WHO's Early Release Guidelines

When to Start and PreP

IATT Webinar

October 13, 2015

World Health Organization

Contents of this Webinar

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New guidelines recommend universal ART for pregnant and breastfeeding women

ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong

Strong recommendation, moderate-quality evidence

- *In 2010 we had Option A and B*
- *In 2013 Option A was no longer recommended and we had Option B and B+*
- *Now lifelong ART is recommended not only for pregnant and breastfeeding women but also for ALL people diagnosed with HIV Therefore, the new guidelines do not speak of "options" but "universal ART"*
- *But the rationale behind this isn't from PMTCT literature….*

Temprano is one of the key studies that has driven the recommendation for universal ART

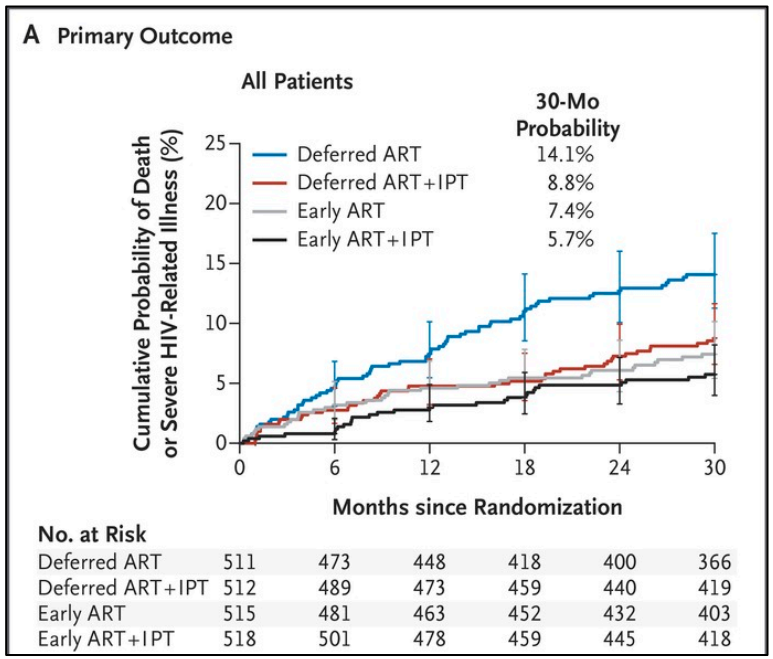
- Multi-centre RCT looking at immediate ART vs. WHO-guided ART
  - Isoniazid preventive therapy (IPT) vs. no IPT
- 9 centres in Abidjan, Côte d'Ivoire
- Well Asymptomatic HIV+ adults with CD4 <800 cells/µL, randomized to 4 arms

1 WHO-guided ART, no IPT (N=511)	2 WHO-guided ART, IPT (N=512)
3 Immediate ART, no IPT (N=515)	4 Immediate ART, IPT (N=518)

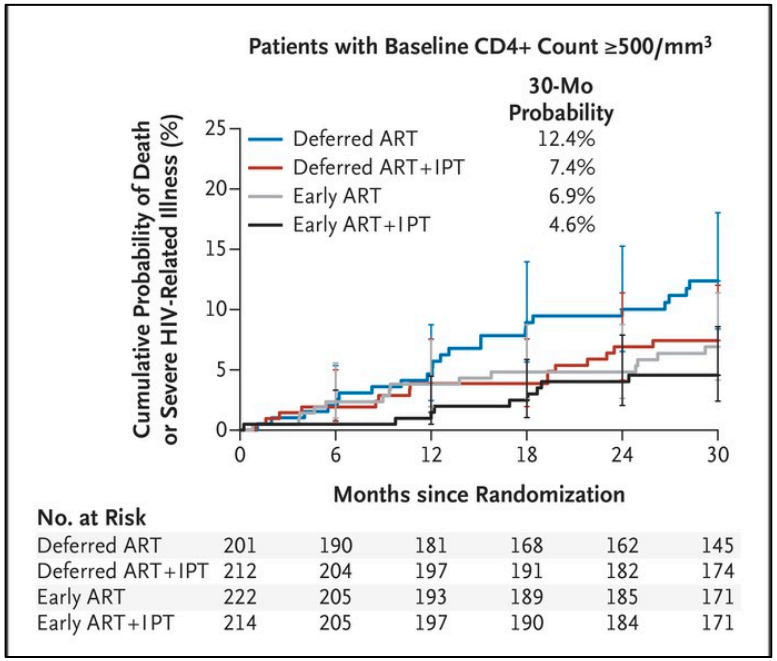
- Definitions of WHO-guided changed as the guidelines evolved so about half of the patients were enrolled under 2006 guidelines (<200 CD4) and half under the 2010 guidelines (<350 CD4)

Considering primary outcome, early ART was beneficial in all and also those with CD4 ≥500

