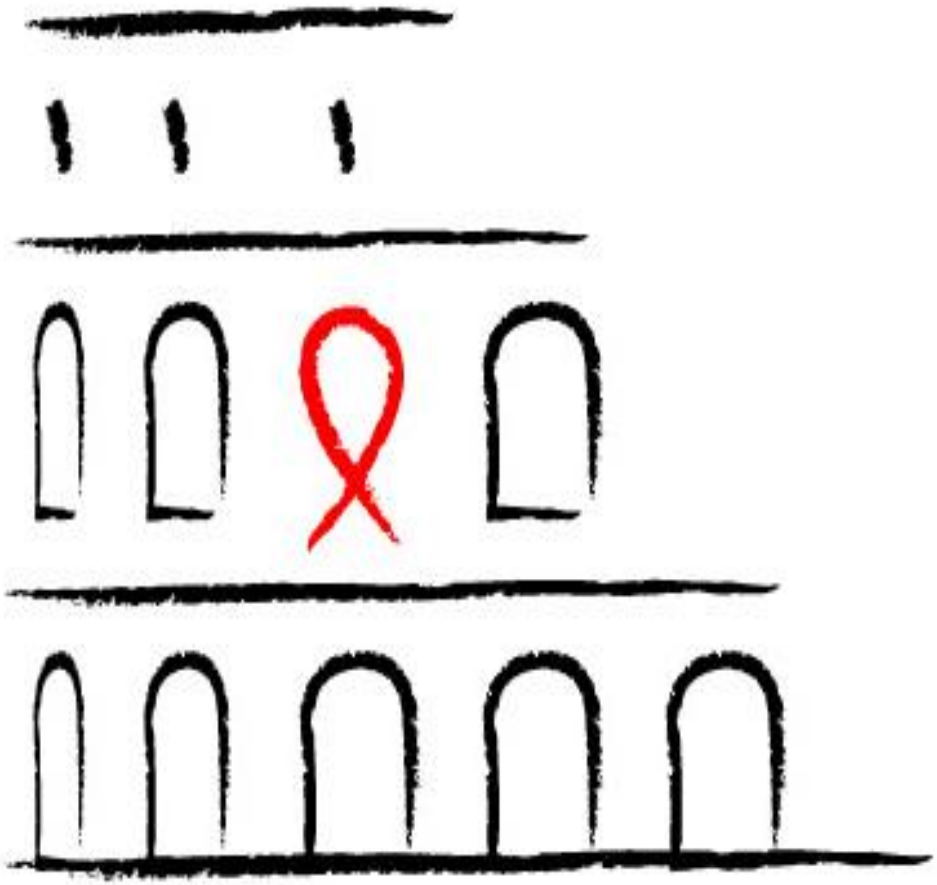
Treatment 2.0 as a catalyst for Tasp through Drug / Treatment Optimization

STEFANO VELLA MD

ISTITUTO SUPERIORE DI SANITÀ – ROME - ITALY



IAS 2011

17-20 JULY ROME, ITALY

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 11, 2011 VOL. 365 NO. 6

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D., Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D., Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*


THE 1ST
IAS CONFERENCE
ON HIV PATHOGENESIS
AND TREATMENT
IAS

Lancet 2006; 368: 531–36

The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic

Julio S G Montaner, Robert Hogg, Evan Wood, Thomas Kerr, Mark Tyndall, Adrian R Levy, P Richard Harrigan

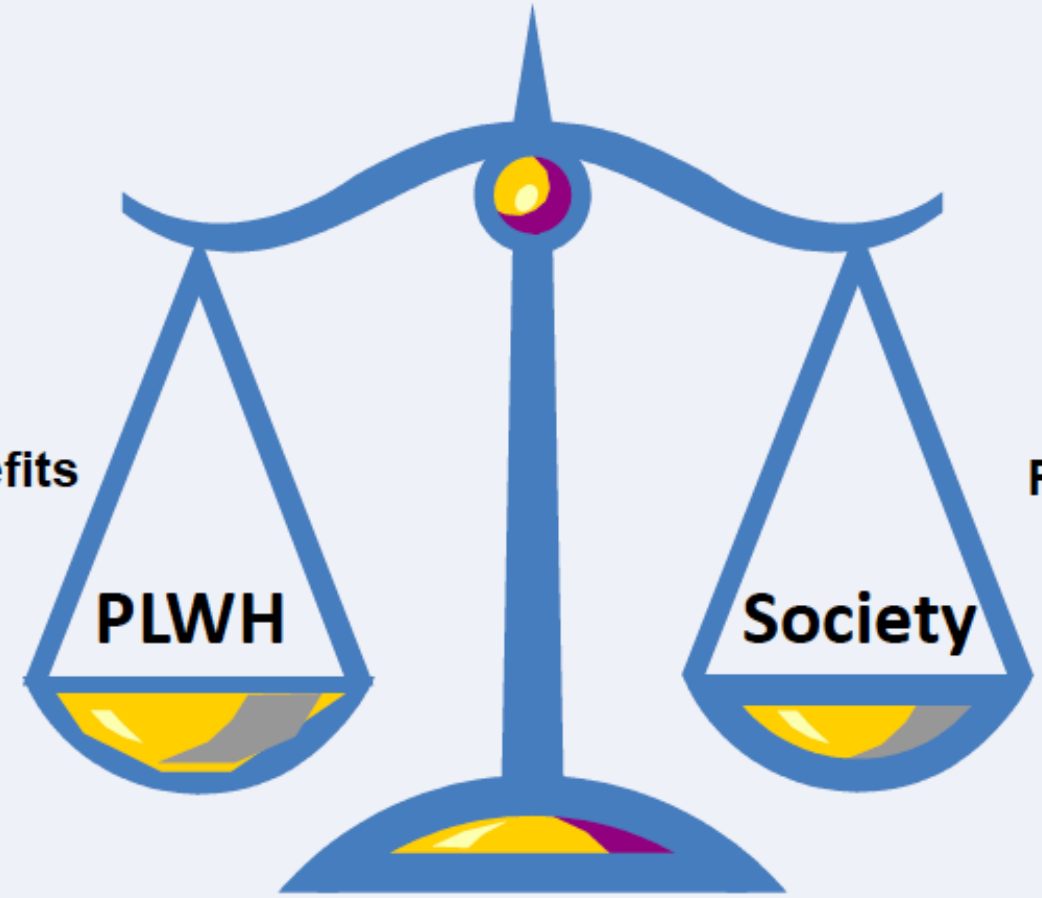
"The upshot of this widespread failure to recognize that AIDS is an exceptional crisis and threat is that the response to the pandemic is not made commensurate to the challenges—and so the epidemic escalates even while it erodes our capacities to check it."

Dr Peter Piot, UNAIDS Executive Director[1]

Balancing the Individual and Society

Health Systems
Ethics
Equity
Resources

Risks versus Benefits



Risks versus Benefits

WAFAA EL SADR, CROI 2012…

The problem is in how
to efficiently and progressively
implement the potential ability of
treatment to curb the epidemic….

HIV to ART: Testing, Care, and Treatment-- Mozambique

23,430 Tested for HIV

7,005 Tested HIV positive (30%)

3,049 (43%) not enrolled in HIV care

3,956 Enrolled HIV care < 30 days after HIV test (57%)

910 (23%) No CD4 test drawn

3,046 CD4 test <30 days after enrollment (77%)

1,540 (51%) Not eligible for ART Initiation

1,506 Eligible for ART Initiation (49%)

1,035 (69%) did not initiate ART

471 Initiated ART < 90 days after CD4 test (31%)

65 (14%) Lost to follow up after ART

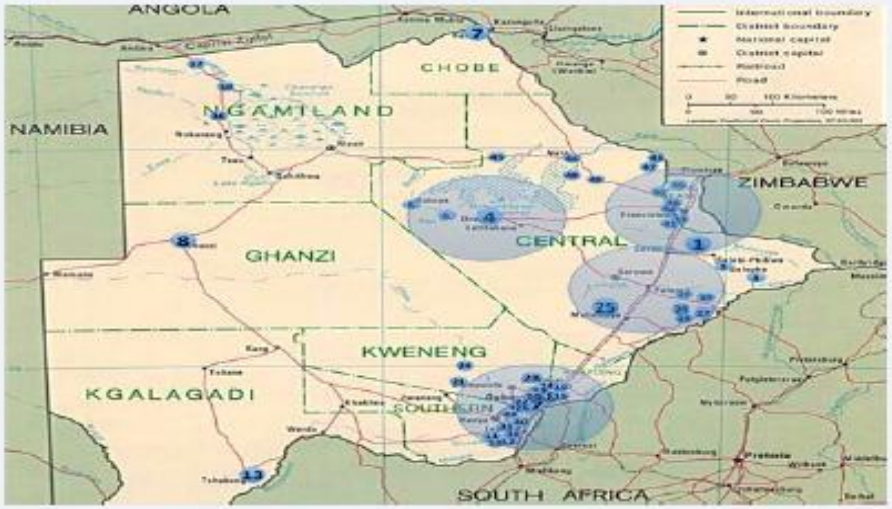
317 Adherent to ART for 6 months (83%)

