Challenges of HIV drug resistance in resource-limited settings

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Overview

- HIV epidemiology (resource-limited setting)
  - Impact of ART on HIV incidence and mortality/life expectancy

- ART programmes
  - The programme in the primary health care clinic
    - HIV testing and linkage to care
    - Challenges for providers and clients
  - Adherence
  - Acquired drug resistance
  - Transmitted drug resistance
  - Issues re resistance in light of expanding treatment criteria and consequences for treatment as prevention

- PMTCT programmes
  - ART and MTCT, ART impact on mother and child survival
  - Challenges in PMTC programme delivery
  - Challenges re adherence during- and after pregnancy
  - Evidence re resistance in PMTCT setting(related either to non-adherence or to biological sub-dosing) for mother or child

Global Burden of HIV

- Worldwide, by end 2013, an estimated 35 million people were living with HIV, of whom nearly 25 million in sub-Saharan Africa
- In that year, there were 2.1 m (1.9-2.4m) new HIV infections globally, a decline of 38% from 2001
- Almost half of all people (48%) living with HIV are estimated to know their status; in sub-Saharan Africa, 86% of those who know their HIV status are receiving antiretroviral treatment, suggesting that first contact with services is still in relative advanced HIV disease
- HIV-related mortality has declined considerably in all world regions: in sub-Saharan Africa the number of HIV-related deaths fell by 39% between 2005 and 2013

UNAIDS Gap report 2014

HIV in children

The overwhelming majority of children born to HIV-infected women are also in sub-Saharan Africa:

- Globally, in 2013, 240,000 (210,000-280,000) children were newly infected with HIV, 58% fewer than in 2002
- Which means that an estimated 650 new paediatric infections occur each day in children < 15 years of age, nearly all attributable to mother-to-child transmission (MTCT) and mostly in sub-Saharan Africa
- The prevalence of HIV among pregnant women varies from less than 1% in the UK and Europe to over 40% in some areas of southern Africa
- Providing access to ART for pregnant women living with HIV has averted nearly a million new HIV infections in children between 2009 and 2012

UNAIDS GAP report 2014

Global ART programmes

- By mid-2014, 13.6 million people were on ART globally
- The percentage of HIV infected adults on ART increased to 37% in 2013
- 3 out of 4 people on ART are living in SSA; in South Africa alone, approx 3.5m of the 6.5m HIV-infected people are on ART

ART	Eligibility criteria	Year
HAART, combination therapy	• CD4 < 200 cells/μl, • WHO stage 3 or 4 disease	2004
HAART, combination therapy	• CD4 < 350 cells/μl pregnant women and adults with TB disease	2010
HAART, Atripla®	• CD4 < 350 cells/μl for all adults	2011
HAART, Atripla®	•CD4 < 500 cells/μl for all adults	2013