ALL



CD4 ≥ 500



Comparing early ART with deferred p=0.0002

Comparing early ART with deferred p=0.027

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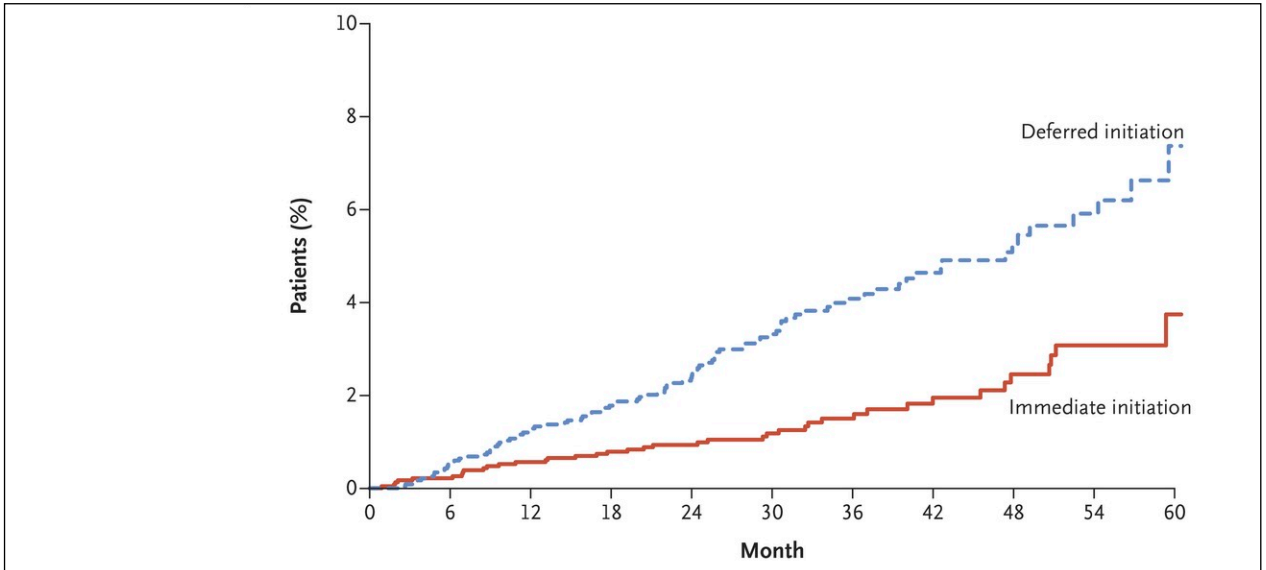
Source: N Engl J Med 2015; 373:808-822

The START trial enrolled over 4000 people with CD4>500 at 211 sites in 35 countries

- Europe 33%, South America 25%, Africa 21%, North America 11%, Asia 10%
- Median age 36 years and 25% were women
- Med CD4: 651 (range 503 to 2296) and Med VL: 12,000
- Study design was straightforward – patients randomized to either early start or waiting until CD4 fell below 350
- Trial was closed early by the DSMB because of higher than expected benefit of ART

When looking at the primary outcome of death or severe disease, immediate ART was protective



No. at Risk											
Immediate initiation	2326	2302	2279	2163	1801	1437	1031	757	541	336	110
Deferred initiation	2359	2326	2281	2135	1803	1417	1021	729	520	334	103
Estimated Percentage											
Immediate initiation		0.2	0.6	0.8	0.9	1.2	1.5	2.0	2.5	3.1	3.7
Deferred initiation		0.5	1.2	1.8	2.4	3.3	4.1	4.6	5.3	5.9	7.4

Overall there were 42 "events" in the arm and 96 in the deferred arm p=<0.001
No difference in drug toxicities between arms and no evidence of harm caused by ART even in clients with HIV CD4

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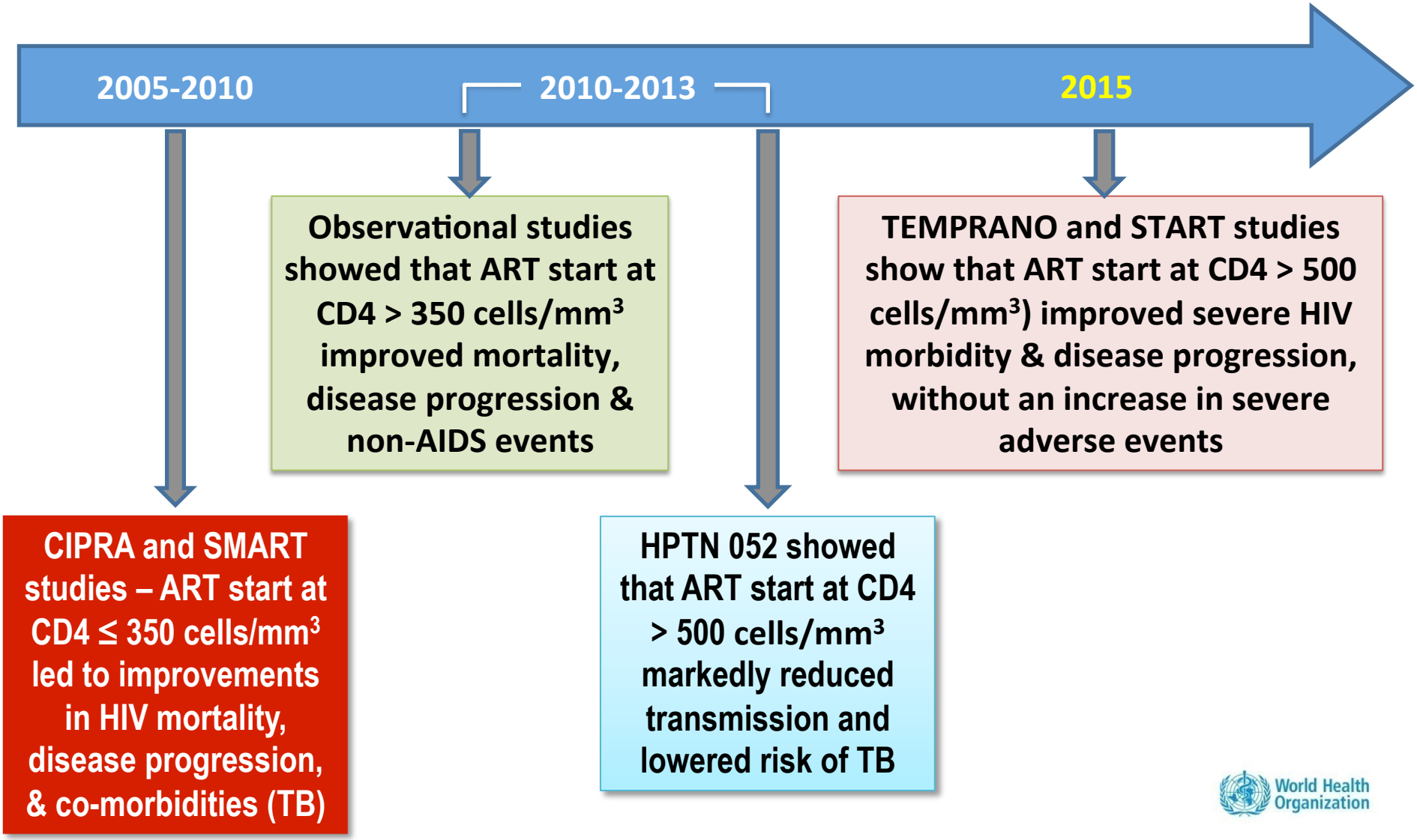
Source: N Engl J Med 2015; 373:795-807