WAFRA EL SADR, CROI 2012…

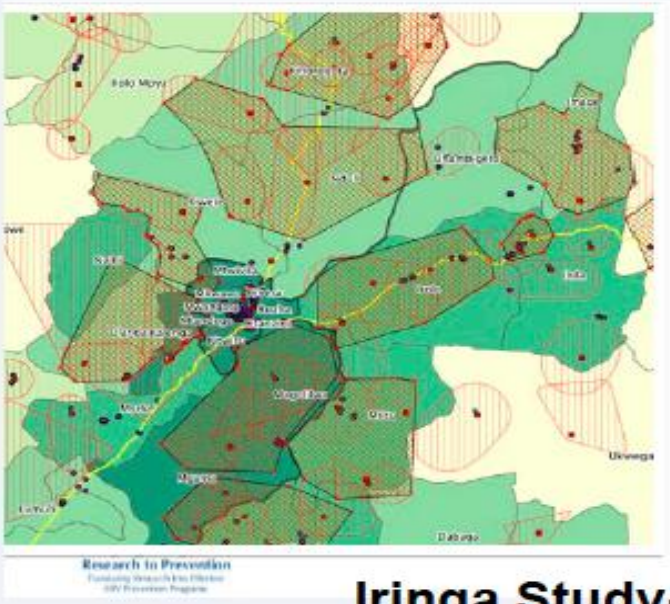
Micek et al. JAIDS 2009

Q. What should be the
ART coverage “threshold”
to have an impact at the population level ?

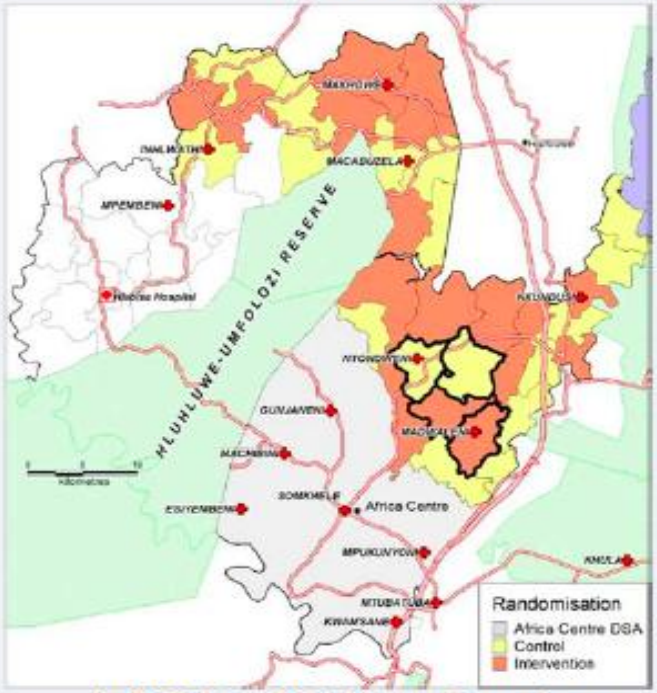
WAFA EL SADR, CROI 2012…



Botswana- CDC



Iringa Study- USAID



TASP- Africa Centre

ANRS

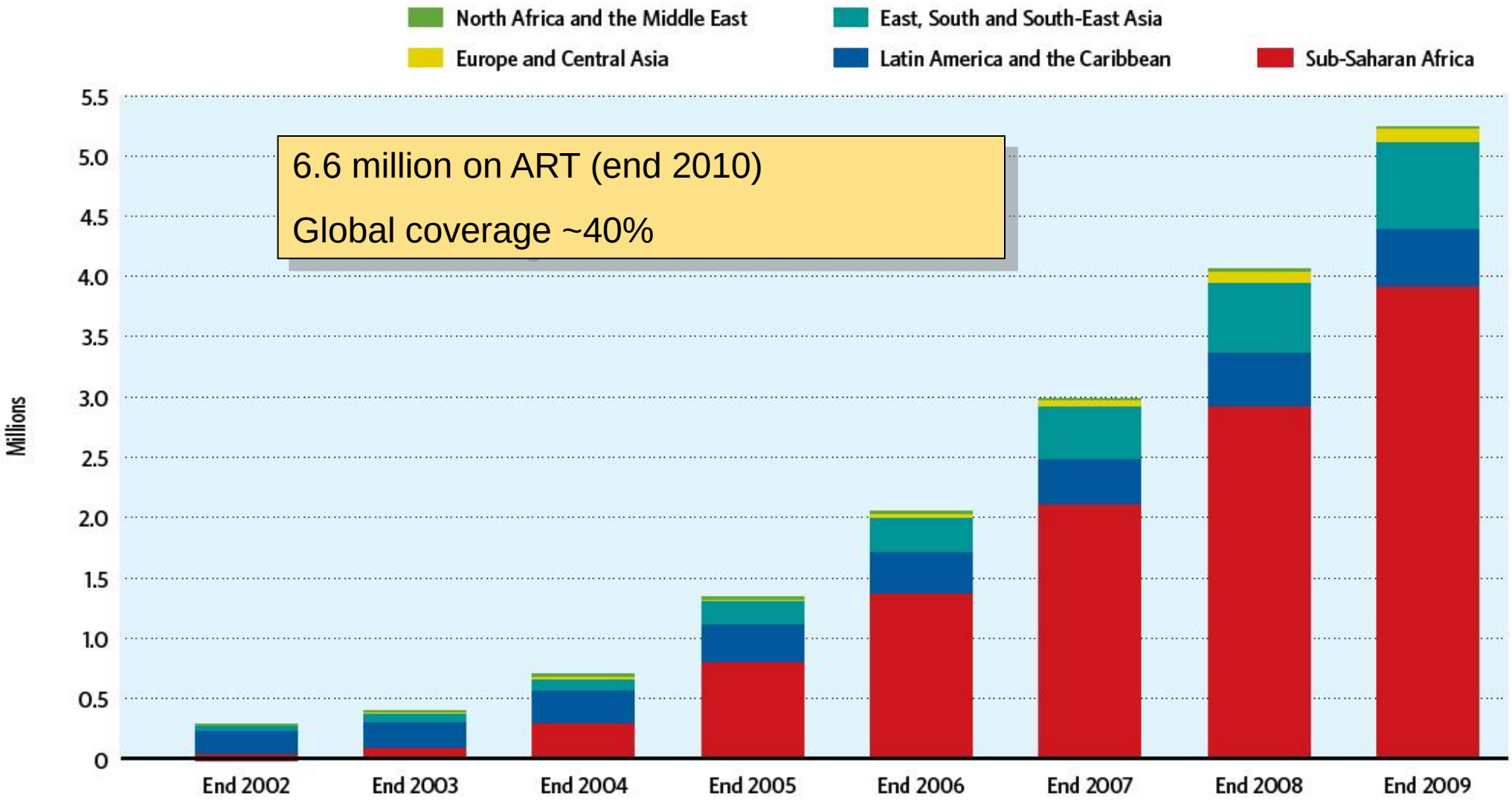
HPTN 071 –NIH

PopART

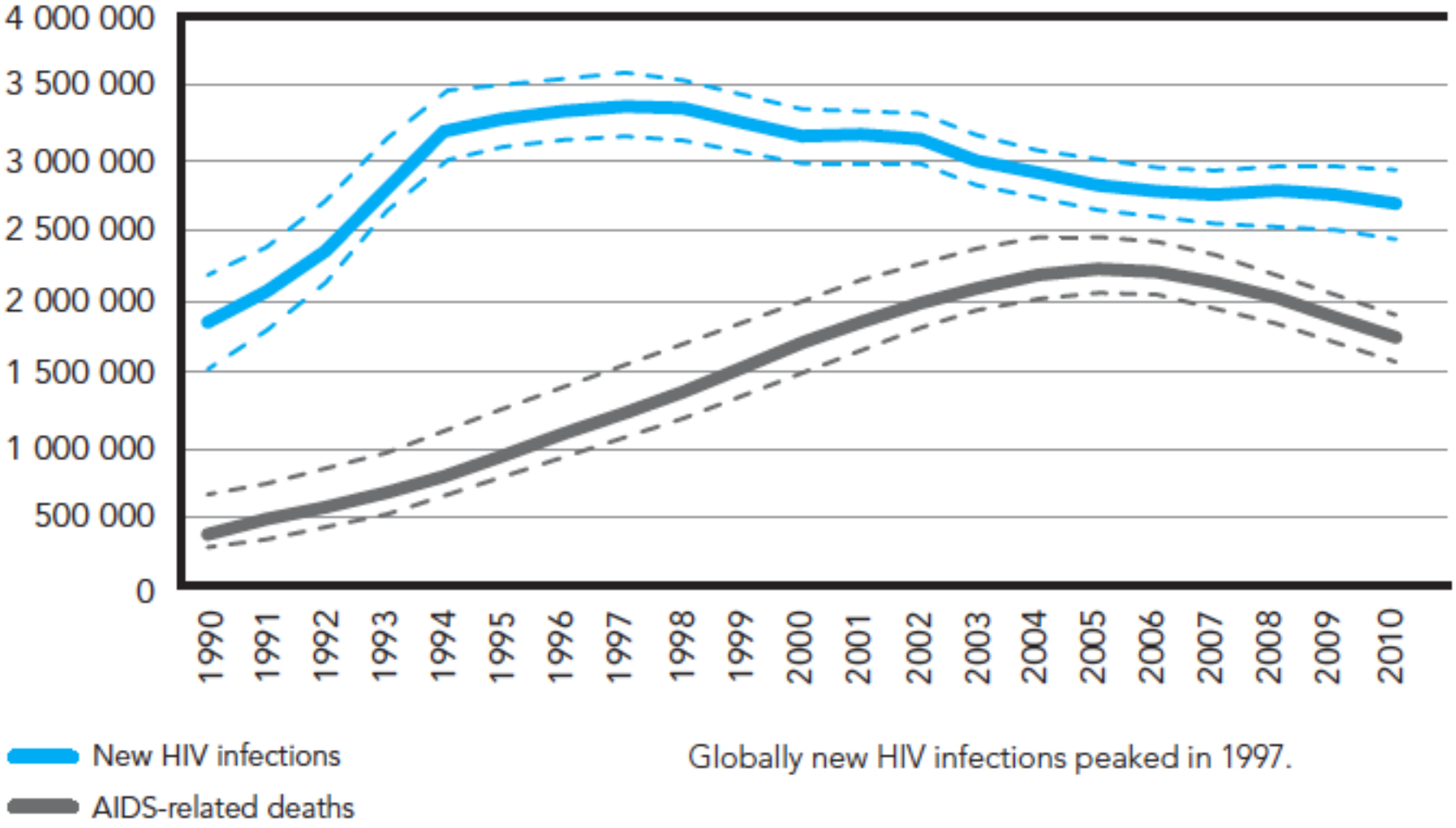
A definite way forward for Tasp:

working towards universal access

Progress on ART Access



NEW HIV INFECTIONS AND AIDS-RELATED DEATHS



Globally new HIV infections peaked in 1997.

Table 5.3 Number of adults and children (combined) receiving and eligible for antiretroviral therapy, and estimated percentage coverage in low- and middle-income countries by region, December 2009 to December 2010[a,b,c]

Geographical region	December 2010			December 2009		
	Number of people receiving antiretroviral therapy	Estimated number of people eligible for antiretroviral therapy [range][a]	Antiretroviral therapy coverage [range][d]	Number of people receiving antiretroviral therapy	Estimated number of people eligible for antiretroviral therapy [range][a]	Antiretroviral therapy coverage [range][d]
Sub-Saharan Africa	5 064 000	10 400 000 [9 700 000–11 000 000]	49% [46–52%]	3 911 000	9 600 000 [9 000 000–10 200 000]	41% [38–43%]
Eastern and southern Africa	4 221 000	7 600 000 [7 100 000–8 000 000]	56% [53–59%]	3 203 000	7 000 000 [6 600 000–7 400 000]	46% [43–48%]
Western and central Africa	842 000	2 800 000 [2 600 000–3 100 000]	30% [28–33%]	709 000	2 600 000 [2 400 000–2 800 000]	27% [25–30%]
Latin America and the Caribbean	521 000	820 000 [710 000–920 000]	63% [57–73%]	469 000	780 000 [670 000–870 000]	60% [54–70%]
Latin America	461 000	720 000 [620 000–810 000]	64% [57–74%]	416 000	690 000 [590 000–780 000]	60% [53–70%]
Caribbean	60 300	100 000 [91 000–110 000]	60% [53–67%]	52 400	93 000 [84 000–110 000]	56% [50–63%]
East, South and South-East Asia	922 000	2 300 000 [2 100 000–2 500 000]	39% [36–44%]	748 000	2 300 000 [2 000 000–2 400 000]	33% [31–37%]
Europe and Central Asia	129 000	570 000 [500 000–650 000]	23% [20–26%]	114 500	520 000 [450 000–600 000]	22% [19–25%]
North Africa and the Middle East	14 900	150 000 [120 000–190 000]	10% [8–13%]	12 400	140 000 [110 000–180 000]	9% [7–12%]
Total	**6 650 000**	**14 200 000 [13 400 000–15 000 000]**	**47% [44–50%]**	**5 255 000**	**13 300 000 [12 400 000–14 100 000]**	**39% [37–42%]**

Note: some numbers do not add up because of rounding.

a See Box 5.9 for further information on the methods for estimating the need for and coverage of antiretroviral therapy in 2010.

b The 2009 figures may differ from those previously published because countries have submitted newly available data.

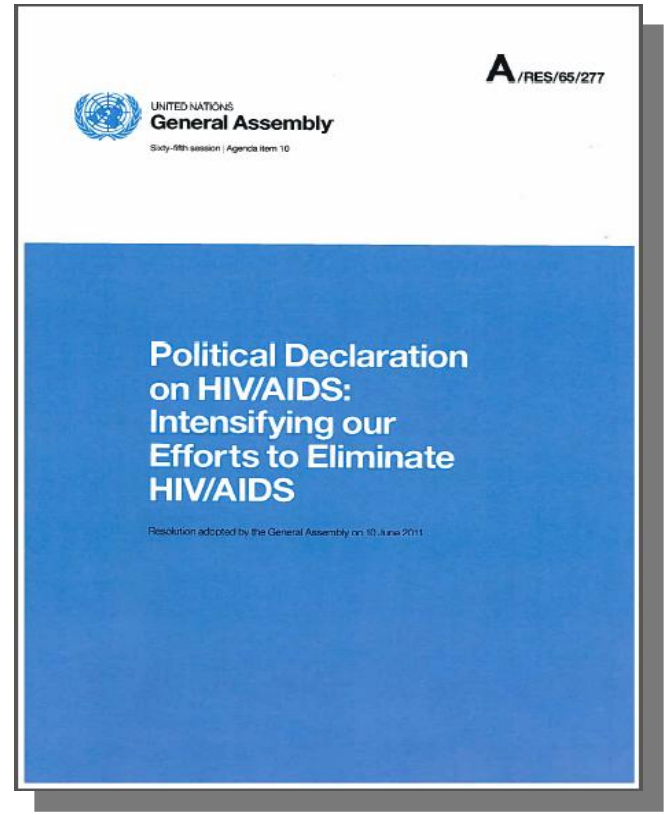
c All estimated needs have been developed according to 2010 WHO guidelines and criteria for initiating treatment.

d The coverage estimate is based on the unrounded estimated numbers of people receiving and needing antiretroviral therapy.

Bold targets for 2015

- Eliminate new HIV infections in children
- TB deaths among PLHIV reduced by 50%
- Intensify HIV prevention
  - men who have sex with men
  - people who inject drugs
  - sex workers
- 15 million people on ART

  (may be 20 million if we include discordant couples)



Challenges to Narrowing the Treatment Gap

- Financing
- Complexity of treatment and monitoring
- Inefficiencies in service delivery
- Late presentation
- High rates of attrition

Hirnschall, IAS, ROME, 2011

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Hirnschall, IAS, ROME, 2011

Treatment 2.0 as a catalyst for Tasp through Drug / Treatment Optimization

1. The problems of ART implementation in RLS
2. A couple of tools which may be helpful….
    a. Treatment 2.0 / Treatment Optimization process
    a. The new WHO guidelines process

Treatment 2.0 as a catalyst for Tasp through Drug / Treatment Optimization

1. **The problems of ART implementation in RLS**
2. A couple of tools which may be helpful….
    a. Treatment 2.0 / Treatment Optimization process
    a. The new WHO guidelines process

Operational Issues

- Task shifting
- Integration of services / health system strenghtening
- Access and Retention
- Community involvement

Clinical issues

- Early mortality from late start
- Coinfections (TB / Hepatitis B & C)
- Aging / Comorbidities
- Non Communicable Diseases *(the next epidemic…)*

Clinical issues

- **Early mortality from late start**
- Coinfections (TB / Hepatitis B & C)
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CD4+ Cell Count at ART initiation

Country	CD4 count (cells/mm^3)	Type of estimate	n	Source
Multiregion (ART-Link)	114 (61-181)	Median	29,175	ART-Link, AIDS, 2008
Uganda	142 (70-206)	Median (IQR)	23,315	Mills et al. AIDS 2011
Treat Asia Cohort	112 (37- 209)	Median (IQR)	4,056	Zhou et al, BMC Infect Dis. 2010
Ethiopia	113.6 71	Mean (sd)	1,166	Huruy et al., AIDS Res Ther. 2010
South Africa	81 (36–132)	Median (IQR)	538	Bassett et al., AIDS 2010
Ethiopia, Kenya, Nigeria, Lesotho, Mozambique, Rwanda, South Africa, Tanzania (ICAP)	136	Median	121,506	Nash et al. AIDS 2011

Adapted Vitoria et al, ICASA 2011

Response to antiretroviral therapy in sub-Saharan Africa: improved survival associated with CD4 above 500 cells/μL

David Maman[a,b], Mar Pujades-Rodriguez[a], Sarala Nicholas[a], Megan McGuire[a], Elisabeth Szumilin[c], René Ecochard[a] and Jean-François Etard[a,d]

Objective: We investigated the association between immune response and mortality in four HIV African programs supported by Médecins Sans Frontières.

Design: Multicentric retrospective cohort study.

Methods: All ART naïve adults (>15 years) who initiated therapy between March 2001 and November 2010 and receiving therapy for 9 months or more were included. We described the evolution of mortality over time. Mixed Poisson models were used to assess the effect of updated CD4 counts and other potential risk factors on mortality.

Findings: A total of 24,037 patients, of which 68.0% were women, contributed 69 516.2 person-years of follow-up. At ART initiation, 5718 patients (23.7%) were classified as WHO clinical stage 4, 1587 (6.6%) had a BMI below 16 kg/m^2 and 2568 (10.7%) had CD4 count below 50 cells/μL. A total of 568 (2.4%) deaths were recorded during the study period. In the CD4 response categories ≥500, 350–499, 200–349, 50–199 and <50 cells/μL, unadjusted mortality rates were 0.36; 0.58; 0.88; 1.91 and 7.43 per 100 person-years, respectively. In multivariate analysis, higher mortality was observed in patients with CD4 response levels 350–499 cells/μL (aHR 1.70, 95% CI 1.26–2.30) and for those between 200–349 (aHR 2.56; 95% CI 1.93–3.38), compared to those with ≥500 cells/μL.

Interpretation: The observed higher survival of patients with a CD4 response to ART higher than 500 cells/μL supports the need of further research to evaluate the individual benefit of initiating ART at higher CD4 levels in sub-Saharan Africa.