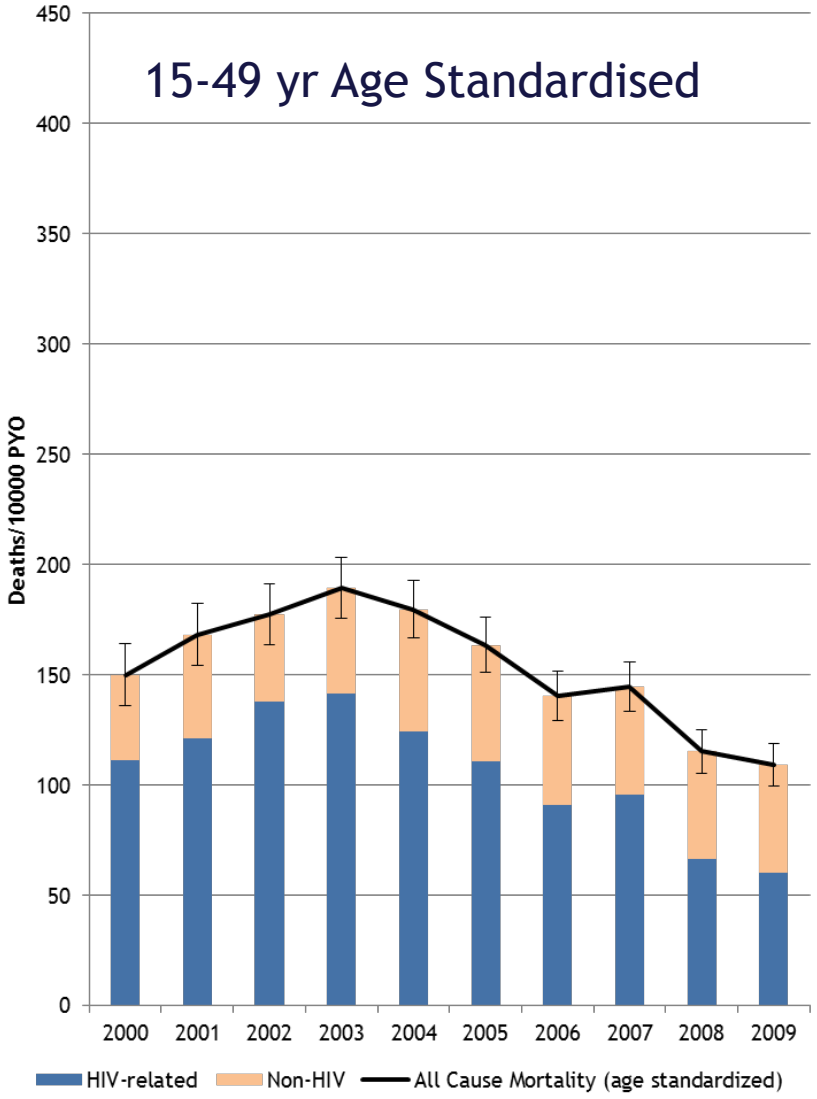
Impact of ART at population level

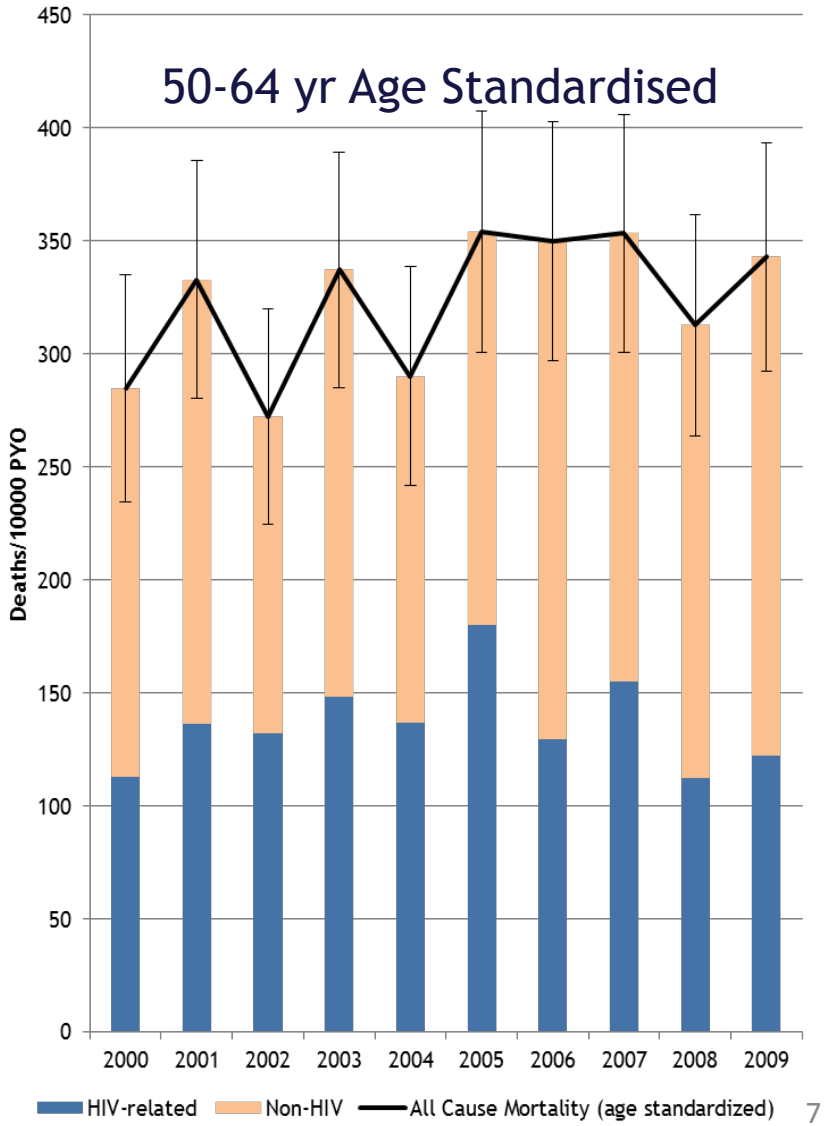
Adult mortality

Child mortality

HIV incidence

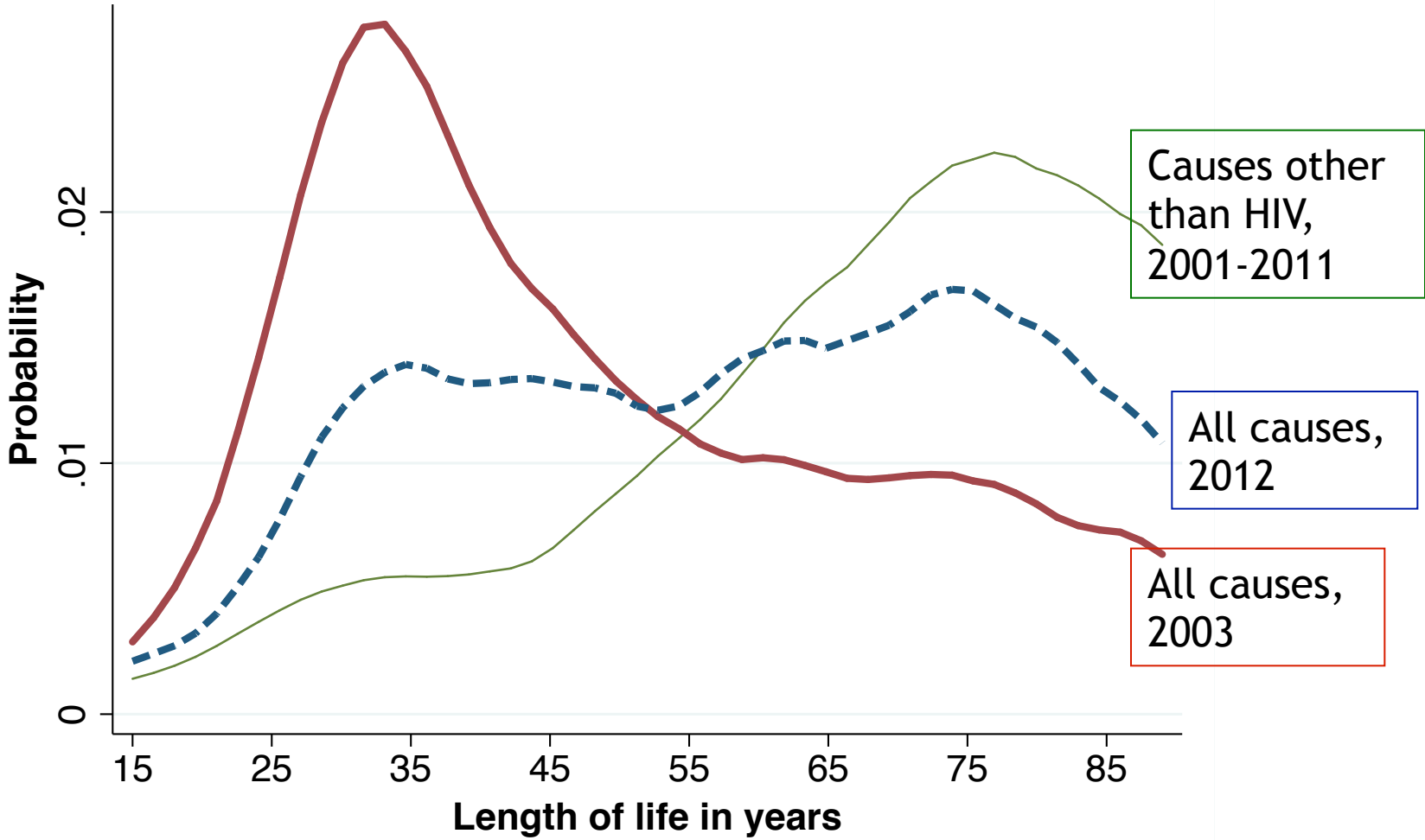
Mortality in adults 2000-2009, deaths per 10,000 PYO





