3. McGrath et al 2011
4. Laughton et al 2012
5. Picat et al 2013
6. Szubert et al 2015

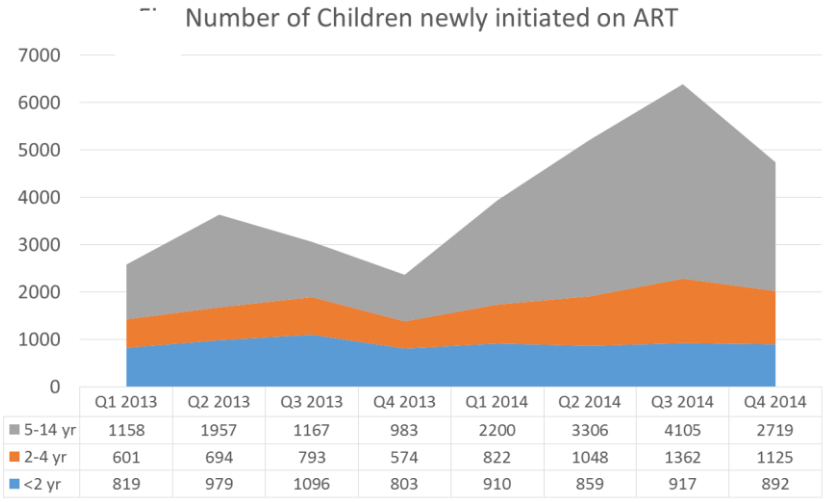
WHEN TO START - EVIDENCE

Programmatic Rationale Children and Adolescents

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





	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

Need adherence support (particularly in adolescents), careful planning, strengthening laboratory services and improvement of procurements and supply of key commodities

ce: Uganda National programme - Rapid assessment May 2015

ACCEPTABILITY

Community – led Global Consultation:

AFROCAB ICW VIA LIBRE Pangaea APN PLUS POSITIVE CHANGE EATG European AIDS Treatment Group AHF UKRAINE

Acceptability of Earlier Initiation of ART

- 24 workshops, 8 countries, 8 sub populations, 206 people living with HIV, 74 service providers.
- Earlier initiation was deemed **acceptable**, specific considerations were highlighted
- **Collaborative decision-making** with the ultimate decision to initiate ART being client-driven
- The requirement for **comprehensive and accurate information** to ensure an informed decision as well as readiness
- Initiating ART is relatively easy however **maintaining adherence is challenging**
- **Stigma and discrimination** were uniformly raised as fundamental concerns by all and seen to constrain treatment access and adherence

WHO guidance on PrEP: 2012 – 2015

2012

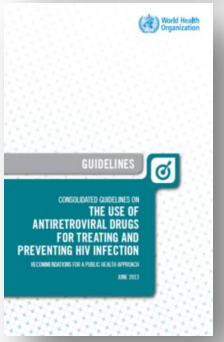
Guidance for MSM & Serodiscordant Couples in the context of demonstration projects

to encourage countries to conduct such demonstration projects

2014

Consolidated Key Populations Guidelines - *Recommendation for MSM*

Among men who have sex with men, PrEP is recommended as an additional HIV prevention choice within a comprehensive HIV prevention package



2015

Oral PrEP (containing TDF) should be offered as **an additional prevention choice** for people at **substantial risk** of HIV infection as part of **combination prevention approaches**

- Not population specific
- *Significant HIV risk* means HIV incidence > 3 per 100 py