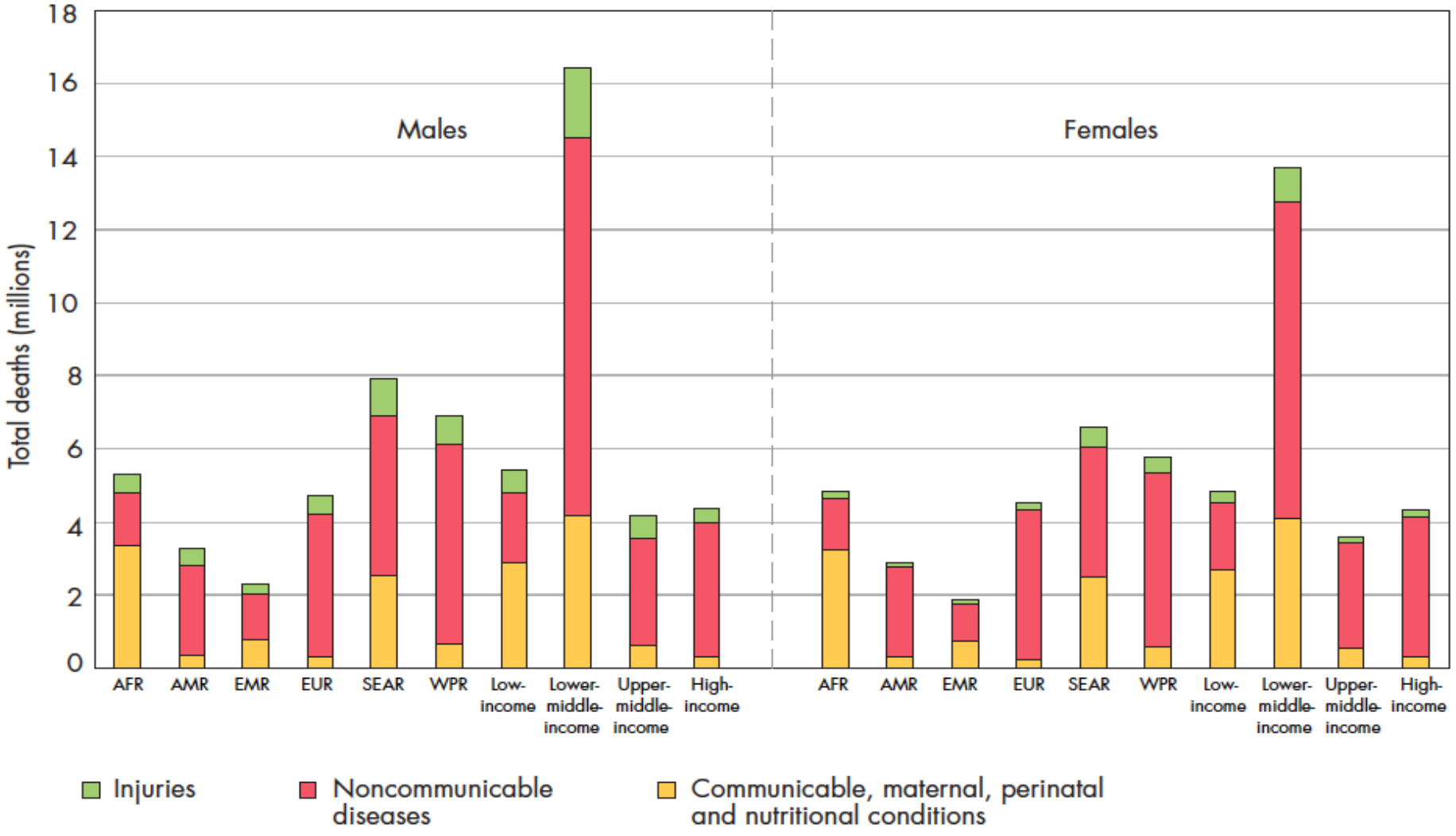
AIDS 2012, **26**:000–000

Keywords: antiretroviral therapy, CD4, epidemiology, HIV, mortality, sub-Saharan Africa

Clinical issues

- Early mortality from late start
- Coinfections (TB / Hepatitis B & C)
- Aging / Comorbidities
- **Non Communicable Diseases (the next epidemic…)**

Figure 1. Total deaths by broad cause group, by WHO Region, World Bank income group and by sex, 2008



(Note: AFR=African Region, AMR=Region of the Americas, EMR= Eastern Mediterranean Region, EUR= European Region, SEAR=South-East Asia Region, WPR=Western Pacific Region).

Societal Issues

- Social determinants

- Stigma and discrimination (and human rights issues)

CLOSING THE GAP:
POLICY INTO PRACTICE ON SOCIAL DETERMINANTS OF HEALTH

| DISCUSSION PAPER |

All for Equity

World Conference on Social Determinants of Health

RIO DE JANEIRO | BRAZIL | 19–21 OCTOBER 2011

World Health Organization

Impact of malnutrition and social determinants on survival of HIV-infected adults starting antiretroviral therapy in resource-limited settings

Xavier Argemi[a], Som Dara[b], Seng You[b], Jean F. Mattei[c], Christian Courpotin[c], Bernard Simon[c], Yves Hansmann[a], Daniel Christmann[a] and Nicolas Lefebvre[a]

Objectives: Determining the impact of malnutrition, anaemia and social determinants on survival once starting antiretroviral therapy (ART) in a cohort of HIV-infected adults in a rural HIV care centre in Sihanoukville, Cambodia.

Methods: Retrospective and descriptive cohort study of adults starting ART between December 2004 and July 2009. We used the Kaplan–Meier and Cox regression survival analyses to identify predictors of death.

Results: Out of 1002 patients, 49.7% were men; median age was 40; median time of follow-up was 2.4 years and 10.4% died during the follow-up. At baseline, median CD4 cell count was 83 cells/μl, 79.9% were at WHO stage III or IV. In multivariate analysis, malnutrition appeared to be a strong and independent risk factor of death; 11.2% had a BMI less than 16 kg/m^2 and hazard ratio was 6.97 [95% confidence interval (CI), 3.51–13.89], 21.5% had a BMI between 16 and 18 kg/m^2 and hazard ratio was 2.88 (95% CI, 1.42–5.82), 30.8% had a BMI between 18 and 20 kg/m^2 and hazard ratio was 2.18 (95% CI, 1.09–4.36). Severe anaemia (haemoglobin ≤8.4 g/dl) and CD4 cell count below 100 cells/μl also predicted mortality, hazard ratio were 2.25 (95% CI, 1.02–4.34) and 2.29 (95% CI, 1.01–2.97), respectively. Social determinants were not significantly associated with death in univariate analysis.

Conclusion: Malnutrition and anaemia are strong and independent prognostic factors at the time of starting ART. Nutritional cares are essential for the clinical success of HIV programs started in developing countries.

AIDS 2012, **26**:1161–1166

Keywords: anaemia, HIV, malnutrition, mortality, social determinants

Societal Issues

- Social determinants

- Stigma and discrimination (and human rights issues): *they will hamper the "finding of the unknown" despite any increase of CD4 treshold for starting therapy and despite the dissemination of the knowledge regarding the individual health benefit of treatment.*

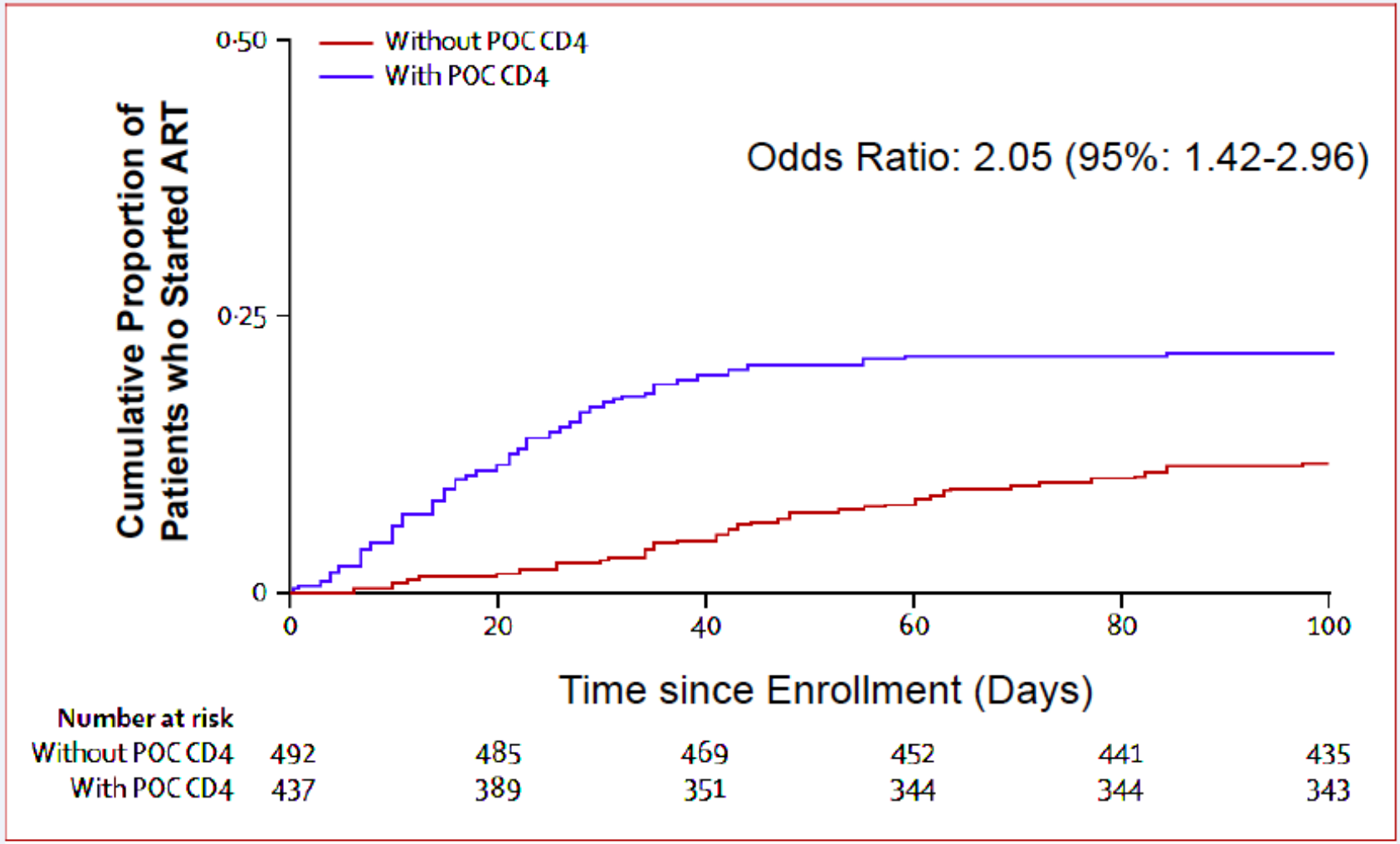
Monitoring and Drug / Treatment issues

- Point of care CD4
- HIV-RNA
- Quality of drugs / regimens

Monitoring and Drug / Treatment issues

- **Point of care CD4** ***(essential, not only for monitoring ART)***
- HIV-RNA
- Quality of drugs / regimens