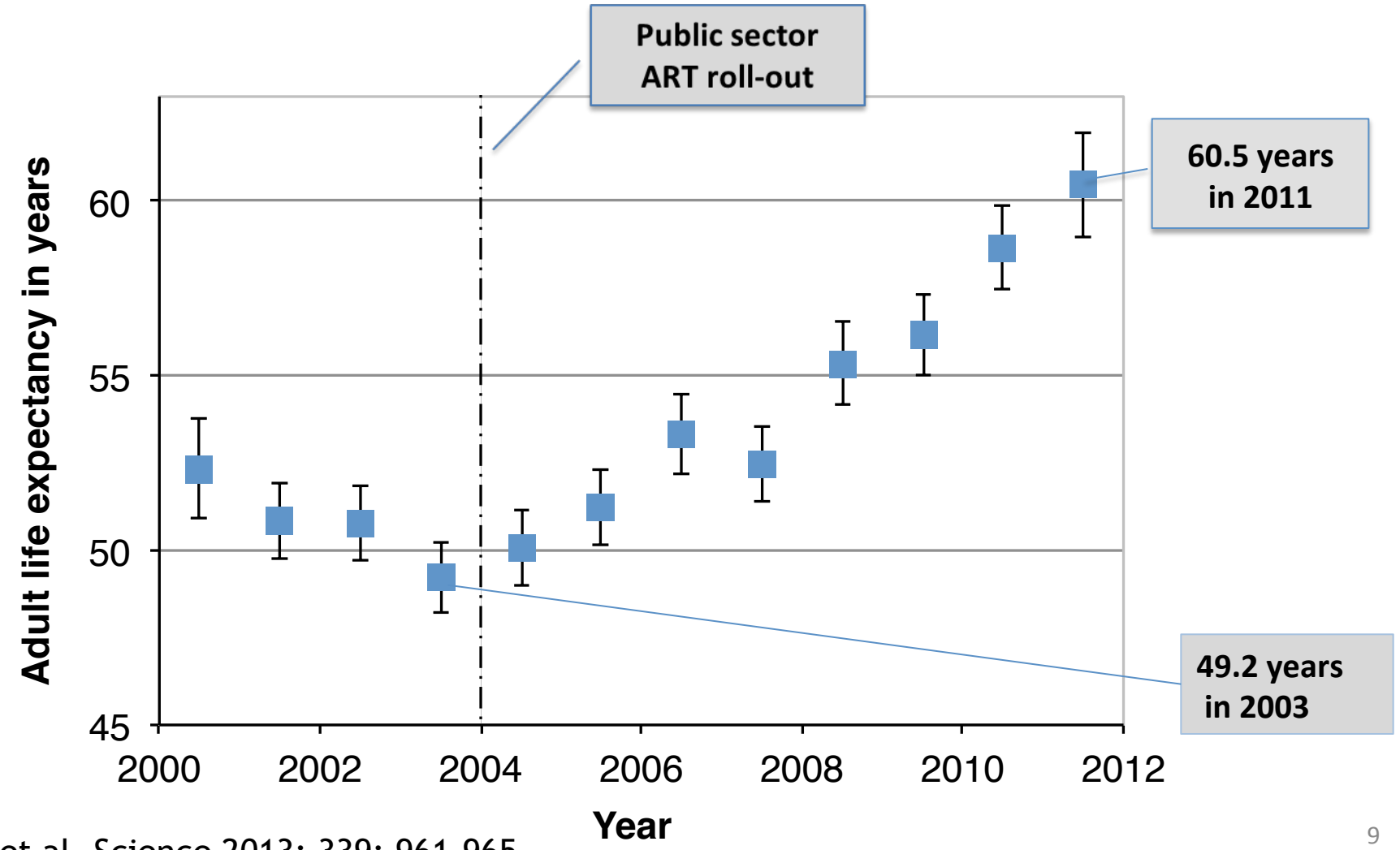
Herbst et al; Population Health Metrics 2011