Temprano/START represent the end of a chain of evidence that has led us to universal ART



So…the "When to Start" recommendations for adults say "treat everyone"

ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count

strong recommendation, moderate-quality evidence

As a priority, ART should be initiated among all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤350 cells/mm^3

strong recommendation, moderate-quality evidence

For the first time in the history of ARV guidelines…

- ONE recommendation for *everyone*
- erase the distinction between pregnant women and everybody else that has long contributed to poor ART access for women who happen to be pregnant

A community led Global Consultation on the acceptability of ART showed that our clients want this!

- **24 workshops, 8 countries, 8 sub populations, 206 PLHIV, 74 clinicians**
- Earlier initiation was deemed **acceptable**, however 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

There are no studies comparing B with B+ but…we do have some data on the effects of stopping

Effect	Findings from 26 observational studies describing what happens when ARVs stopped
CD4+ decline	Postpartum women who discontinue ART experience CD4 decline, but there is large heterogeneity with findings of studies: • Using **CD4 at BASELINE**, CD4 <500 resulted in 6-20% of women reaching treatment threshold within 6 mo of stopping. But if CD4 was >500, only 1.5% reached threshold • Using **CD4 at TREATMENT STOP**, CD4>550 was associated with 7% of women reaching threshold 18m later, whereas if CD4 was <550 varied from 27-50% women reached threshold at 18m
Immune activation	In IMPAACT P1025, all inflammatory biomarkers decreased after delivery, but continuation of ART was associated with more rapid decline esp in D-dimer levels.
Disease progression	Discontinuation when baseline CD4 was <500 resulted in a 2.5-fold higher risk of WHO Stage 2 or 3 clinical events.
Drug resistance	Paucity of data but in one study, there was a low rate of resistance found in women who stopped NVP-based ART after the period of MTCT risk.
Retention	Pre-B+, women with high CD4 in Malawi had a 10-fold higher risk of loss to follow up after delivery. In UK 2 out of 3 women who presented at ANC for a *second* pregnancy were below eligibility threshold.

Summarizing this additional evidence…

Women who stop ART post partum will have *inevitable* progression of disease:

- Clinical events
- CD4 decline
- Inflammatory markers

What is not clear is how quickly this progression occurs

- Higher the CD4, the longer it will take
- For all CD4 counts, the TIME TO THRESHOLD in 2015 will be shorter – simply because the thresholds are higher!

Looking beyond the science at the programme, retention for "non-eligible" women is very poor, even in developed countries. Its hard for the system to catch pre-ART patients before they fall, and a treat all approach can prevent this loss to follow-up…but what are the downsides?

B+ (ART for all) will add costs in the short term, but is cost effective compared with option B

- In a CDC led costing exercise total cost (including drugs, diagnostics and service delivery) of maintaining a woman on option B+ for 5 years was estimated to be US$ 2069 on average*
- But a woman off ART also incurs costs of monitoring and follow-up and in time needs ART, so ***incremental*** cost of moving from option B to option B+ was relatively low (92 to 605 US$ depending on baseline CD4 count and BF status)
- In modelled cost effectiveness analyses, Option B and B+ are cost-saving or highly cost-effective compared to option A.
- When outcomes such as maternal health, preventing the mother-to-child transmission of HIV in future pregnancies and preventing horizontal transmission are considered, option B+ has been found to be highly cost-effective compared with option B

*O'Brien, L. (2014) The incremental cost of switching from Option B to Option B+ for PMTCT of HIV. Bull of the WHO

Costs vary but all studies indicate that cost per infection averted is comparable for B and B+