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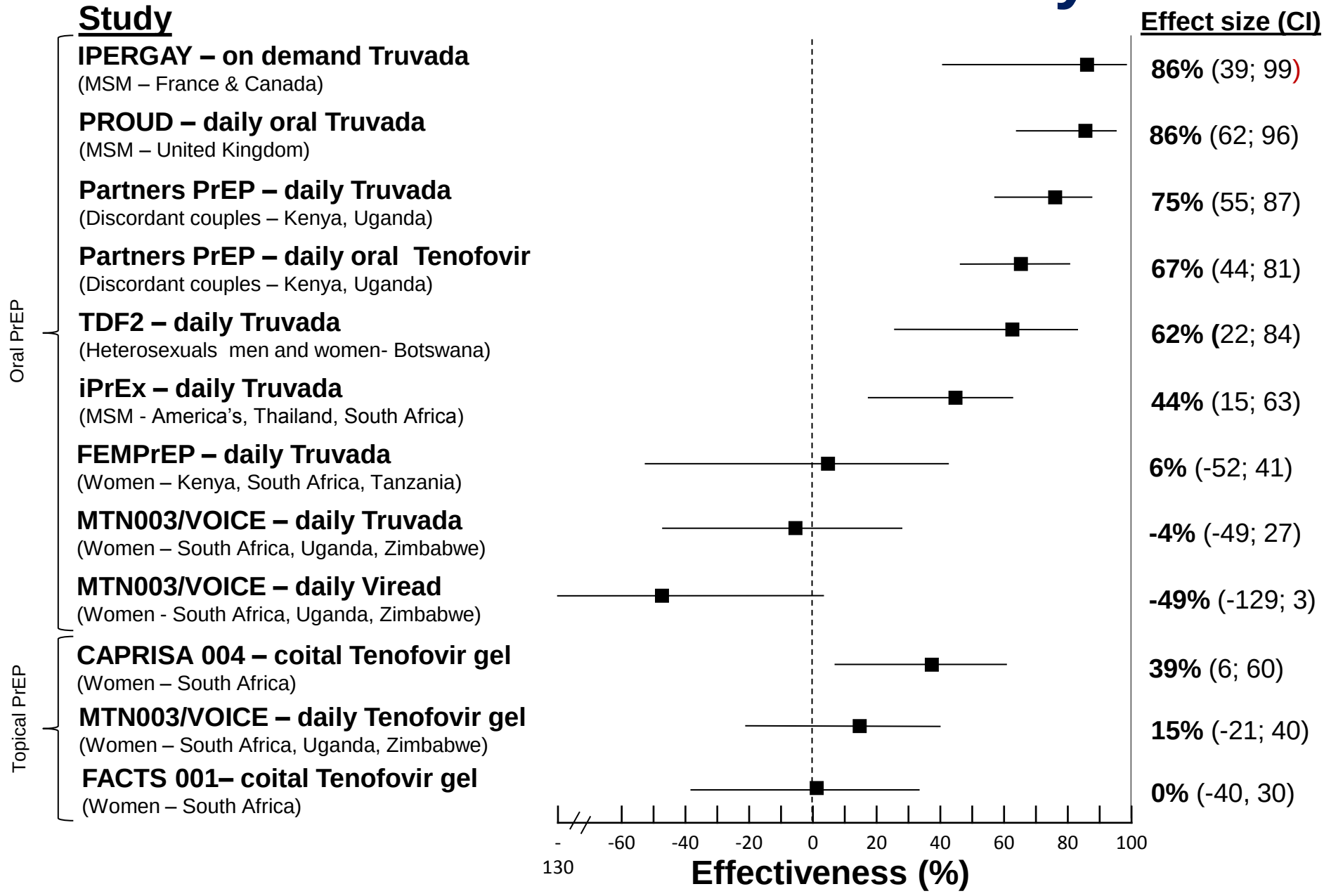
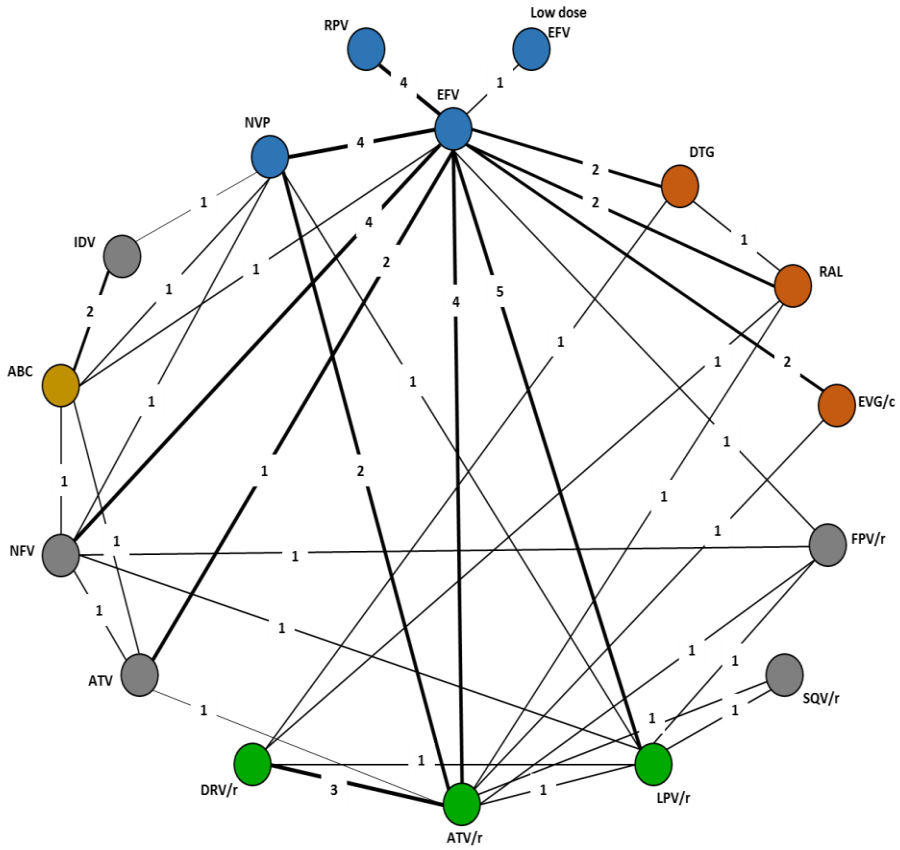
Overall evidence for PrEP: July 2015