Mortality in adults 2003 and 2012: Age at death



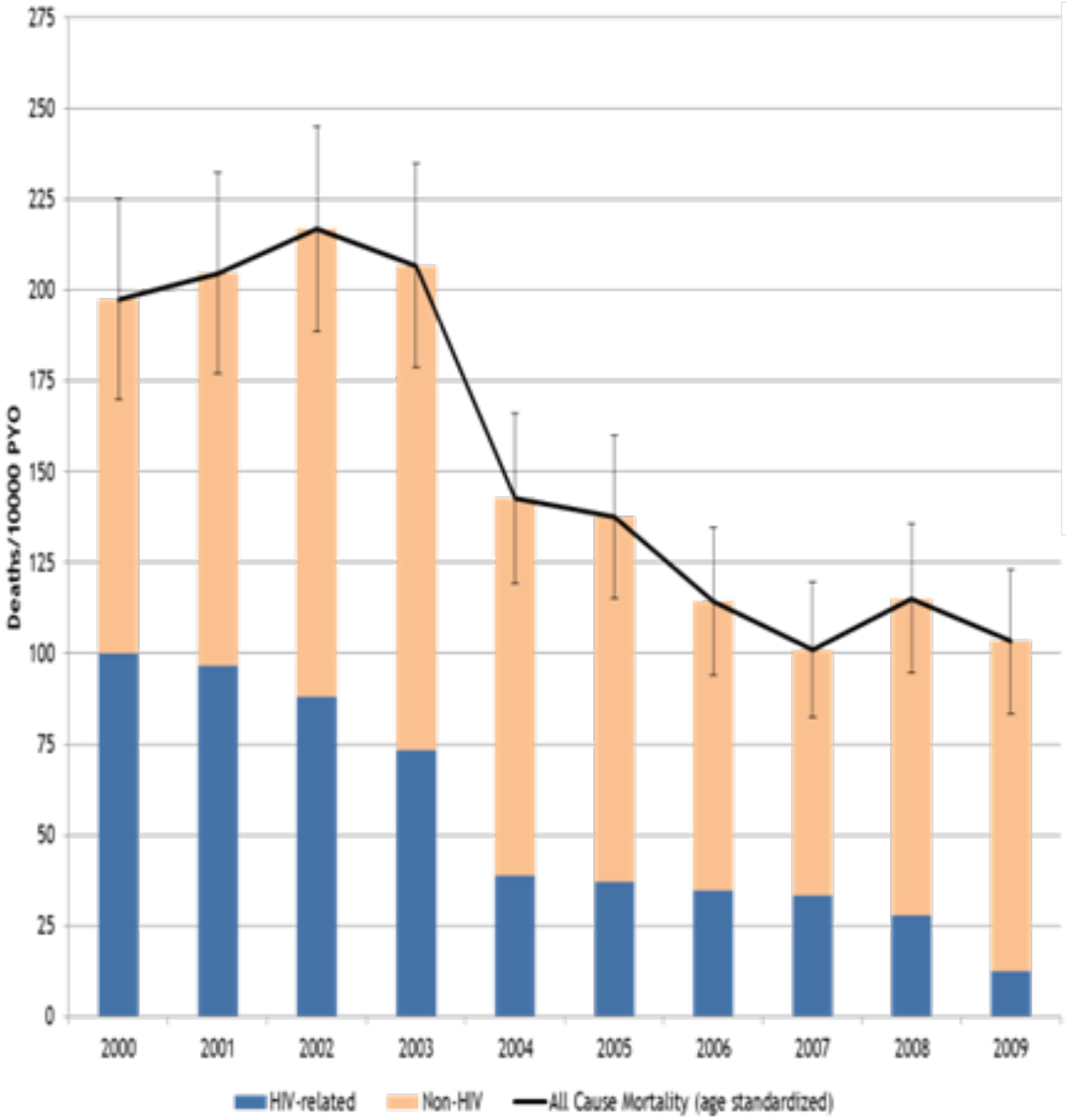
Bor, Newell, Herbst & Bärnighausen *Science* 2013

Mortality reductions lead to major gains in life expectancy



Bor, et al. Science 2013; 339: 961-965

Mortality (per 10,000) in 0-4 year old children; 2000-2009



Example based on data from the Africa Centre surveillance, rural KZN, South Africa

Child mortality and association with PMTCT and ART roll-out

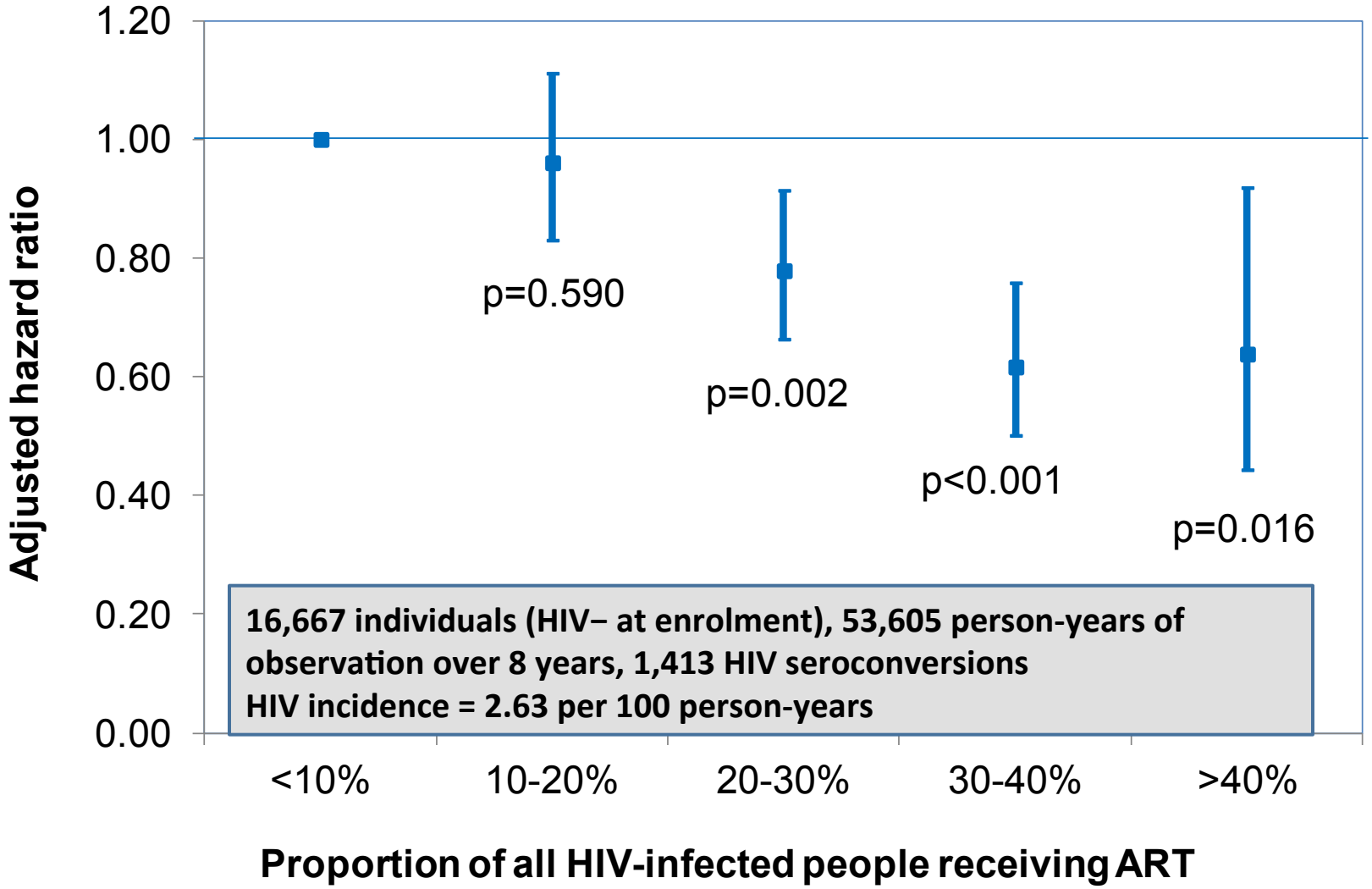
- In an ecological study, under- 2 child mortality rates declined substantially from 2001 with the roll-out of public health programmes:
  - sdNVP PMTCT programme roll-out was associated with a 15% decrease in U2MR
  - ART programme was associated with a reduction of between 34% - 55% (depending on coverage)