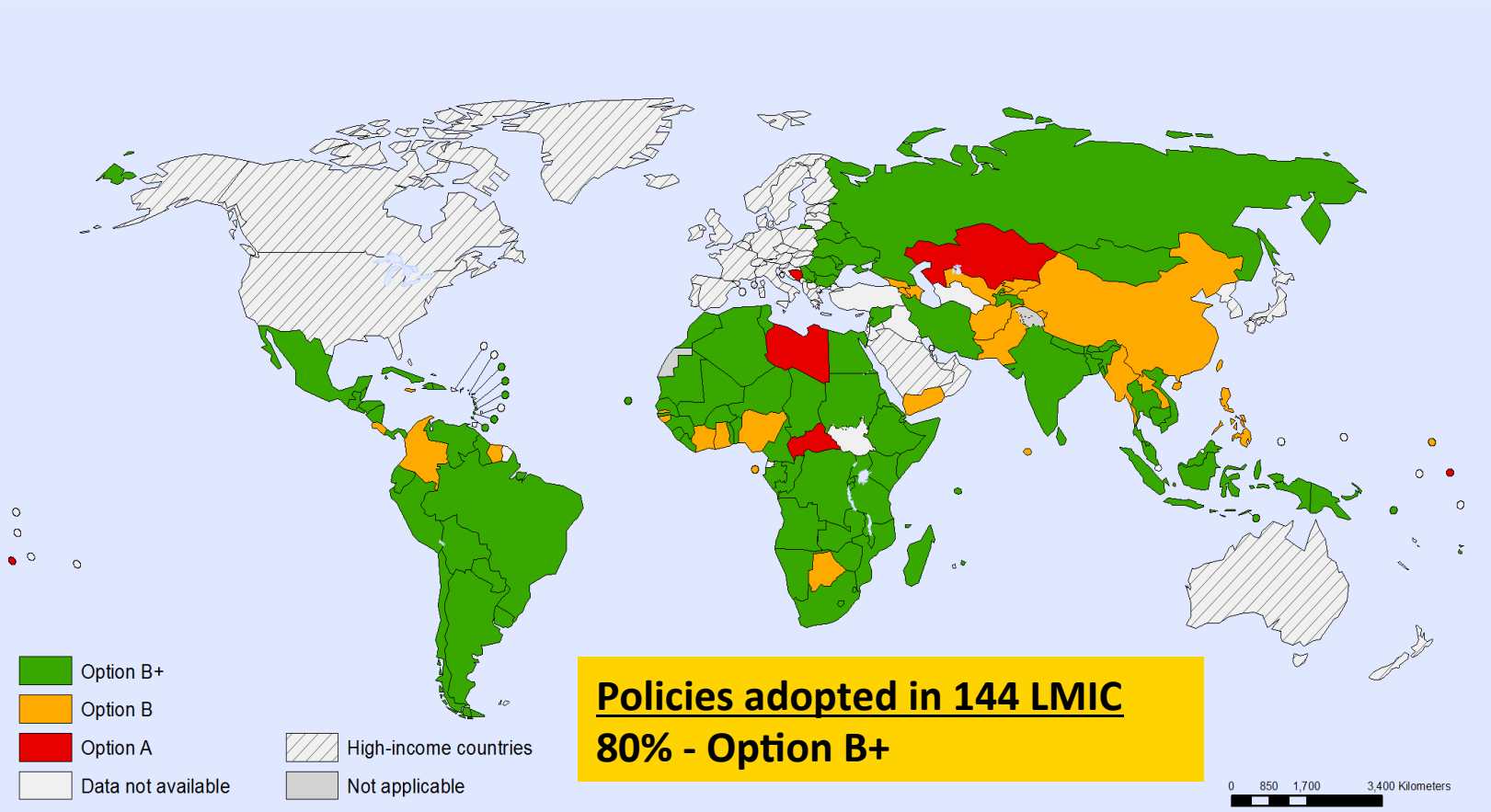
Study	Comparator	CE (DALY/QALY)	CE (Cost per infection averted)	CE (Life Exp.)
Fasawe et al., 2013 (Malawi)	Option A & B	$60/DALY averted (B) $57/DALY averted (B+)	$1,331 (B) $1,265 (B+)	$338 per LYG (B) $455 per LYG (B+)
VanDeusen, et al., (Ghana)	Option B (incremental CE over B)	$785/QALY gained		$618 per LYG
Ciaranello et al., 2013 (Zimbabwe)	Option B (incremental CE over B)			$1370 per LYS
Gopalappa et al., 2014 (multi-country)	Option A		$6,000 - $23,000	
Ishikawa, et al., 2014 (Zambia)	Option A & B	$74/QALY gained (B) $132/QALY gained (B+)	$1,023 (B) $1,254 (B+)	
Adesina, A. & Alkenbrack, S. 2015 (Nigeria)	Option B (average CE across 13 states)*		US$83,000 (B) US$65,000 (B+)	

Balance of Risks and Benefits favours universal ART for Pregnant and Breastfeeding Women)

BENEFITS	HARMS
Preventing transmission in future pregnancies MTCT if **on ART at conception** is **0.7%***	Additional potential risk of toxicity because of additional time on ART
Reduced transmission to uninfected partners **(hypothesised)**	Programmes are seeing high rates of LTFU….this is a systems issue but may have implications for resistance
Avoid potential downsides to women of stopping and restarting for future pregnancies	Potential risk of loss in transition from MCH delivered ART services to routine ART services
No need to establish eligibility prior to initiating ART regimen. Makes ART initiation faster and improves PMTCT benefit.	Increased net immediate cost (although like cost effective in the long term)
Improved maternal mortality & slower disease progression with continuous vs. interrupted ART	Additional potential risk of resistance, especially if women stop ART or are poorly compliant
Reduces need and cost of CD4 for initial and ongoing eligibility	
Women less likely to drop out of HIV care if they are placed on lifelong ART vs “short term” ARVs	