Point of Care CD4+ Cell Count
Time from Enrollment to ART Initiation



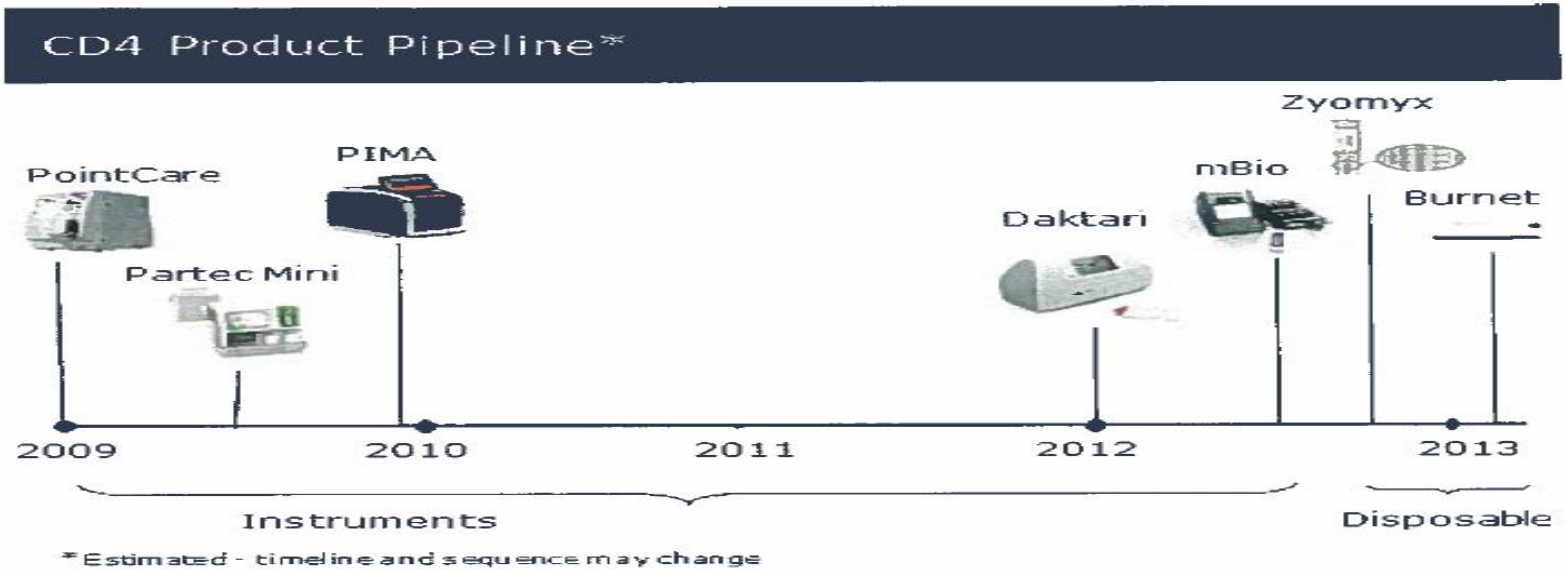
Adapted--Jani et al. Lancet 2011

Monitoring and Drug / Treatment issues

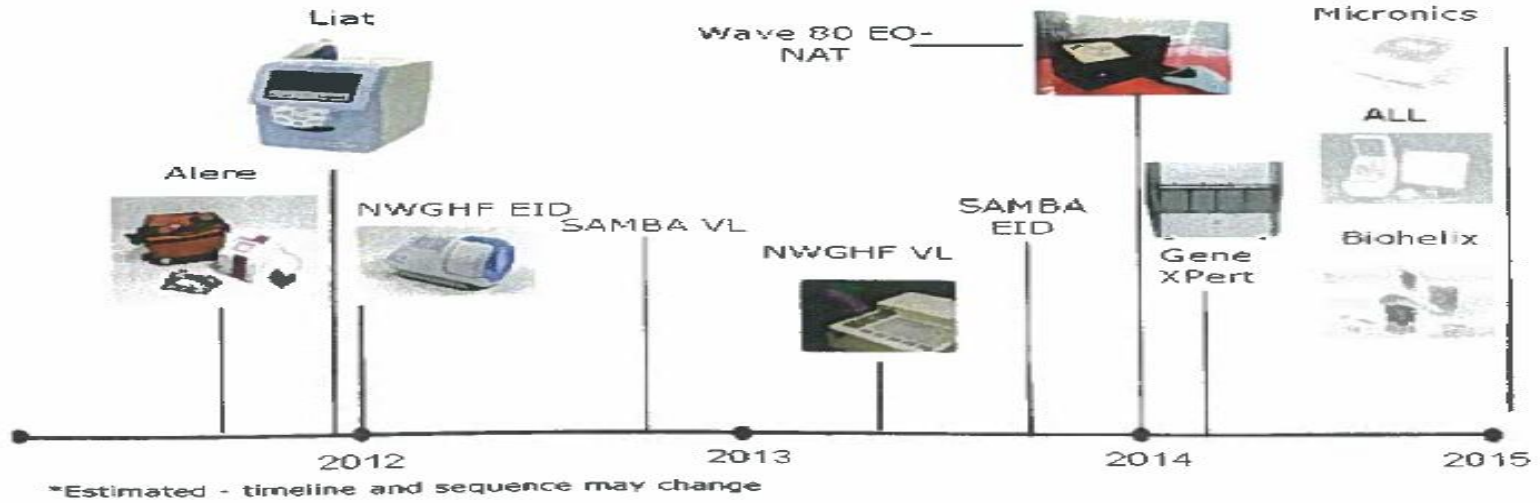
- **Point of care CD4** ***(essential, not only for monitoring ART)***
- **HIV-RNA** ***(may take some time to be widely available)***
- Quality of drugs / regimens

CD4 and Viral Load Technology Pipelines

CD4 Platforms



Viral Load and EID Platforms

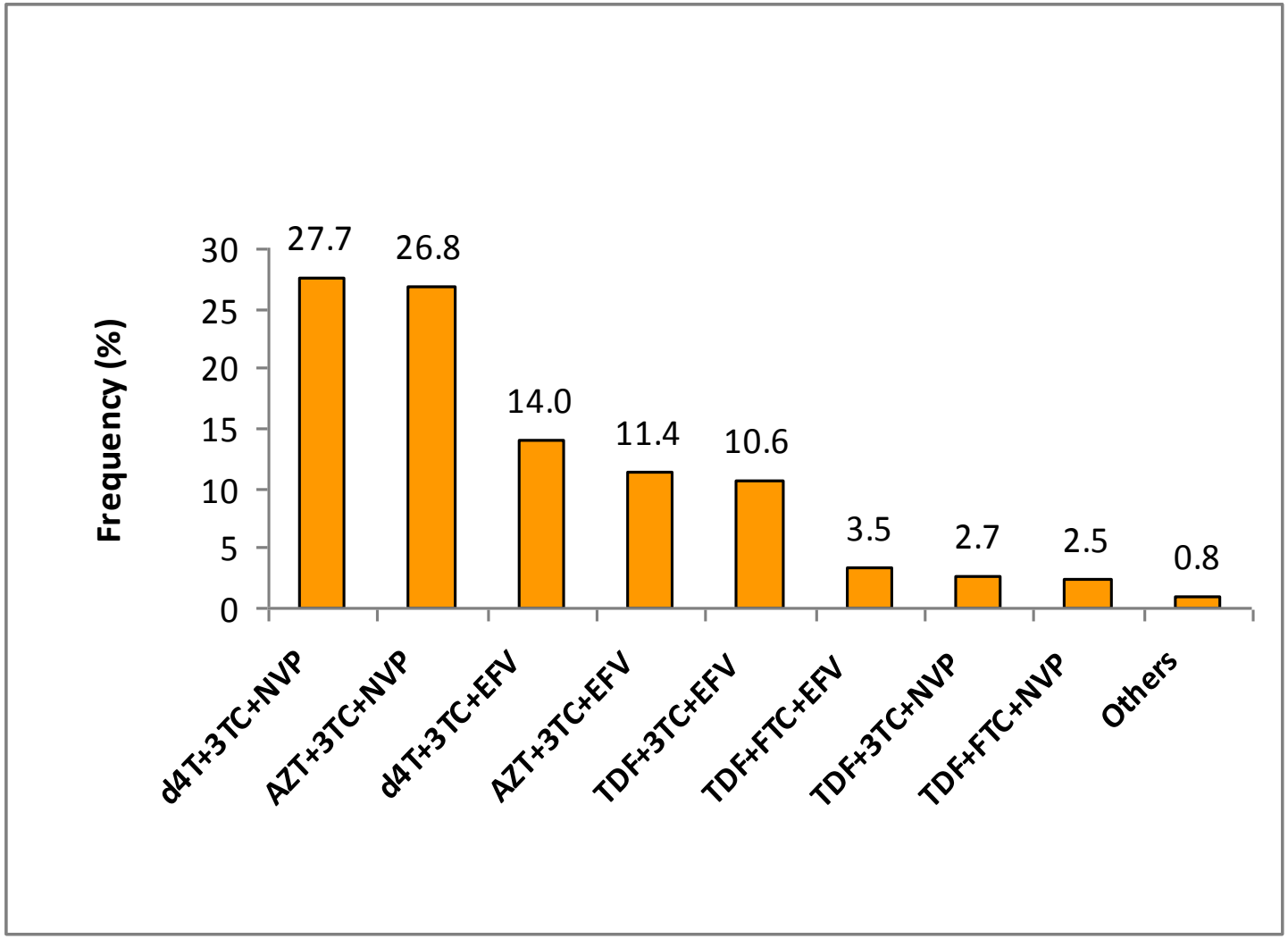


Monitoring and Drug / Treatment issues

- Point of care CD4
- Availability of HIV-RNA
- **Quality of drugs / regimens**


Efavirenz
Tablets 600 mg
ESTIVA-600
30 Tablets
NEVIRAPINE
TABLETS USP 200 mg
Nevivir
60 Tablets
60 Comprimés
Lamivudine, Stavudine &
Nevirapine Comprimés Dispersible
Triomune
Baby
Comprimés Dispersible
Cipla
60 Tablets
Lamivudine
150 mg &
Zidovudine
300 mg Tablets
MACLEODS
LAMIVUDINE,
STAVUDINE &
NEVIRAPINE TABLETS
NEVILAST - 30
60 Tablets
60 Tablets
Lamivudine, Zidovudine
and Nevirapine Tablets
Duovir-N
Cipla
Fumarate de Ténofovir
Disoproxil/Lamivudine
Comprimés
300 mg/300 mg
POM
Schedule 2
PP
30 Comprimés
LAMIVUDINE &
STAVUDINE TABLETS
LAMISTAR - 30
60 Tablets

Main first-line regimens used in adults in LMI countries (except America region)

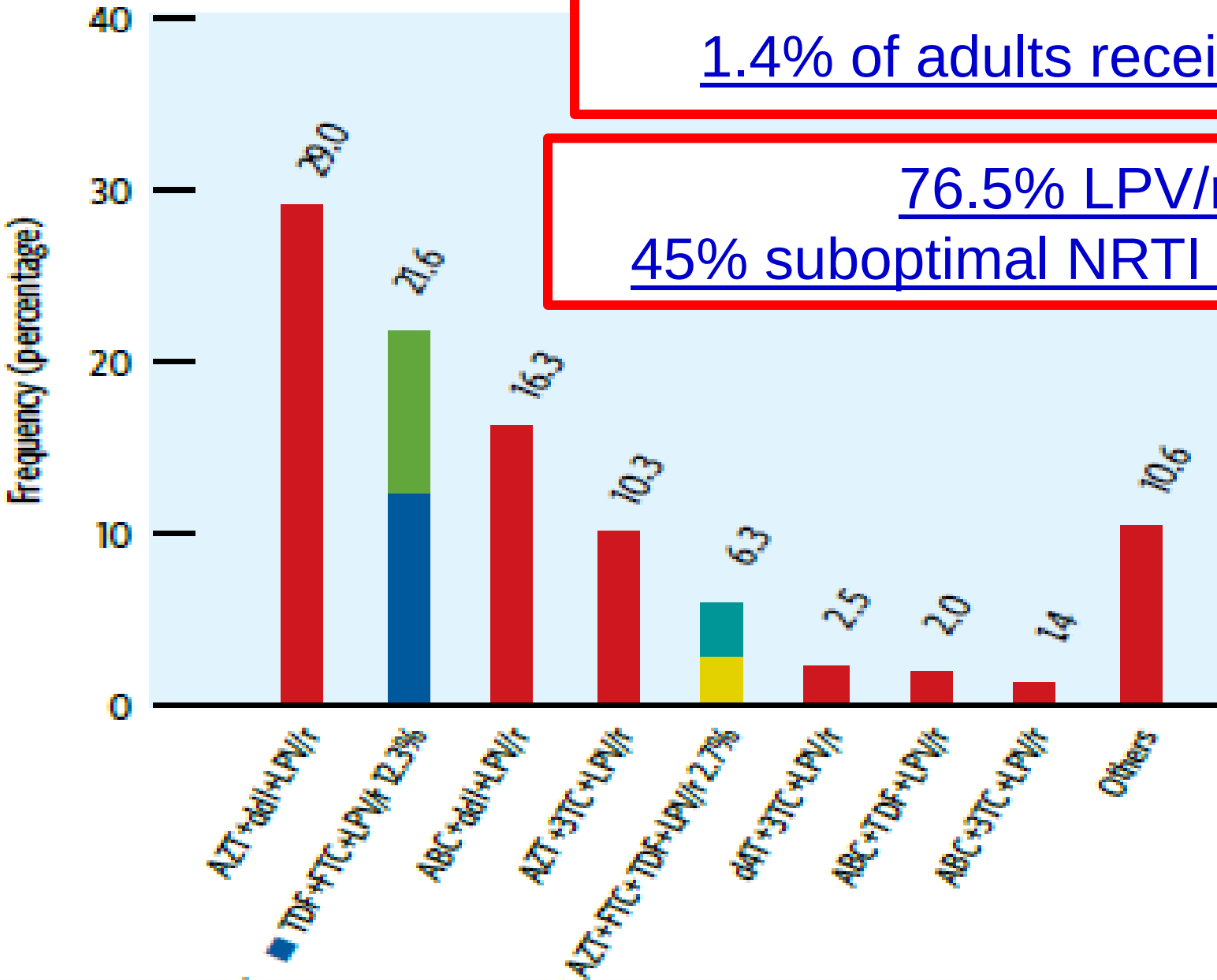


- ✓ 97.1% adults on 1st line
- ✓ 38.5% used AZT and 19.3% TDF
- ✓ 59.9% used NVP and 39,7% EFV

World Health Organization

Update 1 December 2011

Main second-line regimens among adults
(number of patients: 95 900)



1.4% of adults receiving ART

76.5% LPV/r

45% suboptimal NRTI regimen??

Second-Line Antiretroviral Treatment Successfully Resuppresses Drug-Resistant HIV-1 After First-Line Failure: Prospective Cohort in Sub-Saharan Africa

Kim C. E. Sigaloff,[1,2] Raph L. Hamers,[1,2] Carole L Wallis,[3] Cissy Kityo,[4] Margaret Siwale,[5] Prudence Ive,[3] Mariette E. Botes,[6] Kishor Mandaliya,[7] Maureen Wellington,[8] Akin Osibogun,[9] Wendy S. Stevens,[3] Michèle van Vugt,[10] and Tobias F. Rinke de Wit,[1,2] the PharmAccess African Studies to Evaluate Resistance (PASER)

[1]PharmAccess Foundation and [2]Department of Global Health, Academic Medical Center of the University of Amsterdam, Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands; [3]Department of Molecular Medicine and Haematology, University of the Witwatersrand, Johannesburg, South Africa; [4]Joint Clinical Research Centre, Kampala, Uganda; [5]Lusaka Trust Hospital, Lusaka, Zambia; [6]Muelmed Hospital, Pretoria, South Africa; [7]Coast Province General Hospital, International Center for Reproductive Health, Mombasa, Kenya; [8]Newlands Clinic, Harare, Zimbabwe; [9]Lagos University Teaching Hospital, Lagos, Nigeria; and [10]Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Center of the University of Amsterdam, Amsterdam, The Netherlands

Little is known about the effect of human immunodeficiency virus type 1 (HIV-1) resistance mutations present at time of regimen switch on the response to second-line antiretroviral therapy in Africa. In adults who switched to boosted protease inhibitor-based regimens after first-line failure, HIV-RNA and genotypic resistance testing was performed at switch and after 12 months. Factors associated with treatment failure were assessed using logistic regression. Of 243 participants, 53% were predicted to receive partially active second-line regimens due to drug resistance. The risk of treatment failure was, however, not increased in these participants. In this African cohort, boosted protease inhibitors successfully resuppressed drug-resistant HIV after first-line failure.

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The Journal of Infectious Diseases

DOI: 10.1093/infdis/jis261

INTRODUCTION

With more human immunodeficiency virus type 1 (HIV-1) infected people receiving antiretroviral therapy (ART) in low-resource settings, treatment failure and the need to switch to second-line regimens is likely to increase. Reported regimen switching rates have been lower than expected [1, 2], due in part to actual rates of first-line ART success, but also because of restricted access to virological monitoring and second-line regimens. The absence of virological monitoring is associated with delayed switching and consequent accumulation of resistance mutations to nucleoside reverse transcriptase inhibitors (NRTIs) [3, 4]. Lack of access to genotypic resistance testing further complicates the selection of optimal second-line regimens. Few data exist on the impact of resistance mutations selected for by the first-line regimen on the response to empirically prescribed second-line ART in resource-poor settings [5].