    Ndirangu et al AIDS 2010, 24: 593-602

- Further, with individual-level linked ART programme data, ART was shown to substantially and significantly reduce under-5 mortality rates in children of HIV infected mothers, with the U5MR in the presence of maternal ART not significantly different from that observed in children born to uninfected mothers

  Ndirangu et al, Antiviral Therapy 2012; 17: 81-90

ART impact on HIV incidence



Tanser, Bärnighausen, Grapsa, Zaidi & Newell, Science 2013

Elimination of the HIV epidemic?

- HPTN052 results on discordant sexual couples have strengthened the arguments for Treatment-as-Prevention, with mathematical models suggesting possible elimination of HIV from the population with universal ART (Cohen et al NEJM 2011; 365: 493-505)
- High ART coverage at CD4 <350 cells/μl together with male medical circumcision has been suggested to be most cost-effective in reducing transmission and mortality (Bärnighausen, Bloom and Humair, PNAS 2012; 109)
- High ART coverage at CD4 < 350 cells/μl is modelled to virtually eliminate HIV albeit up to 10 years later than universal ART would (Hontelez et al. PLoS Med 2013; 10(10))

HIV treatment and care programmes

- Major roll-out of public programmes in low- and middle income countries, especially in sub-Saharan Africa, to provide HIV testing for all, and treatment for all HIV infected people eligible under current guidelines
- Funded by international donors (PEPFAR, Global Fund), and some national governments

Hlabisa sub-district, northern KwaZulu-Natal

MAKHOWE
INHLWATHI
MACABUZELA
Hluhluwe
MPEMBENI
HLUHLUWE-UMFOLOZI RESERVE
Hlabisa Hospital
NKUNDUSI
NTONDWENI
GUNJANENI
MADWALENI
MACHIBINI
0 5 10
kilometres
SOMKHELE
Africa Centre
ESIYEMBENI
MPUKUNYONI
KHULA
MTUBATUBA
ZWELISHA
KWAMSANE

UNAIDS/WHO 2020 targets: Seek, Test, Treat and Keep

90:90:90:

1. 90% of all people living with HIV to know their HIV status
2. 90% of all people diagnosed with HIV to receive ART for life
3. 90% of all people on ART to have viral suppression

HIV Counselling and Testing is the first step towards care and treatment appropriate to HIV status;

Linkage to care after a first HIV+ve test is a challenging second step for public health programmes

Linkage to HIV treatment and care

People go to either a fixed HIV clinic, or attend a Home or Mobile Counseling and Testing (HMCT) facility

Rapid HIV ELISA test – result given immediately, with counselling; if HIV+ test: confirmed with a second rapid HIV ELISA test

Venous blood sample (to measure CD4 level) at the fixed clinic

About 1-2 weeks after the first clinic attendace and positive HIV test

Return to the fixed HIV clinic to receive their CD4 results and be assessed for eligibility

Eligible patients:

Attend three group education sessions – over about 2 weeks; further clinical assessments done

Treatment can be initiated

Not yet eligible patients:

Encouraged to remain in pre-ART care, and to return for further CD4 measurements and assessment every 6-12 months

Initially monthly clinic attendance and ART pick-up, which may become less frequent once stable; viral monitoring where available

Systematic review of community-based HIV Counselling and Testing approaches

- 29 studies, all in South and East Africa
- About 555,000 people were offered the opportunity to test, of whom 488,000 accepted, for an overall uptake of 80% (95% confidence interval 77%-83%)
- Uptake ranged form 56% in one study in South Africa to 99% in a study in Uganda
- Overall uptake was about 80% in index, self, mobile and door-to-door HCT programmes, and about 60% in workplace and school-focussed programmes

Suthar et al, PLoS Medicine 2013; 10, 8: e1001496

Pooled relative risk of community-based HCT versus facility-based HCT

Compared to facility-based HCT:

- Uptake was > 10 times more likely
- First-time testing was 23% more likely
- Testing coverage was 7 times higher

in community-based HCT

- However: community-based HCT was 40% less likely to identify an HIV-positive person and had a 40% higher likelihood of seeing a person with a high CD4 count

Suthar et al, PLoS Medicine 2013; 10, 8: e1001496

Linkage to care: Challenges for providers and clients

- Evidence to date suggests poor programme performance for linkage to care
  - In Lesotho, only 25% of newly diagnosed HIV infected adults were enrolled in care within 1 month
  - In rural SA, about 50% of newly diagnosed adults were in care within 6 months of diagnosis

- Poor evidence for any intervention to improve linkage to care

- Unclear contribution of health care providers, the system and the clients

Healthcare providers' perspective: an example from rural KwaZulu-Natal

Healthcare providers' challenges

- Staff shortage

"I think if we can motivate for more staff we would need the infrastructure to be modified too, and there are few counsellors so the line is usually long…they have to queue maybe for up to 3 hours maximum" (Operational Manager)

"We are short-staffed, sometimes when you are seeing more patients and you are tired physically and mentally you end up taking it to the client and the client won't understand that and that's because you are tired and overworked." (ART nurse)

- Drug and equipment shortage

"So as for instance, we don't have Efavirenz…they don't get double issue because of this Efavirenz…even the clinic, sometimes we do have out of stock of Bactrim" (ART Nurse)

"Sometimes medication is not here…medication these days is a problem especially Alluvia, Abacavir but we have discussed it with the pharmacist." (Operational Manager)

- Need for more training

"I think they must employ someone who is having NIMART, who can stay there and not go there and there and there…" (ART Nurse)