*Hoffman RM et al. Journal of AIDS March 2010

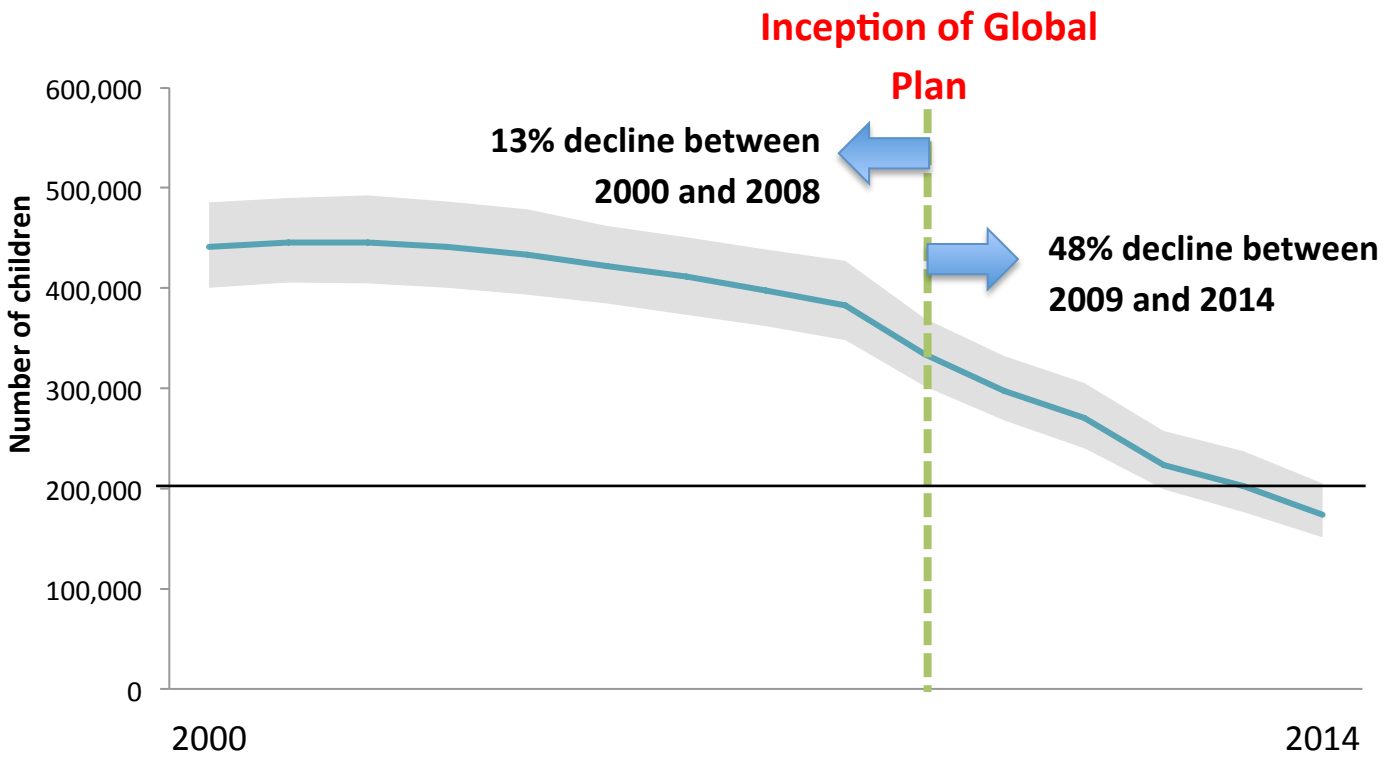
For most countries, Universal ART for pregnant women (B+) is already national policy



Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

New HIV infections among the 21 Global Plan countries dropped below 200,000 in 2014



Source: UNAIDS Estimates derived from GARPR 2015 data

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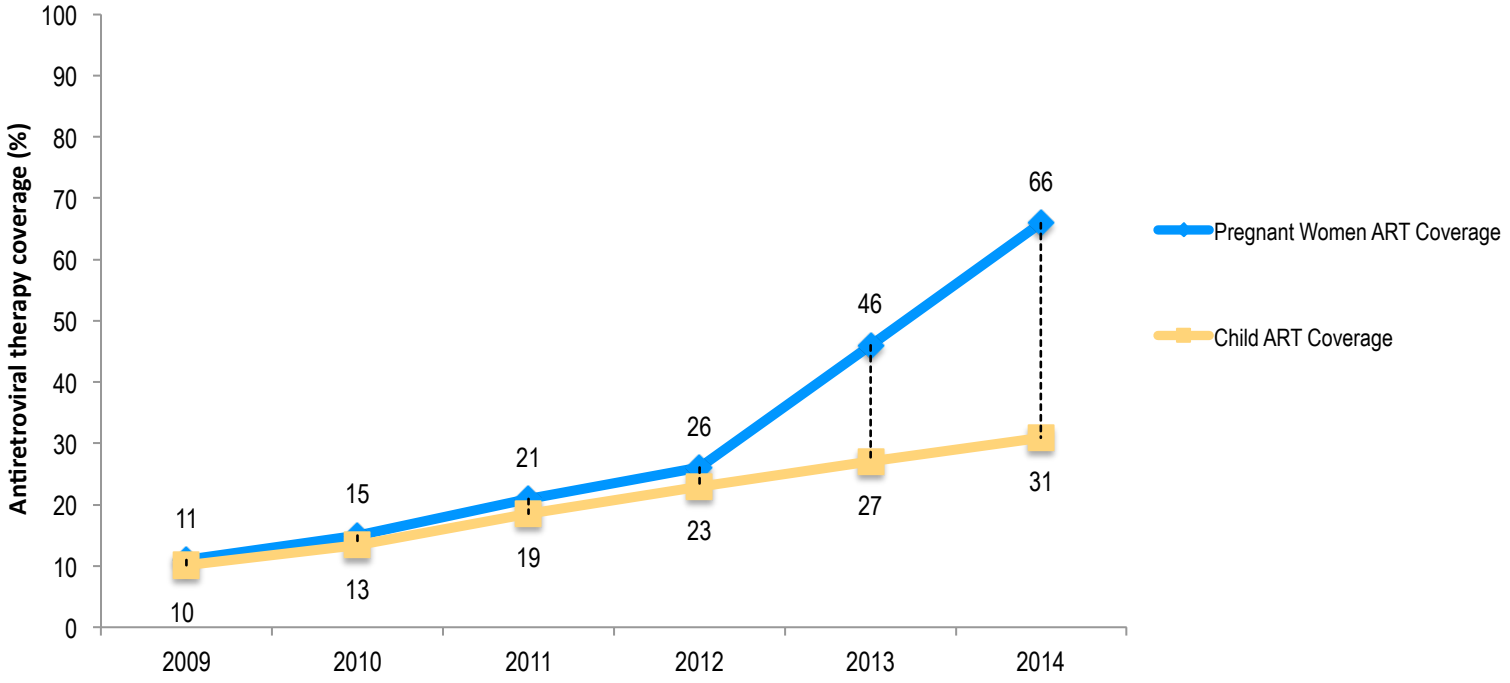
ART access for pregnant women has Increased with the adoption and implementation of B+