What to use in first line ARV Therapy



Edward Mills, Steve Kanters, M. Eugenia Socias, For WHO ARV GDG, June 1-5 2015

- **systematic review using a comparative pairwise and network meta-analysis** evaluated 76 trials for direct and indirect evidence
  - 35,270 patients randomized to 171 treatment arms
- **Direct evidence for comparative efficacy and safety of INSTIs compared to EFV** was obtained from 6 RCTs
  - SINGLE, PROTOCOL 004, GS 102 study, GS 104 study, SPRING-1 and STARTMRK.
- The evidence on low dose EFV (EFV 400) came from ENCORE 1.

Directions of the Systematic Review

Edward Mills, Steve Kanters, M. Eugenia Socias, For WHO ARV GDG, June 1-5 2015

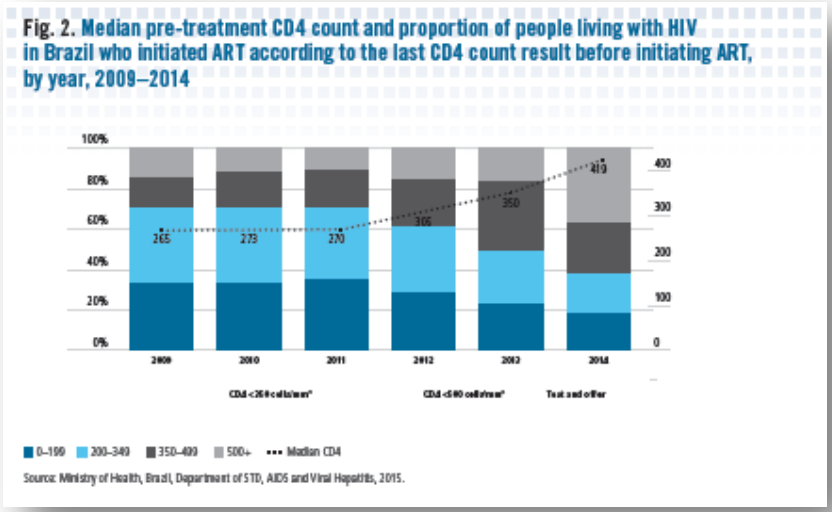
- All treatment regimens are comparable with respect to mortality or AIDS defining illnesses.
- Evidence that DTG and EFV400 superior with respect CD4 recovery at 24, 48 and 96 weeks
- INSTIs (DTG > RAL) are more effective than EFV and other regimens for viral suppression at 24, 48 and 96 weeks.
- All treatments tend to be comparable in terms of emergent serious adverse events, with exception of NVP (elevated risk)
- Limitation: Minimal data on DTG + TDF + XTC (SPRING-2)

What will be new in the 2015 ARV guidelines?