This study investigated the impact of acquired HIV-1 drug resistance mutations present at time of regimen switch on the response to second-line ART, within the PharmAccess African Studies to Evaluate Resistance Monitoring (PASER-M) cohort in 6 sub-Saharan African countries.

METHODS

Study Design and Population

PASER-M is a prospective cohort of adults infected with HIV-1 who receive ART at 13 clinical sites in Kenya, Nigeria, South Africa, Uganda, Zambia, and Zimbabwe. Cohort and site characteristics have been profiled elsewhere [6]. Participants were consecutively enrolled during a median site-specific enrollment period of 12 months between March 2007 and September 2009. The present analysis included participants who were switched to second-line ART after first-line failure had been diagnosed using clinical, immunological, and/or virological failure criteria [7]. We excluded participants who had received protease inhibitors (PIs) prior to switch or who were pregnant at study screening. Human immunodeficiency virus type 2 (HIV-2) coinfection was ruled out using an HIV-2 specific antibody test in endemic countries (ie, Nigeria). The study protocol was approved by the appropriate national research ethics committees and the Academic Medical Center of the University of Amsterdam in The Netherlands. Participants provided written informed consent at enrollment.

Procedures

Participants were treated and followed up as per local standard of care, generally in accordance with 2006 World Health

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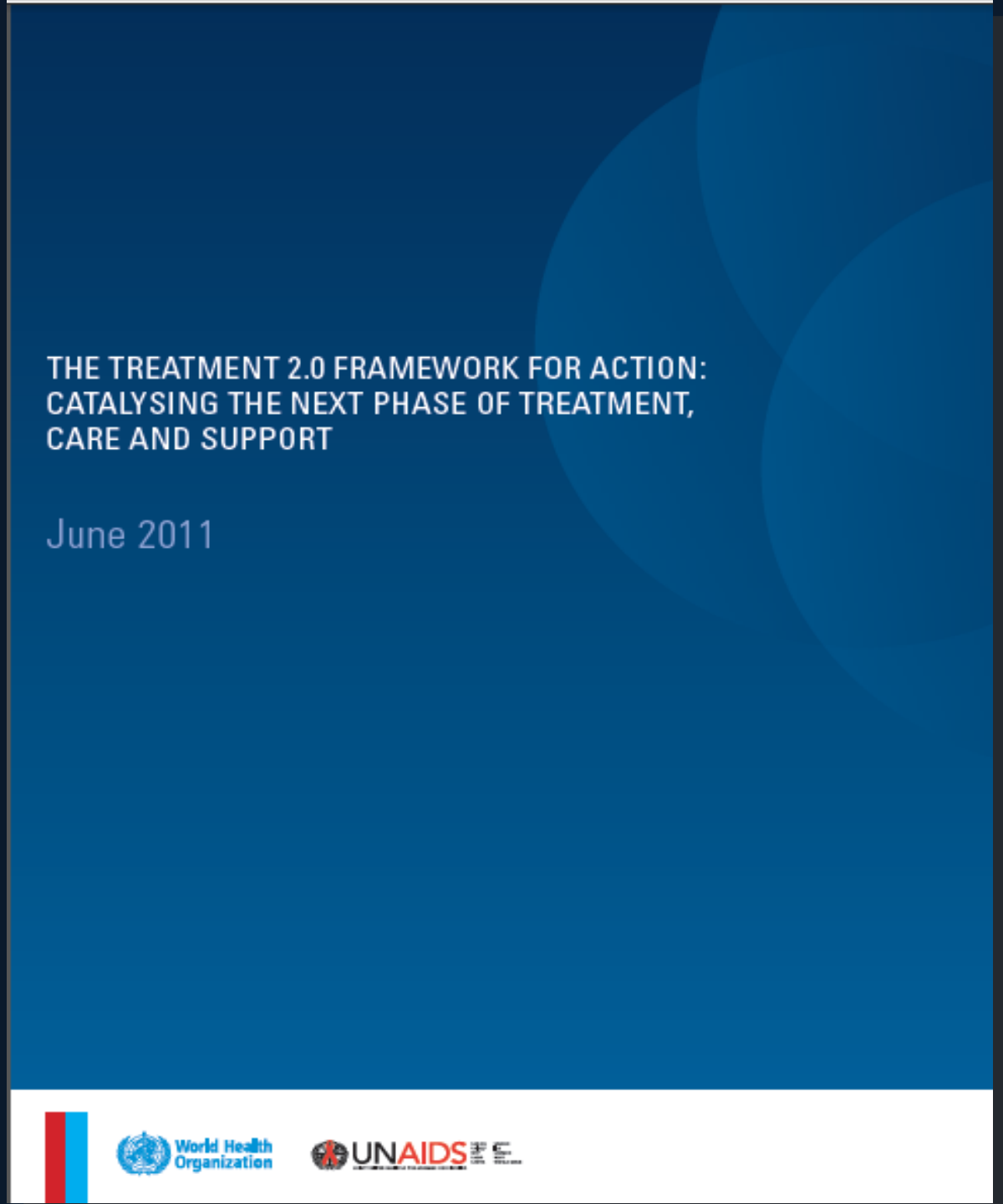
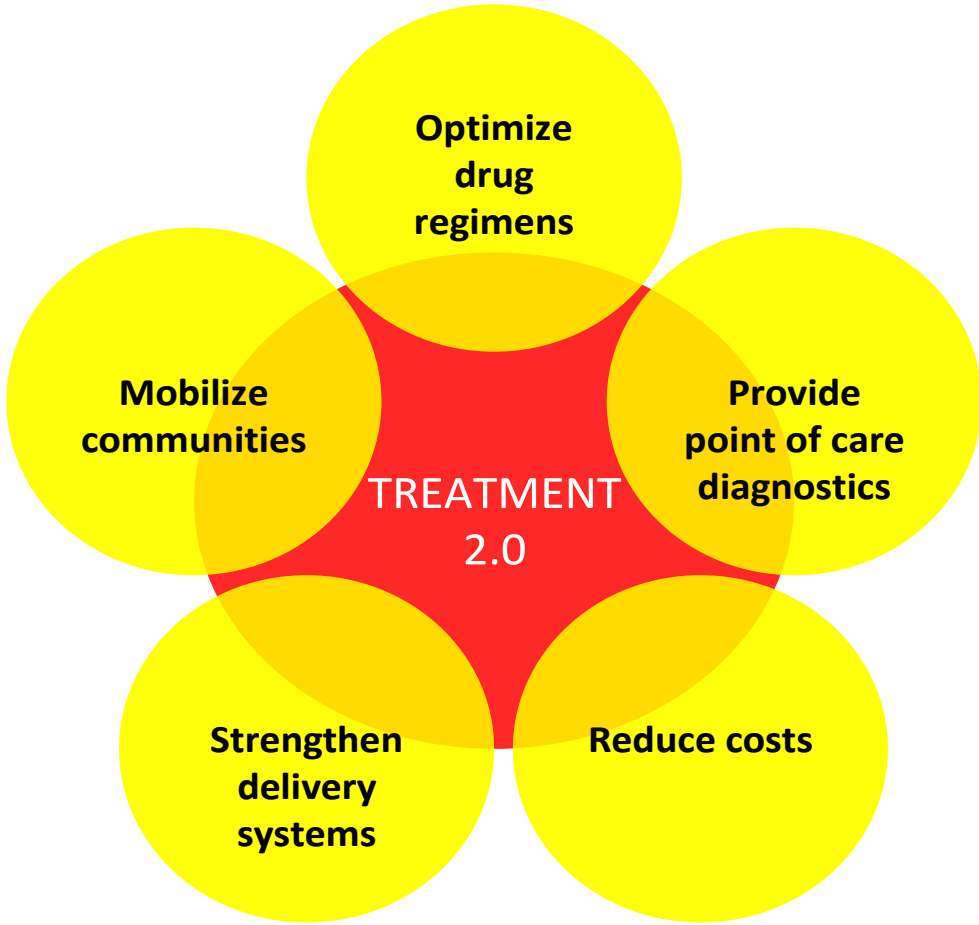

THE TREATMENT 2.0 FRAMEWORK FOR ACTION:
CATALYSING THE NEXT PHASE OF TREATMENT,
CARE AND SUPPORT
June 2011
World Health Organization
UNAIDS

Treatment 2.0

Achieving and Sustaining Universal Access and Maximizing the Preventive Benefits of ART

- Simplification
- Innovation
- Efficiency
- Accessibility and equity
- Affordability
- Decentralization and Integration
- Community involvement



World Health Organization

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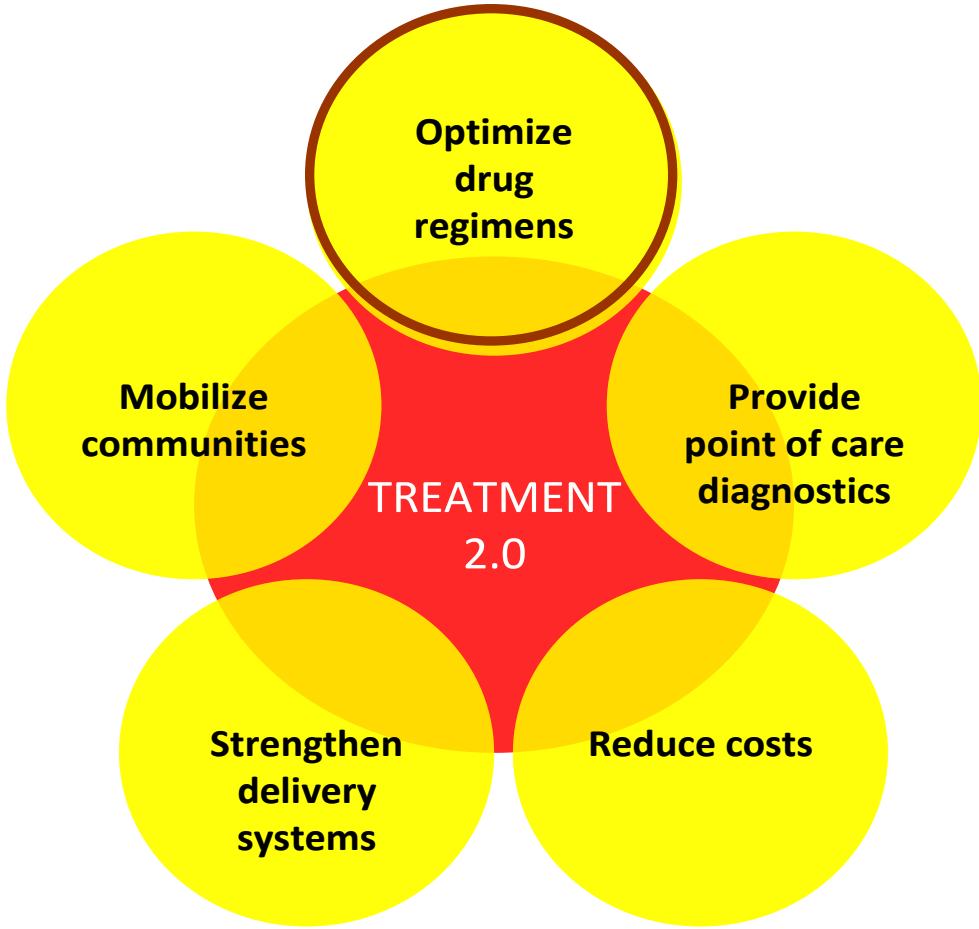
- Decentralization and Integration
- Community involvement



World Health Organization

ART Optimization Strategies

- ✓ Reduce pill burden/pill size
- ✓ Reduce toxicity
- ✓ Minimize drug-drug interactions
- ✓ Minimize laboratory monitoring needs
- ✓ Safe to use in adults, adolescents, children and pregnant women

- Improved adherence & clinical outcomes (maximize time on effective 1st line therapy)
- Improved convenience (patient and programme levels)
- Reduced costs (direct and indirect)

Improve drug bioavailability

Improve API route synthesis

Dose reduction

Substitution of drug components

Use of extended release formulations

Co-formulation (FDC or co-blister pack and pediatric formulation)

Use of new strategies (e.g.: induction-maintenance)

Drug / treatments drawbacks in RLS (I)

- > 25 individual ARVs approved by US FDA, many FDCs available

  →just a few available in RLS

→ Wide variation in prescription and adherence to guideline-based standards-of-care (SOC)
  - No standardized, optimized treatment regimens available
  - Lack of health providers of HIV drug sequencing and resistance basics
  - Limited patient understanding of the importance of adherence
- Patients often treated with the cheapest, not best HIV treatment
- Need for a more standardized approach

Drug / treatments drawbacks in RLS (II)

1. **Drug intolerance and toxicity (D4T, AZT, NVP)**

2. **Long term effectiveness of current drugs/combinations ?**

3. **Mostly clinical / CD4 monitoring**

→ late detection of failure

→ late switches → first line fully “burned”

→ no possibility of recycling first line drug(s)