Aggregate antiretroviral coverage for children (0-14) and pregnant women across 21 Global Plan priority Countries, 2014



Source: UNAIDS Estimates derived from GARPR 2015 data

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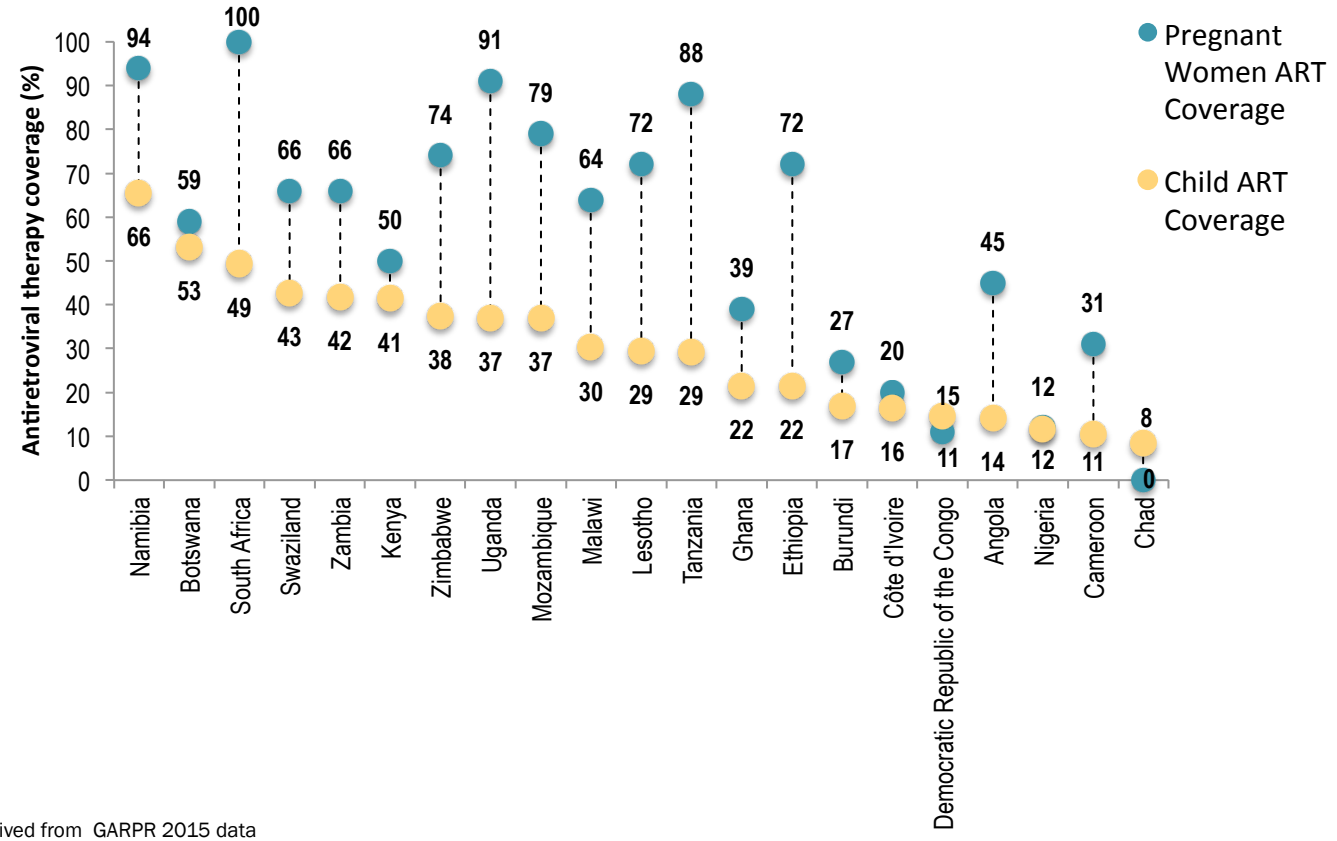
But when you look at individual countries there is a lot of heterogeneity in terms of coverage

Antiretroviral Coverage for children (0-14 years) and pregnant women in 21 Global Plan priority countries, 2014