Chimbindi, Barnighausen and Newell; BMC Health Services Research 2014; 14:32

Healthcare providers' perspective II

Patient-centred challenges

- Lack of travel and food money

"Sometimes they do not come in time to collect their treatment, when you ask them they say they were having financial problems or due to transport problems. I am staying far away from the clinic, there is no transport in time..." (ART nurse)

"Yah, they said that the problem they don't have money, they want the grant so that they can buy food and for the transport, they cannot take the tablets on an empty stomach because they don't have money, so that is the problem of financial."(ART nurse)

- Lack of disclosure

"The cause of the unsuppressed viral load it's because of this disclosure. Because if you didn't disclose you will never eat your tablets." (ART nurse)

"…they just throw it away in front of us, they don't want to be seen taking these containers, carrying these containers at home … I don't know if they are ashamed or what…" (ART nurse)

"The grandmother when you ask them when they came with the child…the grannies said you are eating TB treatment…And if you ask the kids, why are you eating this, they say I am eating for TB. If they found out that TB is for 6 months what is going to happen?" (ART nurse)

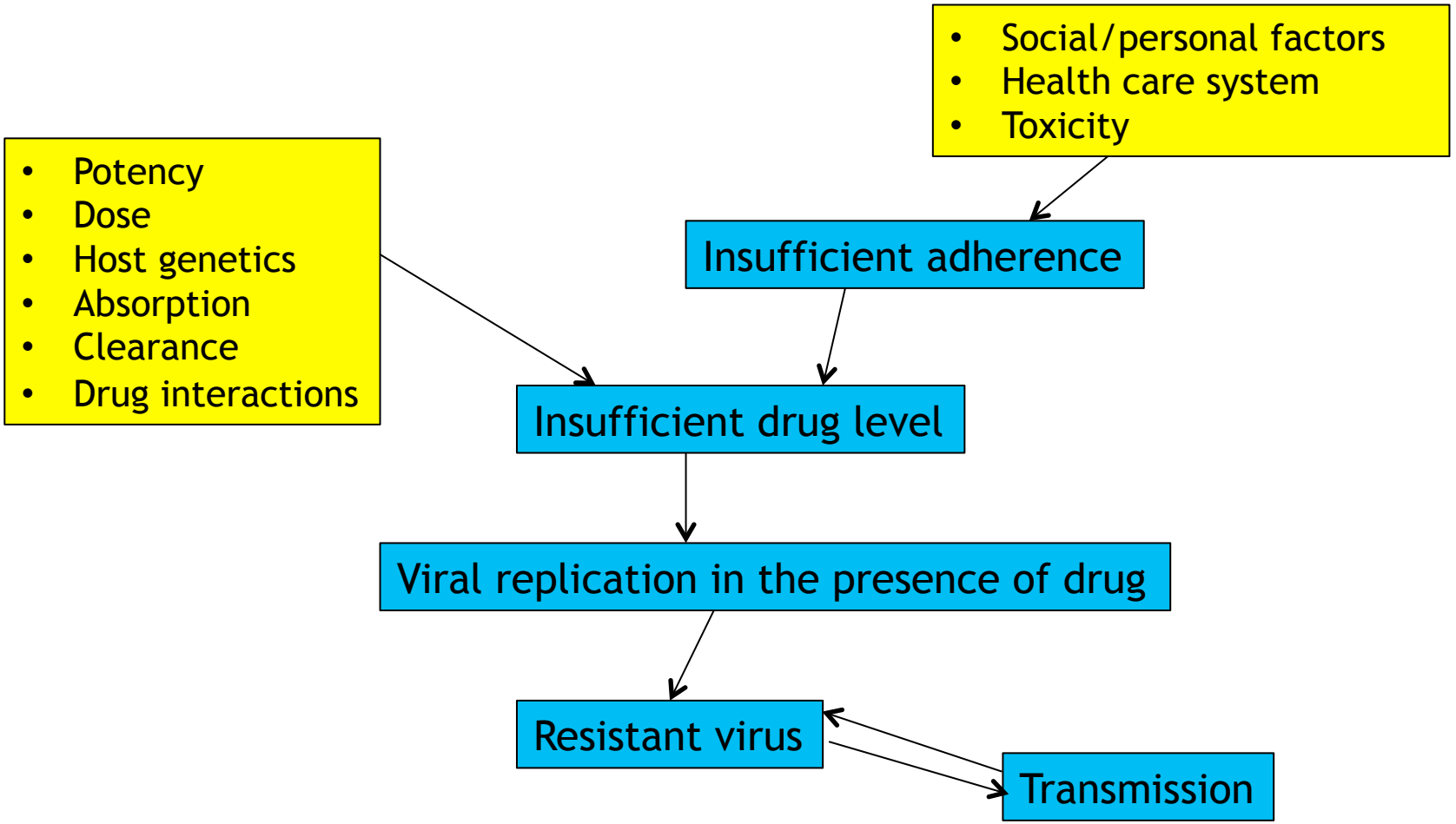
Chimbindi, Barnighausen and Newell; BMC Health Services Research 2014; 14:32

Challenges for the infected individual

- Time and money
  - average cost to attend clinic was high, mainly due to transport costs;
  - about a third of patients reported financial distress (mainly borrowing money)
  - HIV patients spent about three hours on average per clinic visit; TB patients about one hour
- ART for life – now FDC in most settings, but initially many pills
- Often co-morbidities, especially TB which also involves multiple drugs
- Lack of food
- Lack of privacy

Chimbindi et al The cost of utilising HIV and TB treatment and care in rural KZN. JAIDS in press