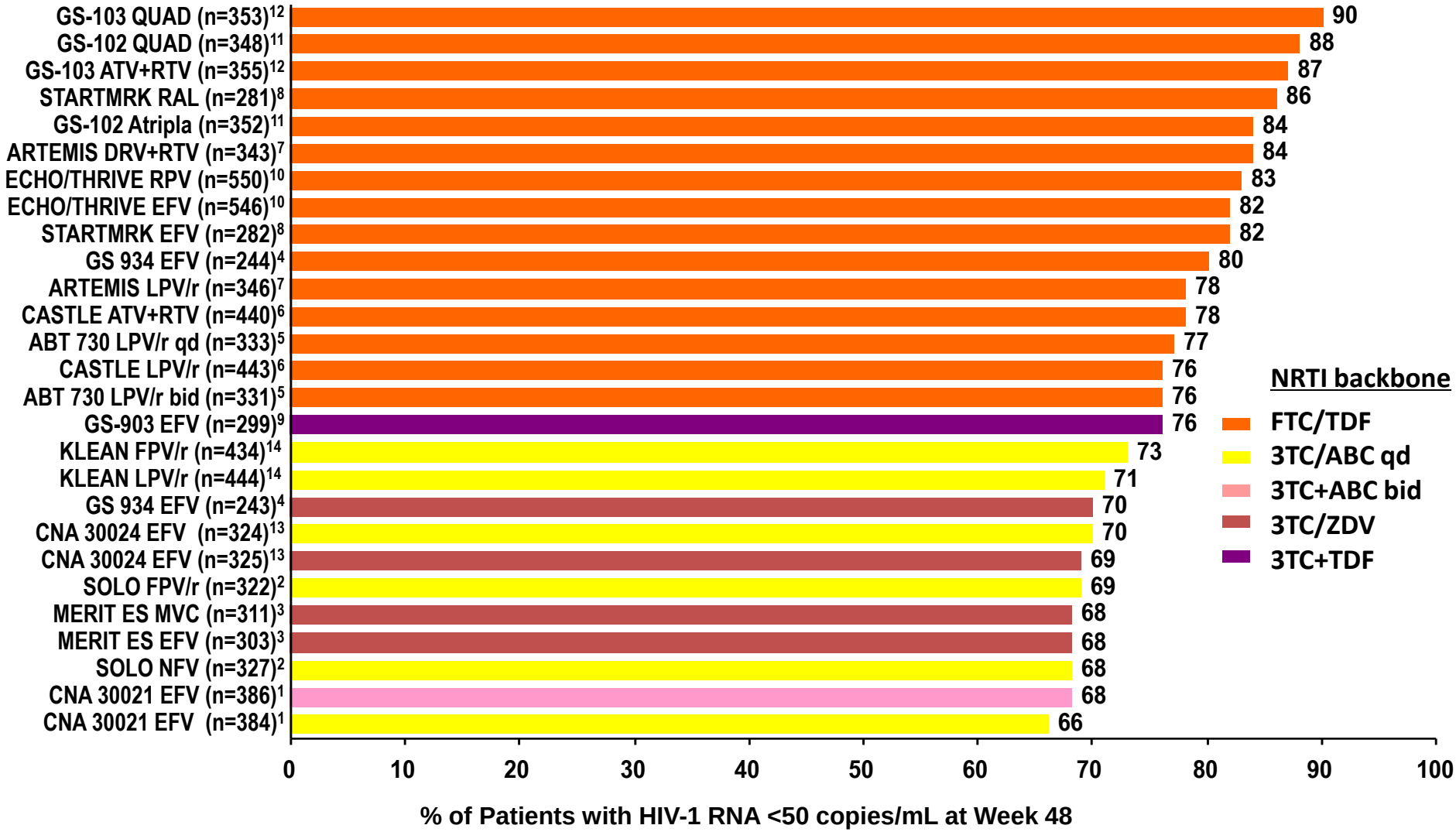
→ Greater chance of resistance spreading

→ 2nd line should contain new drugs

(and of course should be accessible)

FIRST LINE ART WORKS WELL:

Registrational Treatment-Naive Clinical Trials: Cross-Study Comparison HIV RNA <50 c/mL at Week 48*



**This slide depicts data from multiple studies published from 2004-2012. Not all regimens have been compared head-to-head in a clinical trial*

Drug / treatments drawbacks in RLS (II)

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(and of course should be accessible)

In conclusion:

1. *First line should not fail:*
    1. *Convenience (ST)*
    2. *Forgiveness (?)*
    3. *Cost*

In conclusion:

1. *First line should not fail:*
    1. *Convenient (ST)*
    2. *Forgiveness (?)*
    3. *Cheap*

1. ***Second line should be robust:***
    1. ***Two new drugs with predictable efficacy***
    2. ***Compact (?)***
    3. ***Cheap***

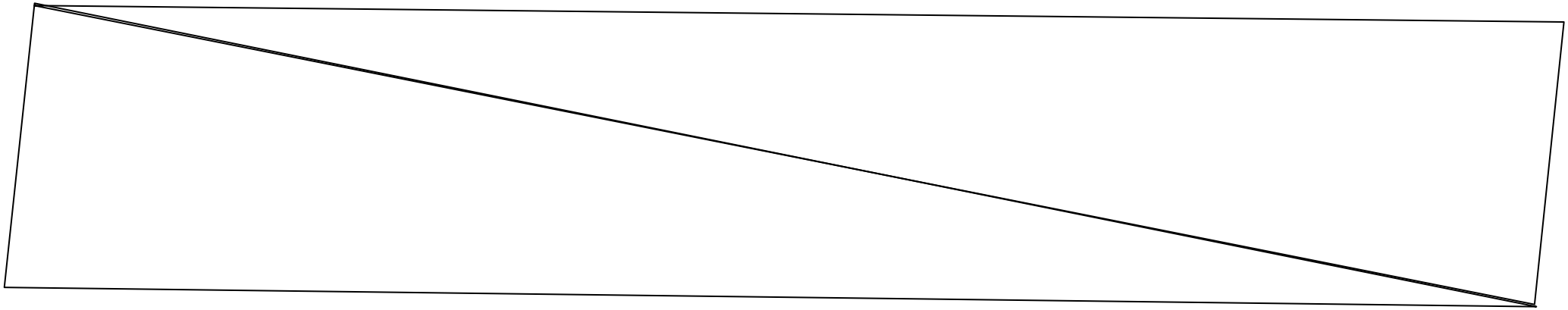
Rationale for standardized approach to treatment regimens

- First line:
  - Uniform, simple regimens, predictable resistance if regimen fails, easy choice of a second line treatment with agents of different mechanism
- Second line and beyond:
  - Uniform regimen, with **new** drugs, sequenced on the basis of *predictable resistance to a standardized first or previous line*, with the highest probability of full virologic suppression

(the term "salvage treatment" disappeared in high income countries)

Elly Katabira, London, 2012

Elements of a potential standardized approach



Treatment A

- Simple
- Tolerable
- Low cost
- Predictable resistance

Monitoring:
- **no VL (POC)**
- **no resistance testing**

Treatment B

- New Classes
- Simple
- Tolerable
- Acceptable cost
- Predictable resistance

Monitoring:
- **VL (?)**
- **Resistance testing (?)**

Treatment C

- New Classes (if possible)
- Tolerable
- Acceptable cost

Years on treatment

Elly Katabira, London, 2012

Potential Advantages of a standardized /simplified approach

- Improved compliance
- Predictability of the responses
- Availability of subsequent lines
- Easier prescription (task shifting)
- Easier monitoring
- Global equity
- Manufacturing / Procurement
- Cost

Examples of STR Regimens for a Public/Global Health Approach

1st line STR

- 2 NRTI + NNRTI
- 2 NRTI + boosted PI
  - Role of 2-drug combinations ?
  - Role of new compact regimens ?

2nd line STR

- boosted PI +/- available/recycled NRTI (current most used)
- boosted PI + Integrase Inhibitor ?
- Next gen NRTI + boosted PI ?
  - Can compact STR 2nd line regimens be constructed ?

3rd Line STR (?)

But there is a need to also consider the special populations

- Major intolerance / toxicity / concomitant drug interactions
- Regimens that prevent or reduce the risk of resistance, and are effective in patients who have failed multiple therapies
- Pediatric regimens (as 90% of HIV-positive children are living in sub-Saharan Africa)
- Regimens appropriate for growing vulnerable populations (including children, pregnant women, and TB / hepatitis co-infected individuals)
- Drugs to be used for prevention that do not conflict with treatment
- Better agents to prevent maternal to child transmission

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- Better agents to prevent maternal to child transmission

(one regimen cannot fit all !)

Two additional questions

1. **What can (already) be the role of the drug/treatment pipeline ?**

Table 1: Summary of pipeline compounds in 2012

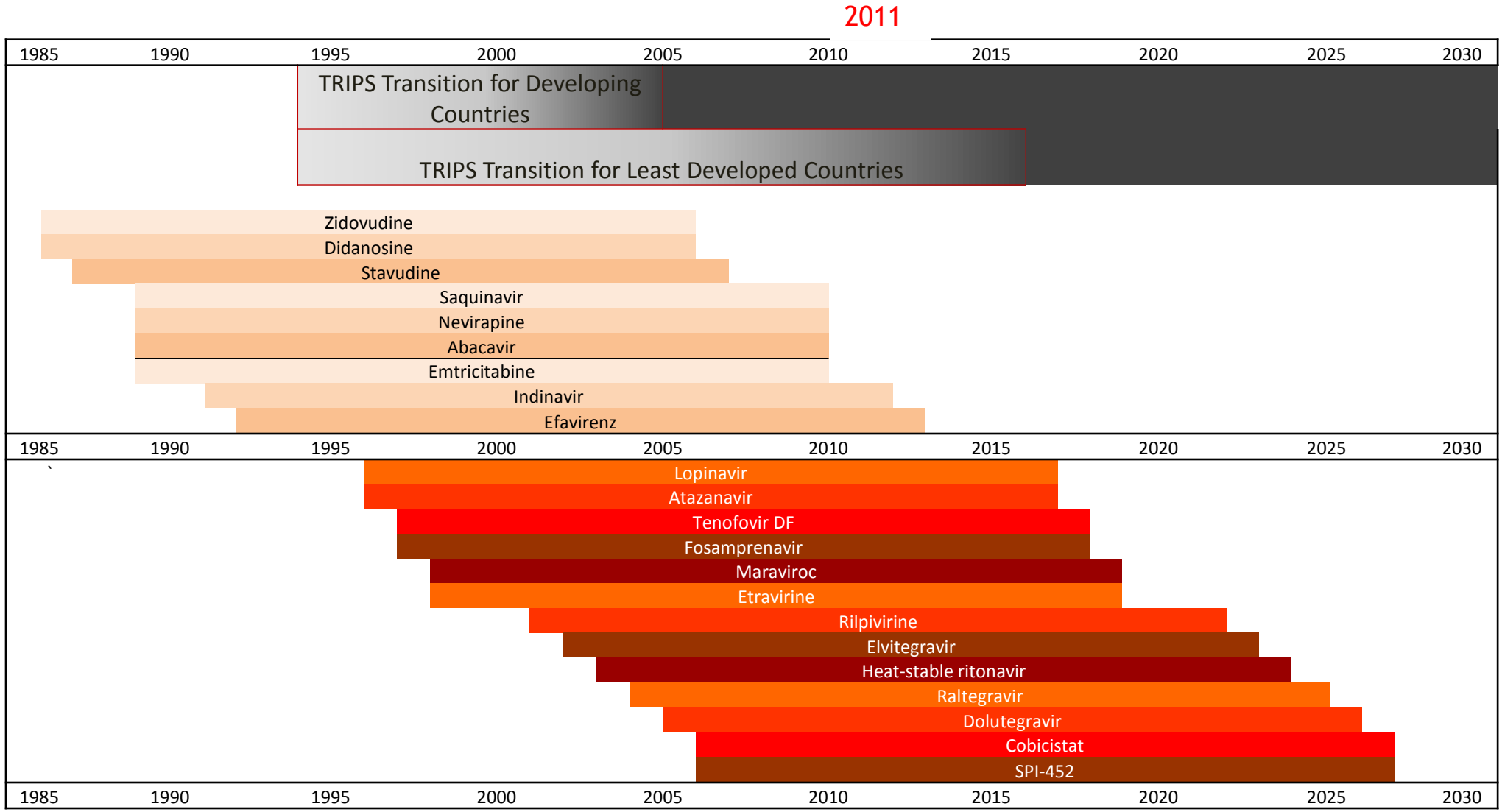
Compound	Company	Class	Stage	Update
rilpivirine / tenofovir / FTC	Tibotec / Janssen	Fixed-dose combination (NNRTI + nukes)	Approved	Approved by FDA in August 2011 and by EMA in September 2011.
Quad™ (tenofovir/FTC/elvitegravir/cobicistat)	Gilead	Fixed-dose combination (boosted integrase inhibitor plus Truvada)	Submitted for approval.	Results from two phase III studies comparing Quad to Atripla™ and atazanavir/ritonavir + Truvada™ were presented at CROI 2012.
Elvitegravir	Gilead	Integrase inhibitor	Phase III	See Quad above. Other studies ongoing, Submission as separate compound expected 2012.
Cobicistat	Gilead	PK booster	Phase III	See Quad above. Ongoing studies include coformulations with darunavir, atazanavir and other 4-drug FDCs, Submission as separate compound expected 2012.
GS-7340	Gilead	Nucleotide (tenofovir prodrug)	Phase III	Approximate -1.7 log (vs -1.0 log with TDF) after 10 days monotherapy. Initially a 25 mg dose selected for development but 10 mg used in FDC with cobicistat. Ongoing studies include in Quad formulation replacing tenofovir and in the first PI-based single-tablet FDC.
Dolutegravir (GSK-1349572)	ViiV / Shionogi	Integrase inhibitor	Phase III / Expanded access	Top line results from 1 out of 4 ongoing Phase III studies have been released. Non-inferior to raltegravir in naïve patients.
GSK-1265744	GSK	Integrase inhibitor	Phase II	Follow-up compound to dolutegravir that may have therapeutic activity at doses of 30 mg or lower. Development currently focused on a monthly injection formulation.
Lersivirine (UK-453061)	ViiV	NNRTI	Phase IIb	Phase IIb 48 week results reported non-inferiority to efavirenz in naïve patients. Ongoing Phase II vs etravirine. No Phase III studies announced.
BMS-986001 (OBP-601,festinavir)	Bristol-Myers Squibb (BMS)	NRTI (similar to stavudine/d4T)	Phase IIb	Dose finding 100, 200 and 400 mg once-daily compared to tenofovir, both with efavirenz + 3TC background nukes.
BMS-663068	Bristol-Myers Squibb (BMS)	Attachment inhibitor (gp120)	Phase IIb	No presentations since CROI 2011. New 24 week Phase II dose finding study ongoing with raltegravir + tenofovir vs atazanvir + ritonavir + raltegravir + tenofovir.
Cenicriviroc (TBR-652)	Tobira	CCR5 inhibitor (also active against CCR2)	Phase II	Ongoing Phase II study in naive patients compared to efavirenz, both with tenofovir/FTC background nukes.
Ibalizumab (TMB-355, was TNX-355)	TaiMed Biologics	CD4-specific humanized IgG4 monoclonal antibody	Phase I	Although a Phase I study is listed for 2011, there has been no new results on this compound for several years.
CMX-157	Chimerix	NRTI similar to tenofovir	Phase I	No further studies over last year.
CTP-518	GSK	Protease inhibitor	Phase I	No further update or studies listed.
Apricitabine	Avexa	NRTI	Phase II	Although a Phase III study was started this was withdrawn Avexa due to uncertainty over financial sponsorship.
Rilpivirine-LA (long acting injection)	Janssen	NNRTI	Phase I	The only study of the long acting formulation (monthly injection) was stopped early by the sponsor. Future studies include as a comparator to a similar formulation of GS-1265744.