- Treat all (at any CD4) - people living with HIV across all ages
- The sickest remain a priority (symptomatic disease and CD4< 350)
- New age band for Adolescents (age 10-19)
- Option B not taken forward; Option B+ as the new standard
- Placement of INSTIs (DTG) and dose reduction options in 1st and 2nd line therapy
- PrEP recommended as an additional prevention choice for all people at substantial risk of HIV infection (> 3% incidence)

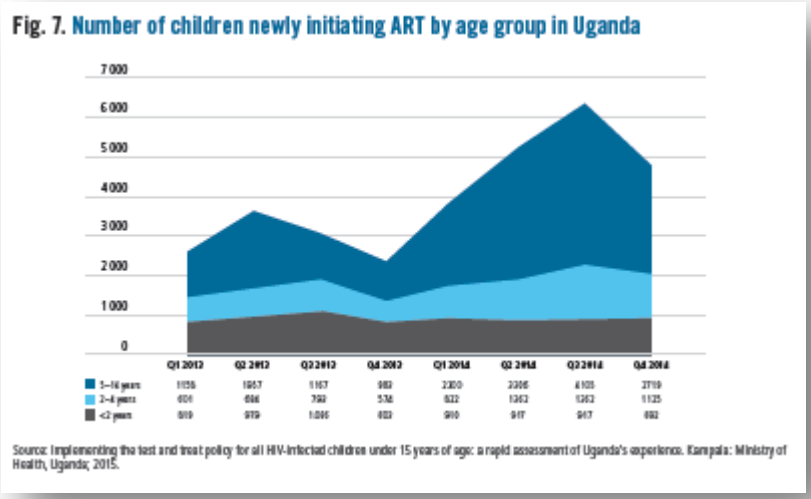
Countries are leading the way

Examples from five countries implementing Treat All or Treating All in specific populations:



- Brazil has been treating all for one year
- Leading to increase in median CD4 at ART initiation (265 to 419)
- Similar retention and VLS at 12 months (81% for CD4 > 500)

- Uganda started to treat all children < 15 years in 2014
- Seen increase in overall number children on ART
- Retention at 12 m similar; VLS = 84%



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Acknowledgements

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Avenir Health

CDC

PEPFAR

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WHO ARV Guidelines Evolution 2002 to 2015

Topic	2002	2003	2006	2010	2013	2015
When to start	CD4 ≤200	CD4 ≤ 200	CD4 ≤ 200 - Consider 350 - CD4 ≤ 350 for TB	CD4 ≤ 350 -Regardless CD4 for TB and HBV	CD4 ≤ 500 - Regardless CD4 for TB, HBV PW and SDC - CD4 ≤ 350 as	**Towards Treat All Adolescents age band**
Earlier initiation						
1st Line ART	8 options - AZT preferred	4 options - AZT preferred	8 options - AZT or TDF preferred - d4T dose reduction	6 options & FDCs - AZT or TDF preferred - d4T phase out	1 preferred option & FDCs - TDF and EFV preferred across all pops	**Continue with FDC and harmonization across age bands**
Simpler treatment						
2nd Line ART	Boosted and non-boosted PIs	Boosted PIs -IDV/r LPV/r, SQV/r	Boosted PI - ATV/r, DRV/r, FPV/r LPV/r, SQV/r	Boosted PI - Heat stable FDC: ATV/r, LPV/r	Boosted PIs - Heat stable FDC: ATV/r, LPV/r	**Greater number of options**
Less toxic, more robust regimens						
3rd Line ART	None	None	None	DRV/r, RAL, ETV	DRV/r, RAL, ETV	**Encourage HIV DR to guide**
Viral Load Testing	No	No (Desirable)	Yes (Tertiary centers)	Yes (Phase in approach)	Yes (preferred for monitoring, use of PoC, DBS)	**Support for scale up of VL using all technologies**
Better and simpler monitoringz						