Pathways to drug resistance



From: Rossouw, Lessells and de Oliveira HIV&TB drug resistance case book 2012

Acquired resistance

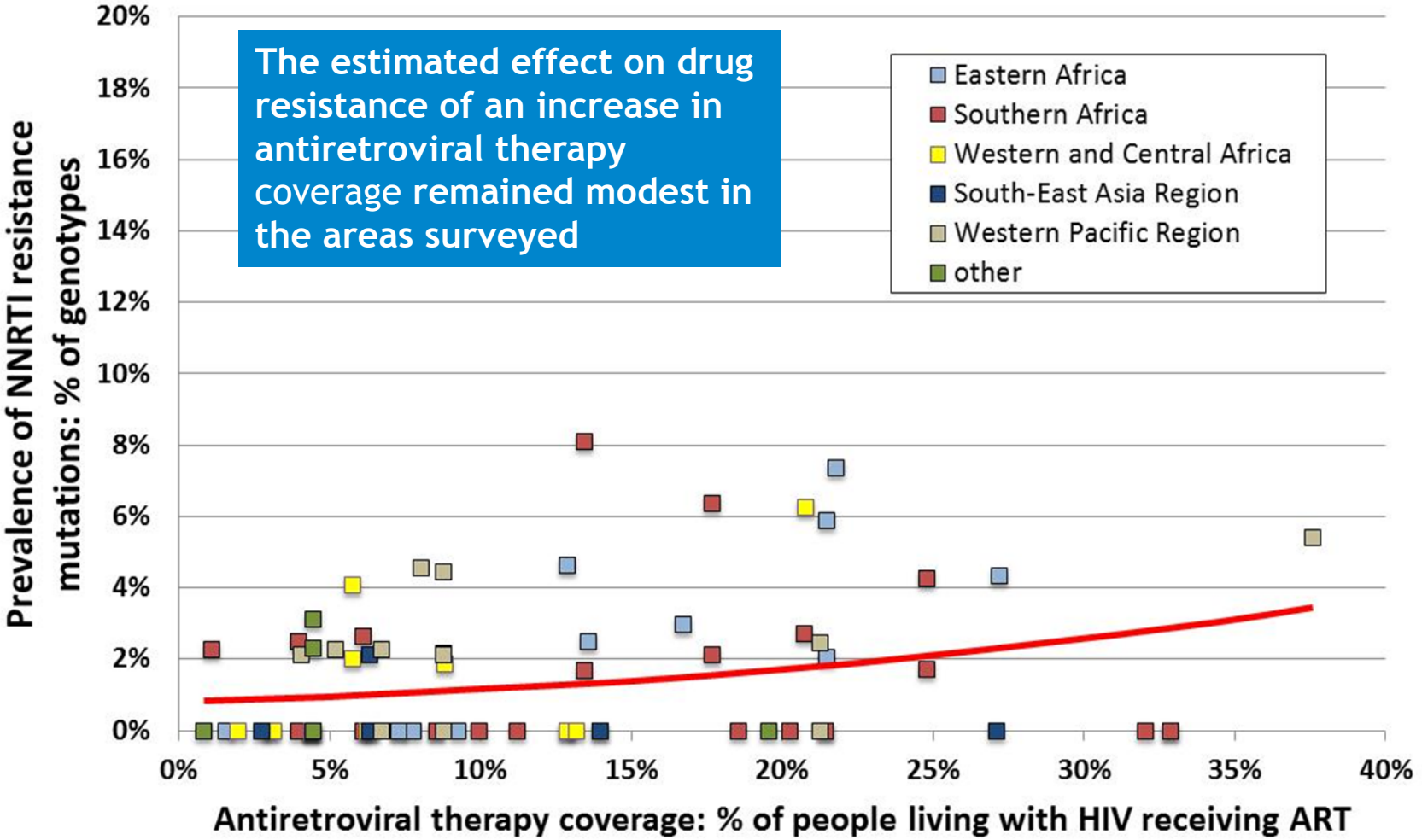
- In a study in rural South Africa, 222 adults initially treated with D4T and ZDV-based ART regimen and with evidence of Viral failure (VL > 1000 copies/ml) were enrolled from 17 primary healthcare centres and genotyped
- Median duration on ART was 42 months and median duration of failure was 27 months
- 191 (86%) had at least one drug resistance mutation; 34 (15%) had extensive resistance that significantly compromised regimen choice

Manasa et al PLoS One 2013

Transmitted HIV drug resistance

- As ART was introduced in Africa after 1996, it was always as triple-drug regimens, but single dose Nevirapine was used in PMTCT programmes
- Over the past decade the response to HIV has evolved to managing HIV as a life-long chronic disease with sustainable and increasingly integrated primary healthcare programmes
- Reported levels of drug resistance have been relatively low to date
- But routine surveillance is not widely performed on the continent
- In South Africa, between 2000 and 2010, the prevalence of transmitted drug resistance remained below 4%

ART resistance in newly diagnosed adults increases with ART programme coverage

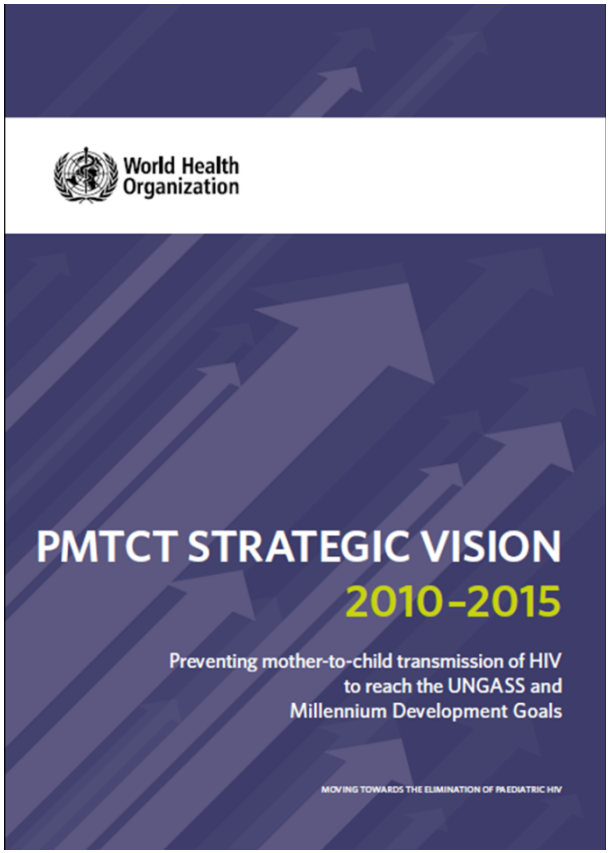


Source: WHO HIV drug resistance report - 2012

Implications for Treatment as Prevention approaches

- Early evidence from one of the five ongoing Treatment as Prevention trials, in rural KZN, suggests high rates of home-based HIV testing, slow linkage to care and high rates of uptake of, and adherence to, ART
- Home-based testing reaches more people, but proportionally less positive people, and when positive with higher CD4 counts
- Current evidence suggest that identification of people as infected before clinical symptoms have developed, at the early stages of HIV progression is associated with a slower pace of access to clinic-based care
- The extent to which levels of acquired and transmitted drug resistance will increase remains unquantified