Two additional questions

1. What can be the role of the drug/treatment pipeline ?

2. **What can/should be the (collective ?) role of the pharmaceutical industry and of the generic manufacturers ?**

Changing ARV Patent Landscape



Plus, of course, the need for research….

Overview on clinical trials with NUC-sparing regimes in ART naïve patients

Trial	Arms	Size	Patient type	Duration follow-up	Setting	Sponsor
ACTG A5262	• DRV/r + RAL	113	ART naïve	Up to 1,5 years	USA	ACTG
CCTG589	• LPV/r + RAL • EFV/TDF/FTC	50	ART naïve	2 years	California / USA	CCTG
GARDEL	• LPV/r + 3TC • LPV/r + 3TC/FTC + NRTI	410	ART naïve	Up to 2 years	Argentina	Huesped
MODERN	• DRV/r + MRV • DRV/r + FTC+TDF	804	ART naïve, only R5 HIV-1	Up to 3 years	USA, Puerto Rico	ViiV
NEAT 001	• DRV/r + RAL • DRV/r + FTC+TDF	800	ART naïve	3 years	Austria, Belgium, Denmark, France, Germany, Great Britain, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Sweden	NEAT/ANRS
PROGRESS	• LPV/r + RAL • LPV/r + FTC/TDF	206	ART naïve	Up to 2 years	USA, Canada, France, Italy, Poland, Puerto Rico, Spain	Abbott
RADAR	• DRV/r + RAL • DRV/r + FTC + TDF	80	ART naïve	2 years	Texas / USA	Dallas VA MC
SALT	• ATV/r + 3TC • ATV/r + 2 NRTIs	392	ART naïve	Up to 3 years	Spain	FSG
SPARTAN	• ATV/r + RAL • ATV/r + TDF + FTC	94	ART naïve	terminated		BMS

Overview on clinical trials with NUC-sparing regimes in ART experienced patients

Trial	Arms	Size	Patient type	Duration follow-up	Setting	Sponsor
DREAM	• EFV / FTC+TDF • LPV/r monotherapy	420	Stable ART VL<50	2 years	France	ANRS
EARNEST	• PI/r + 2NRTIs • PI/r + RAL • PI/r + RAL induct. then PI/r monotherapy maintenance	1277	Patients naïve to PI therapy failing firstline NNRTI+2NRTI ART	3 years	Kenya, Malawi, Uganda, Zambia, Zimbabwe	MRC
MARCH	• MRV + 2 NRTI • MRV + PI/r	560	Patients on stable PI based ART VL<200	Up to 2,5 years	Australia	Kirby Institute
PIVOT	• SOC ART • PI/r monotherapy	587	Treated patients VL<50	Up to 5 years	UK	MRC
PROTEA	• DRV/r + 2 NRTIs • DRV/r + 2 NRTIs induct. then DRV/r monotherapy maintenance	260	Stable ART for at least 48 weeks VL<50	Up to 3 years	?	Janssen-Cilag
SECOND-LINE	• LPV/r + RAL • LPV/r + 2 NRTIs	550	Patients which treatment failure to first-line	Up to 4 years	Argentina, Australia, Chile, France, Germany, Hongkong, India, Ireland, Malaysia, Mexico, New Zealand,	Kirby Institute

Treatment 2.0 as a catalyst for Tasp through Drug / Treatment Optimization

1. The problems of ART implementation in RLS

2. A couple of tools which may be helpful….

   a. Treatment 2.0 / Treatment Optimization process

   a. The new WHO guidelines process

Note #1:

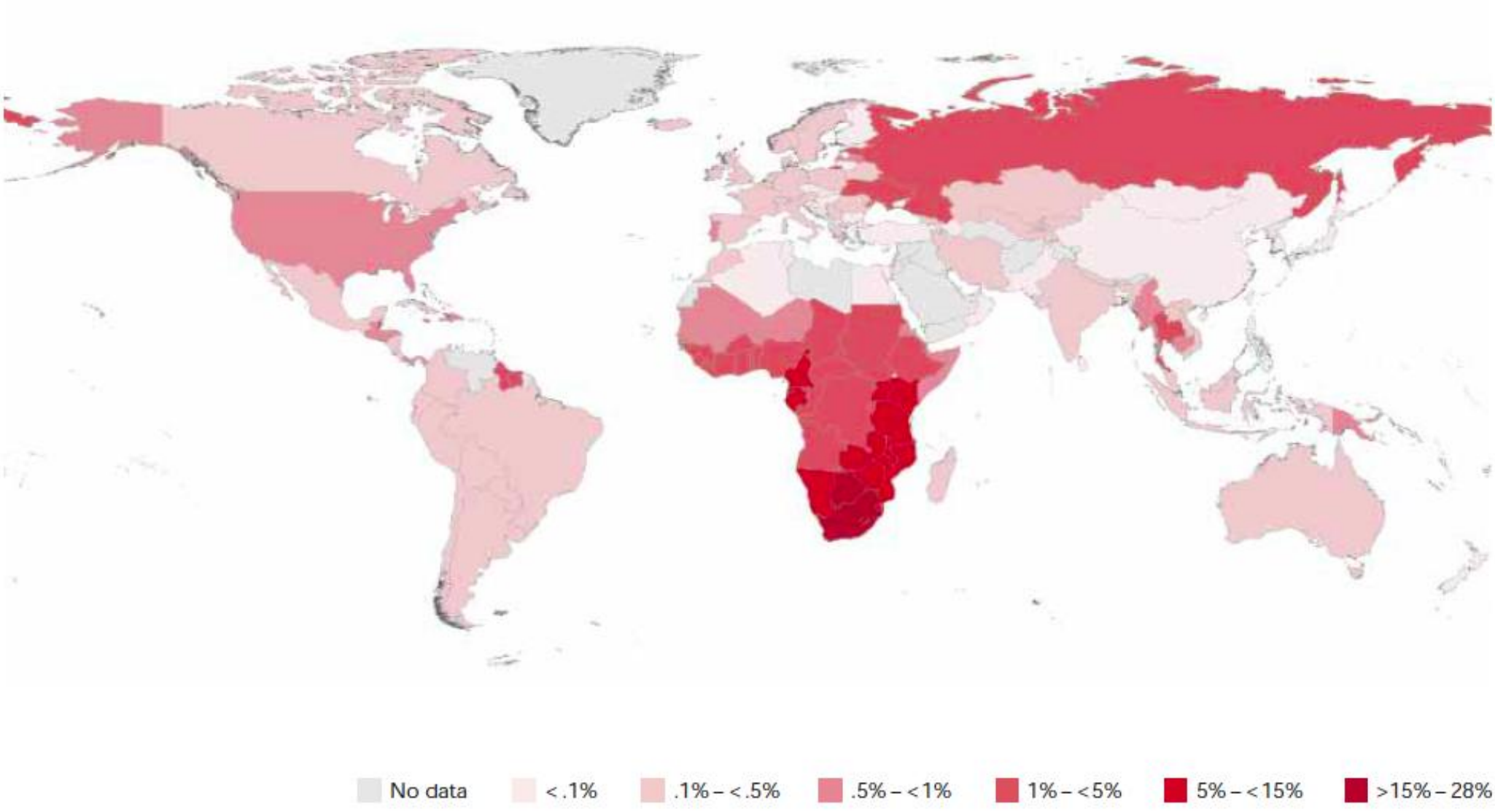
WHO Guidelines shall address

a global epidemic in contexts which may be very differents

- Generalized vs non generalized epidemic
- Different Prevalence / Incidence
- GPD / resources / health expenditure
- Political committment
- Foreign aid
- Rights, gender, community empowerment
- ARV coverage
- ……..

Global prevalence of HIV, 2009

Source: UNAIDS.



Note #2:

A) guidelines shall be a framework or a tool to support individual countries to develop their own guidelines.

B) WHO shall set the global standard and the goals to where countries can immediately or progressively aim to…

Note #3: the public health approach

- WHO published its first ART guidelines for adults and adolescents in 2002, and subsequently revised them in 2003, 2006 and 2010.

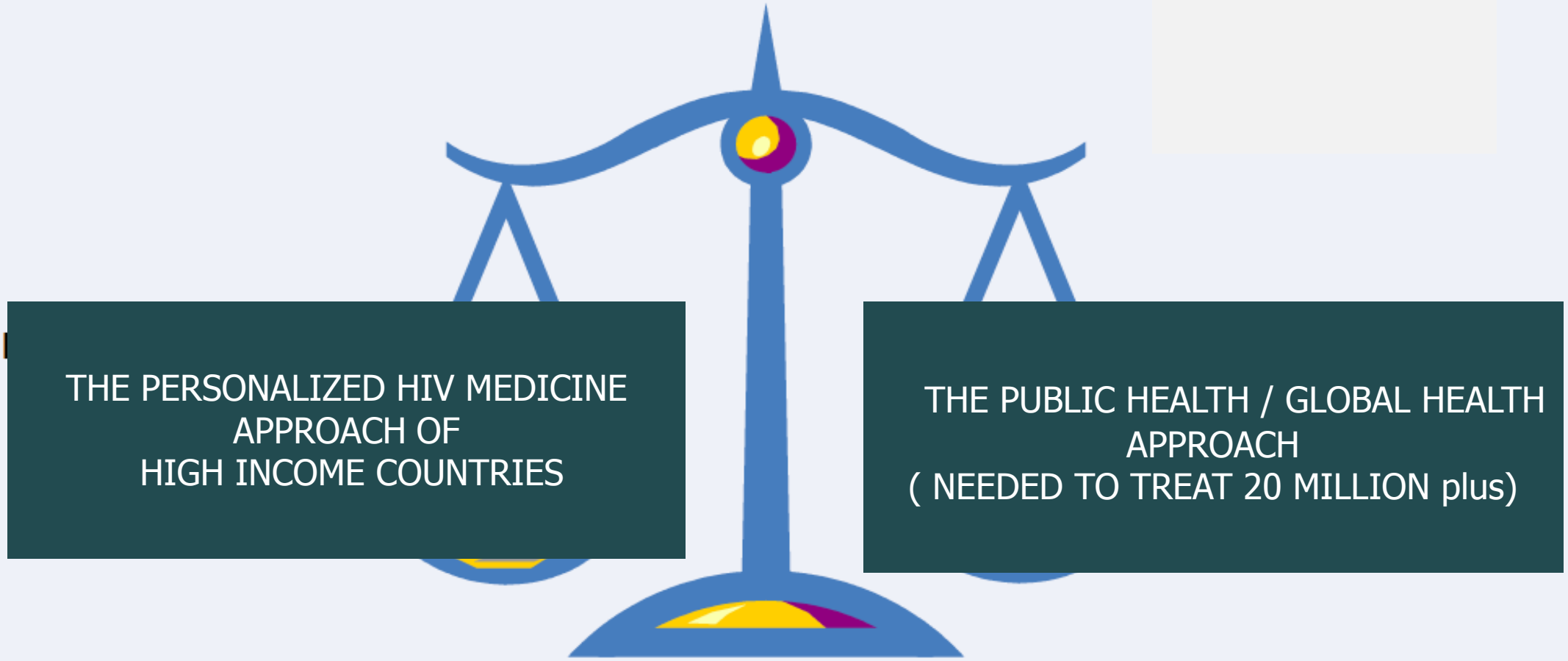
- The 2013 WHO HIV consolidated guidelines will be based on the same public health principles prioritizing the people who are sicker and most at risk to HIV mortality and morbidity and aiming to accelerate progress towards universal access of HIV diagnostics, treatment, care and support to all people in need.

SCALING UP ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS

GUIDELINES FOR A PUBLIC HEALTH APPROACH

World Health Organization
June 2002

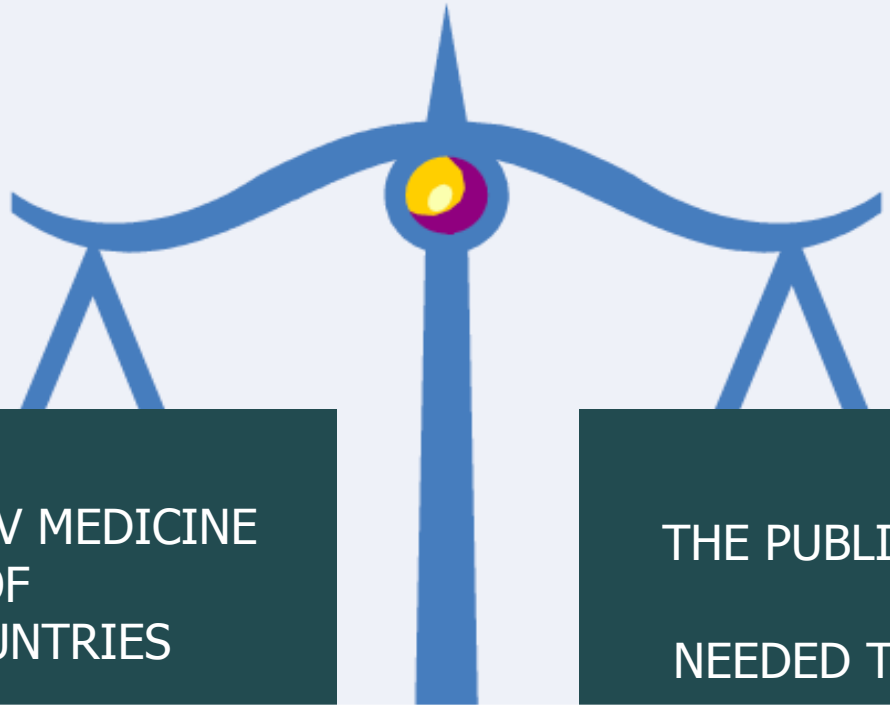
The need to balance….



THE PERSONALIZED HIV MEDICINE APPROACH OF HIGH INCOME COUNTRIES

THE PUBLIC HEALTH / GLOBAL HEALTH APPROACH (NEEDED TO TREAT 20 MILLION plus)

The need to balance….



THE PERSONALIZED HIV MEDICINE APPROACH OF HIGH INCOME COUNTRIES

THE PUBLIC HEALTH / GLOBAL HEALTH APPROACH NEEDED TO TREAT 20 MILLION plus

with, no differences in standards !!!