Source: UNAIDS Estimates derived from GARPR 2015 data

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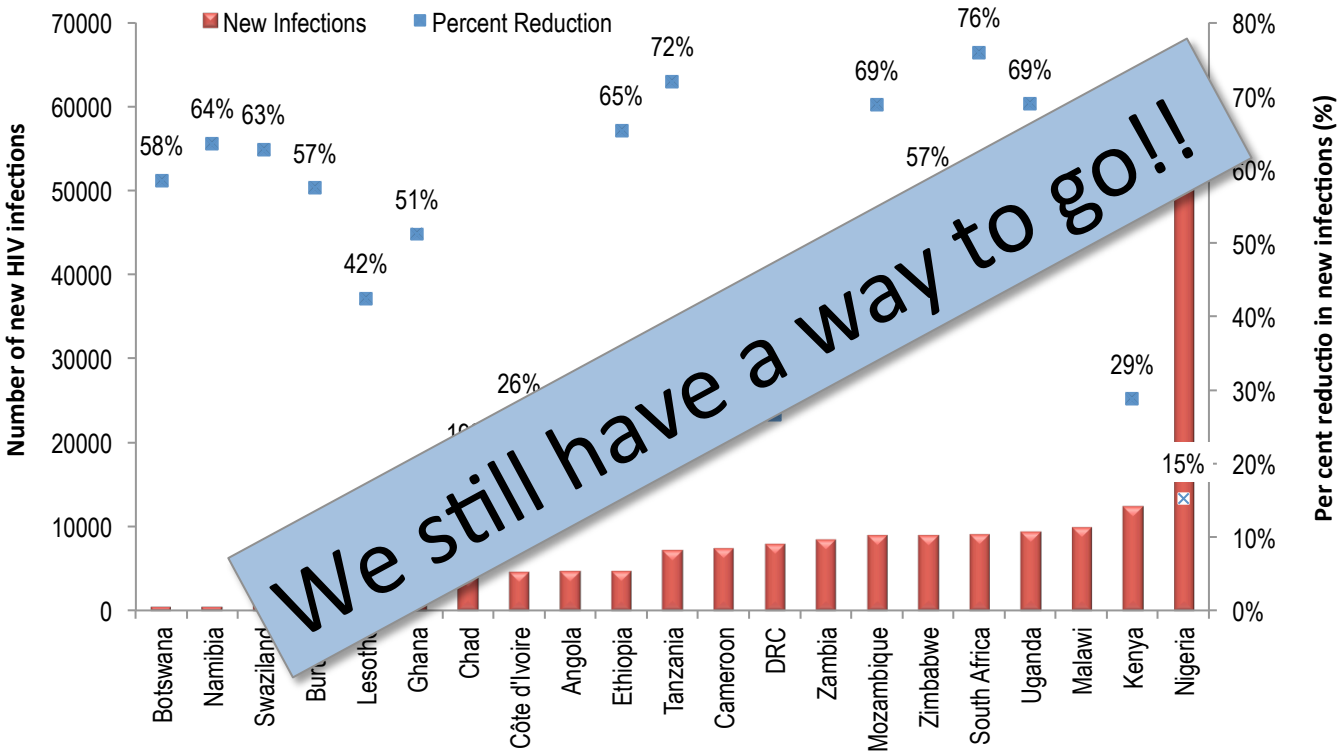
And this is reflected in the "percentage reduction" and "new infections in children" data

Number of new HIV infections among children in 2014 and per cent reduction in new infections since 2009