Prevention of mother-to-child transmission



Guidelines on ART in the prevention of MTCT

	PMTCT	Mother	Child	Year introduced in SA
	Single dose NVP	During labour	At birth	2001
Option A	Monotherapy with ZDV + sd NVP	During pregnancy and delivery	6 weeks NVP	2008
Option B	ZDV +sd NVP OR combination ART	During Pregnancy and delivery when CD4 < 350 cells/µl	6 weeks NVP	2010
	Combination ART (Atripla®)	For all, irrespective of CD4 count; starting early in pregnancy	Maternal ART continued during breastfeeding	2013

PMTCT with ART

Great benefit of PMTCT, potential for virtual elimination of vertically-acquired HIV:

MTCT rates <1-2% at 6 weeks of age,

<4-5% at 18 months of age

Overall, worldwide, in 2012 only 50%-75% of pregnant/breastfeeding eligible women were initiated on ART for life

Increasing exposure to combination antiretroviral therapy for the fetus and young child, nearly all of whom will be uninfected, from pregnancy until cessation of breastfeeding;

Challenges in PMTCT programme delivery

- Antenatal, intra-partum and post-partum
  - Multiple service providers
  - Multiple points of access
  - Ensuring supply of ART at primary health care level

  Integrating HIV services within ANC, and where women can access more than one primary health care clinic for ANC or HIV ensure that information is shared between facilities is essential

- In high prevalence areas, need to test HIV-negative women again in late pregnancy or during breastfeeding
- Support for women to breastfeed, and to continue taking ART for life
- Early diagnosis of HIV in vertically-exposed infants, prolonged follow-up with further HIV testing at 18 months of age, allocation of responsibilities

Further Challenges for PMTCT programmes

- ARVs – issues re pregnant women usually not part of treatment RCTs so now lack of evidence re teratogenicity and long-term effectiveness for the health of the woman
- Lack of evidence regarding impact of ART on pregnancy outcome (premature delivery and/or small-for-gestational age infants)
- Lack of evidence regarding long-term safety of prolonged exposure to ART during fetal and early life

Challenges re adherence during and after pregnancy

- Diagnosis of infection, first ANC, pregnancy, confusion
- Breastfeeding and worries about MTCT
- Adherence often more of a challenge early post-partum
  - In a study in the UK, in women who were viral suppressed on ART, the risk of viral rebound was increased in the first three months post-delivery compared to pregnancy or later post-partum
    - Huntington et al AIDS 2015 in press

Adherence to ART before and after pregnancy – a systematic review

- In 51 studies involving 20,153 HIV infected pregnant women, an estimated 73.5% (95% CI 69.3-77.5%) of pregnant women had adequate (>80%) ART adherence
- Pooled proportion of women with adequate adherence was higher during pregnancy (75.7%) than postpartum (53.0%)
- Reported barriers to non-adherence included physical, economic and emotional stresses, depression (especially post-delivery), alcohol- or drug use, ART dosing frequency and pill burden

Nachega et al AIDS 2012; 26: 2039-2052

Resistance issues in PMTCT

- Mother:
  - Resistance in mother which may be transmitted during pregnancy or breastfeeding
- Infant:
  - Resistance due to exposure to maternal drugs through breast milk
  - Resistance due to exposure to postnatal prophylaxis

Resistance to NNRTI among Pregnant Women in PMTCT life-long ART

- WHO estimates 3.4% pre-treatment NNRTI (Nevirapine, Efavirenz) resistance in pregnant women initiating ART
- Increased likelihood of virological failure due to previous exposure to PMTCT ART for a limited period of time
- A substantial proportion of women will be poorly adherent, especially postpartum

The impact of NNRTI resistance in the mother on her exposed but uninfected child who routinely received NVP or ZDV single dose prophylaxis for 4-6 weeks as part of the PMTCT regimen is unknown

Exposure to ART through breastmilk

- Resistance rates in infected infants are higher when exposed to drugs both through breast milk and directly by taking prophylaxis
  - In 53 HIV-infected 6 week old infants, 23 with daily NVP prophylaxis but no breastfeeding and 30 with both prophylaxis and been exposed to NVP through breastmilk, resistance rates were twice as high in the BF plus prophylaxis arm (33% vs 13%)
- However, adding additional drugs reduces the risk of the infant acquiring NVP resistance
  - NNRTI resistance prevalence was reduced to 16.5% (n=138; CI 8.9-28.3) in study arms with a combination of NVP with either AZT or AZT+3TC compared to 52.6% (n=201; CI 37.7-67.0) in infants who had been exposed to NVP-only prophylaxis.

Schneider S et al. JAIDS 2008; 48:450-4; Pillay CCN et al. IAC 2004;

Moorthy A et al. PLoS ONE 2009; 4:e4096; Lidstrom J, et al. AIDS 2010; 24:381-6; Arrivé E et al. Int J Epidemiol 2007; 36:1009-2

Conclusion

- HIV treatment and care programmes, including PMTCT, have been enormously successful:
  - Substantial decline in mortality; adult life-expectancy now only minimally affected by HIV in people on ART and child mortality in children of HIV infected mothers on ART similar to that of children of uninfected mothers
  - Rates of MTCT have declined to very low levels
- Stretched and fragile healthcare systems
- Little evidence of transmitted resistance, but emerging acquired resistance
  - lack of viral testing and appropriate response to results, adherence support, and creative health care delivery approaches
- ART resistance more likely with expansion of programmes, but whether expanding treatment eligibility criteria will reduce adherence and increase resistance levels, and implications for treatment as prevention approaches, remains unclear

And finally…..

The question is no longer whether the fight against HIV/AIDs can be won; the only questions are: will it be won and when?

Addressing the support needed for health care providers as well as their clients in life-long HIV treatment programmes is an urgent need