2013 and 2015 WHO GUIDELINES

- Expanding the scope: the new updates will move beyond clinical recommendations (*What to do?*) to include operational (*How to do?*) and programmatic (*How to decide what to do and where?*) recommendations to provide comprehensive guidance to national programme managers and policymakers.

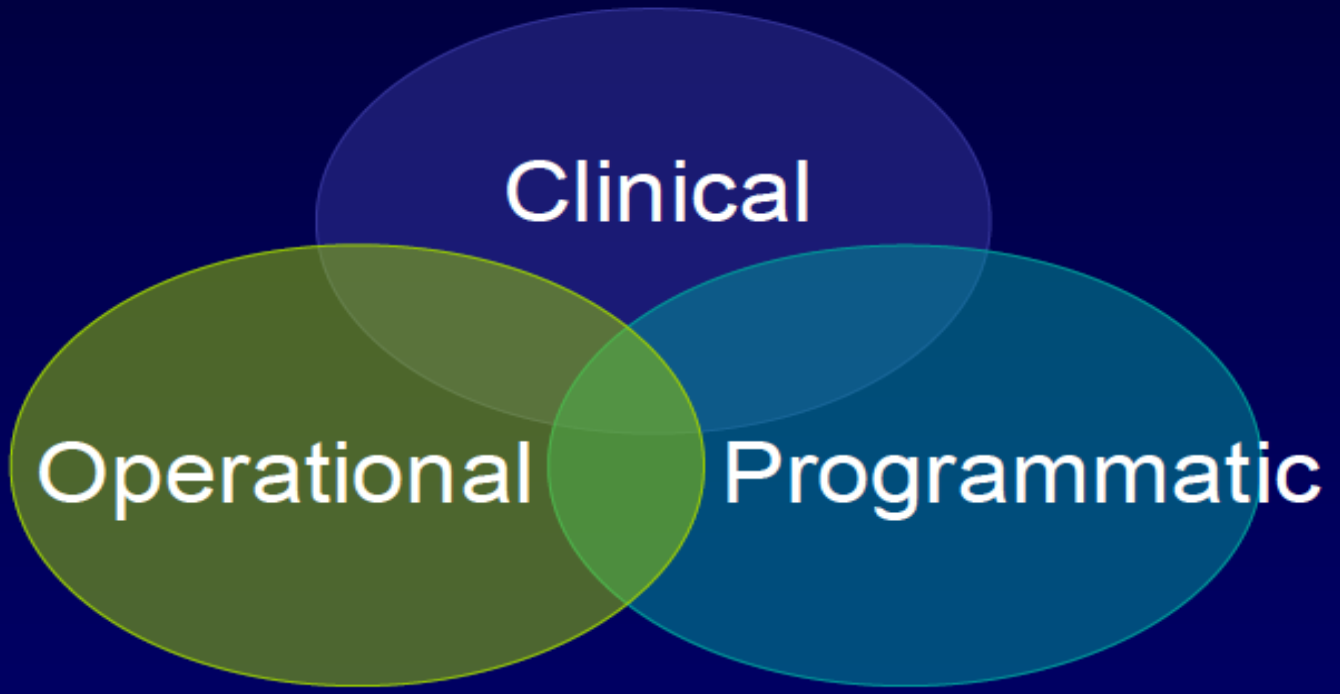
- Addressing all age groups and populations

- Providing guidance across the Continuum of HIV care

- Expanding the evidence-base to support recommendations

2013 Consolidated Guidelines for adults adolescents, pregnant women and children

WHAT TO DO?



HOW TO DO?

HOW TO DECIDE WHAT TO DO, WHEN AND WHERE?

World Health Organization

Draft Roadmap to 2013 WHO guidelines

- Q 2, 2012: Constitution of the Guidelines Development Groups (GDGs)
- Q 3, 2012: Guidelines Development Groups meetings to prepare draft recommendations
- Q 4, 2012: Publication of comprehensive update including anticipated recommendations
- Q 1, 2013: Final draft and Peer review of Consolidate Guidelines and final revisions
- Q 1-2, 2013: Publication and dissemination

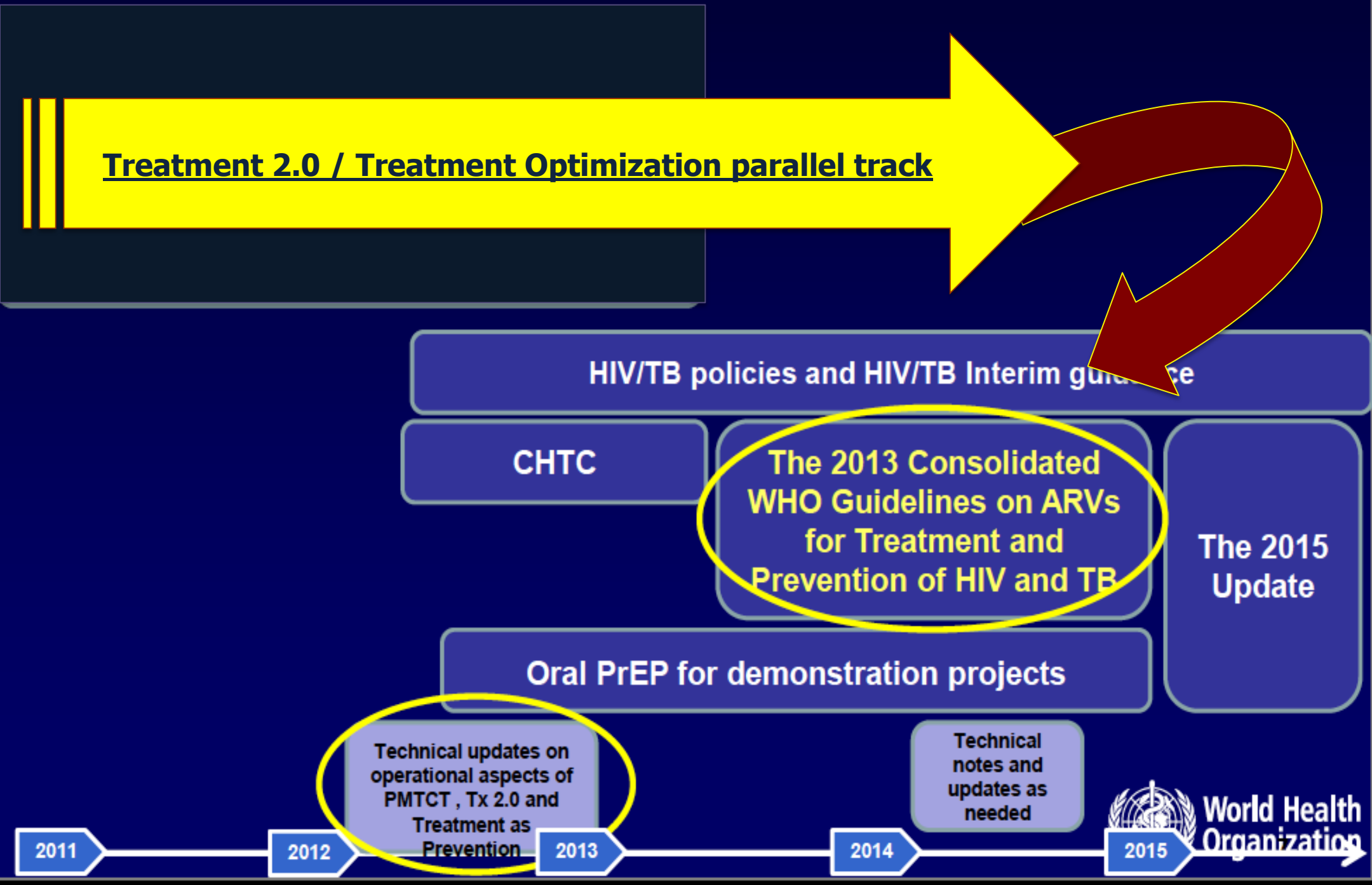
Examples of what should/can be addressed….

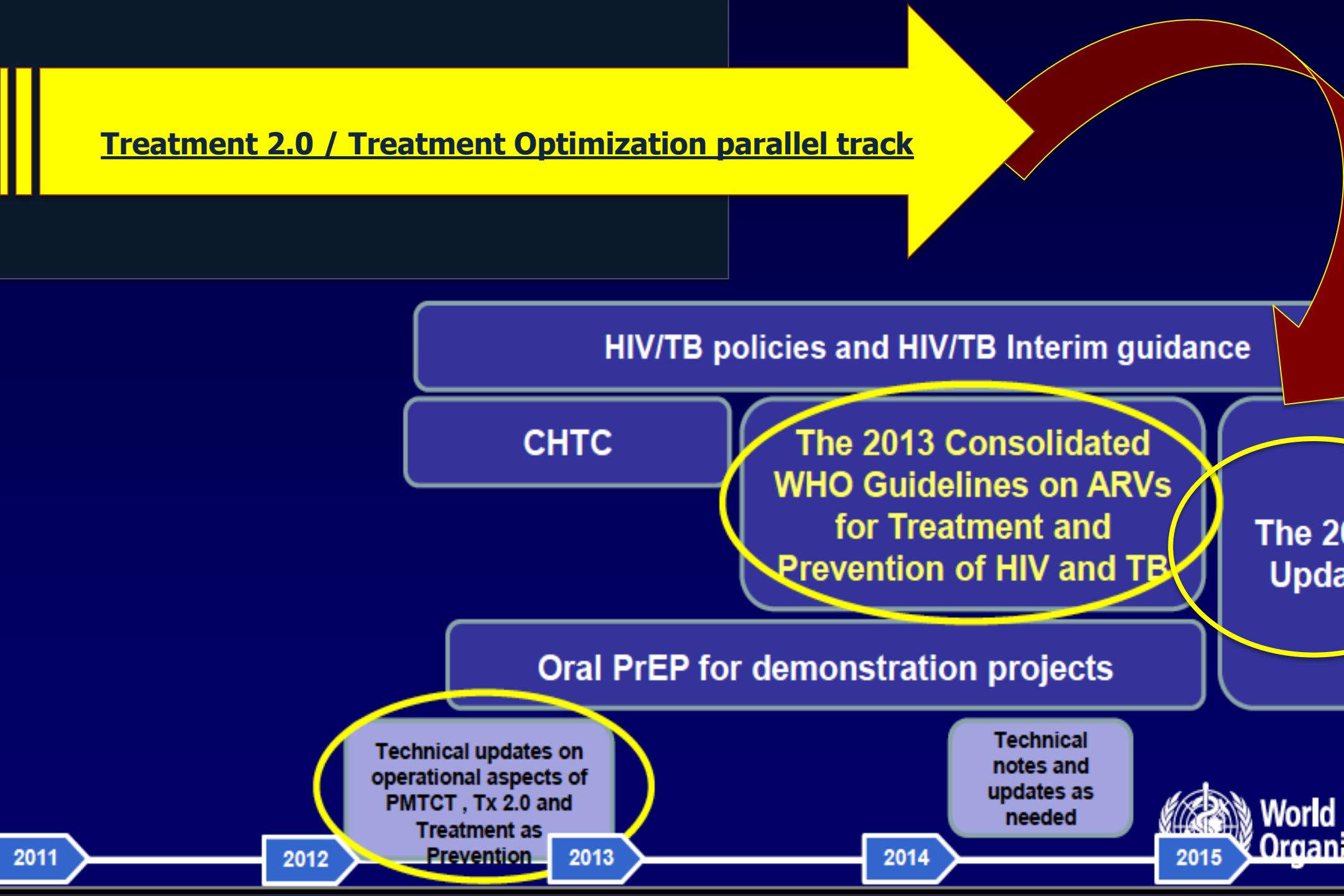
- Redefine “when to start ARV” in RLS
  - At least, initially, for specific groups, then moving to universal treatment anticipation
  - With an eye on clinical priorities and a balance in resource allocation, quality vs quantity (anticipation of timing in high income setting was driven by pathogenesis, but permitted by the increased “quality “ of drugs)
- Improve the quality of ART, driving the recommendations towards
  - potency, long term safety
  - tolerability to promote adherence
  - convenience single tablet / fixed dose combinations
  - Apprpriate sequencing
- Advocate for POC diagnostics (still considering that it may take some time…) to promote increased access, patient retention and treatment monitoring
- Improve and integrate services for special populations
  - Pregnant women and children / coinfected / etc……

In conclusion, WHO and UNAIDS are working on parallel, mutually reinforcing and finally converging pathways:

1. The 2013 and 2015 Guidelines process

2. The Treatment 2.0 / Treatment Optimization process


Treatment 2.0 / Treatment Optimization parallel track
HIV/TB policies and HIV/TB Interim guidance
CHTC
The 2013 Consolidated WHO Guidelines on ARVs for Treatment and Prevention of HIV and TB
The 2015 Update
Oral PrEP for demonstration projects
Technical updates on operational aspects of PMTCT , Tx 2.0 and Treatment as Prevention
Technical notes and updates as needed
2011
2012
2013
2014
2015
World Health Organization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Technical notes and updates as needed
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Thanks to…

Gottfried Hirschall

Marco de Avila

Bernard Schwartlander

SPECIAL REVIEW

The history of antiretroviral therapy and of its implementation in resource-limited areas of the world

Stefano Vella[a], Bernard Schwartländer[b], Salif Papa Sow[c], Serge Paul Eholie[d] and Robert L. Murphy[e]

HIV/AIDS not only represent the most severe epidemic in modern times, but also the greatest public health challenge in history. The response of the scientific community has been impressive and in just a few years, turned an inevitably fatal disease into a chronic manageable although not yet curable condition. The development of antiretroviral therapy is not only the history of scientific advancements: its the result of the passionate 'alliance' towards a common goal between researchers, doctors and nurses, pharmaceutical industries, regulators, public health officials and the community of HIV-infected patients, which is rather unique in the history of medicine. In addition, the rapid and progressive development of antiretroviral therapy has not only proven to be life-saving for many millions but has been instrumental in unveiling the inequities in access to health between rich and poor countries of the world. Optimal benefits indeed, are not accessible to all people living with HIV, with challenges to coverage and sustainability in low and middle income countries. This paper will review the progress made, starting from the initial despairing times, till the current battle towards universal access to treatment and care for all people living with HIV.

AIDS 2012, **26**:000–000

Keywords: AIDS, antiretroviral therapy, HIV, resource-limited settings