Source: UNAIDS Estimates derived from GARPR 2015 data

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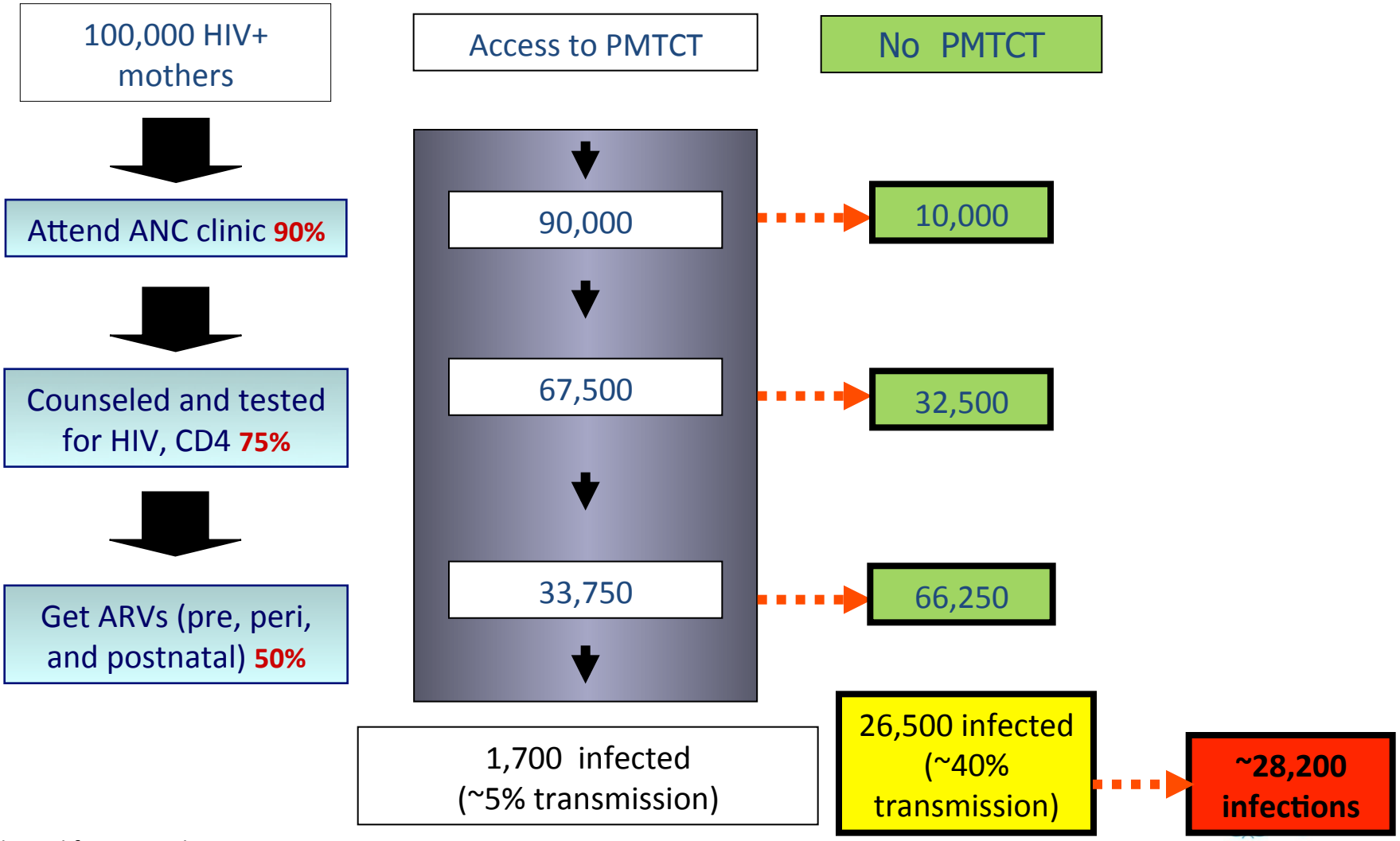
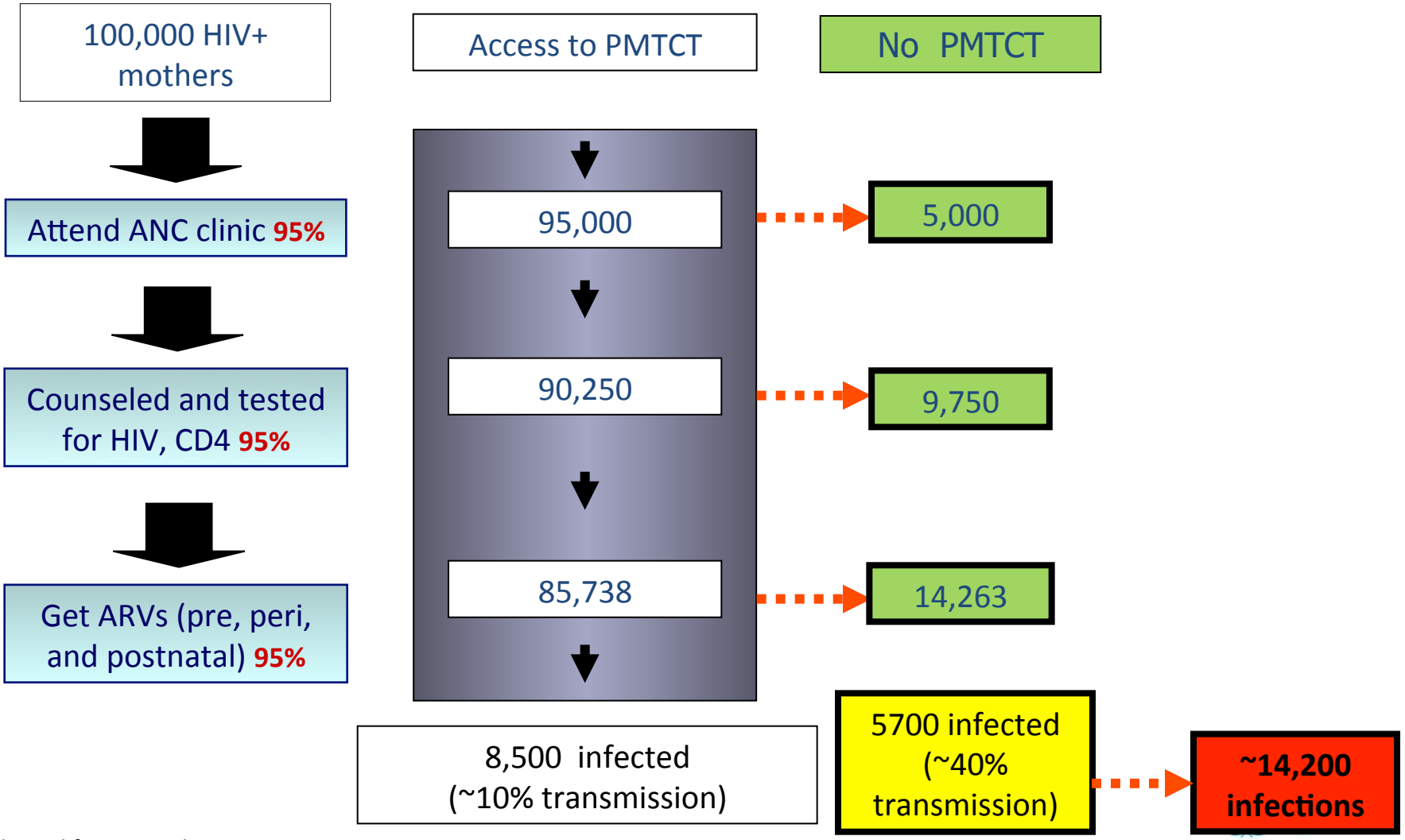
Is the policy shift to Universal ART for Pregnant and Breastfeeding women the magic bullet to control MTCT?

New recommendations may be "effective" but can't work if coverage and retention are poor



Slide adapted from P Barker.

Even a "poor" intervention works when there is good coverage and retention



Slide adapted from P Barker.

Way forwards to eliminate MTCT

- Countries *should* adopt universal ART for PW and BF women
  - Good for mother, good for baby, good for sero-discordant couple
- But the impact of this policy shift is contingent on program performance.
  - Weak health systems need to improve their coverage and retention
  - And to do this will require more money, better systems to track and prevent LTFU, more HCWs and community engagement
- Some areas of implementation focus are emerging
  - Same day Start (ie starting ART on the same day as the test) may result in lack of uptake and high drop off
  - Retesting pos women before ART initiation is essential to ensuring that women who are not truly infected do not get started on ART
  - Postpartum retention is a major problem that could be improved with greater community engagement and facilitated transfer from MCH to ART