HIV OVERVIEW

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EDCTP STAKEHOLDER MEETING
LISBON, PORTUGAL
3-4 SEPTEMBER 2013

OUTLINE

- HIV Origin and Classification
- HIV Spread & Global Evolution
- Evolution of Laboratory Tests to Identify HIV Infections
- Global HIV Epidemic
- HIV Therapeutics- Adherence & Drug Resistance
- HIV Prevention- Biomedical, Behavioural & Structural
- Integration- HIV Prevention/ Treatment /Care
- Global HIV Prevention, Treatment & Care Priorities
- EDCTP II Priorities in HIV Prevention & Treatment

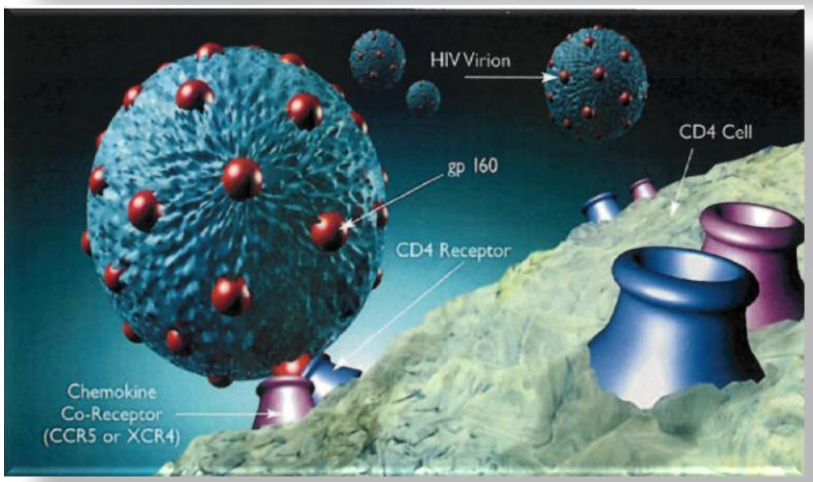
HUMAN IMMUNODEFICIENCY VIRUS (HIV)

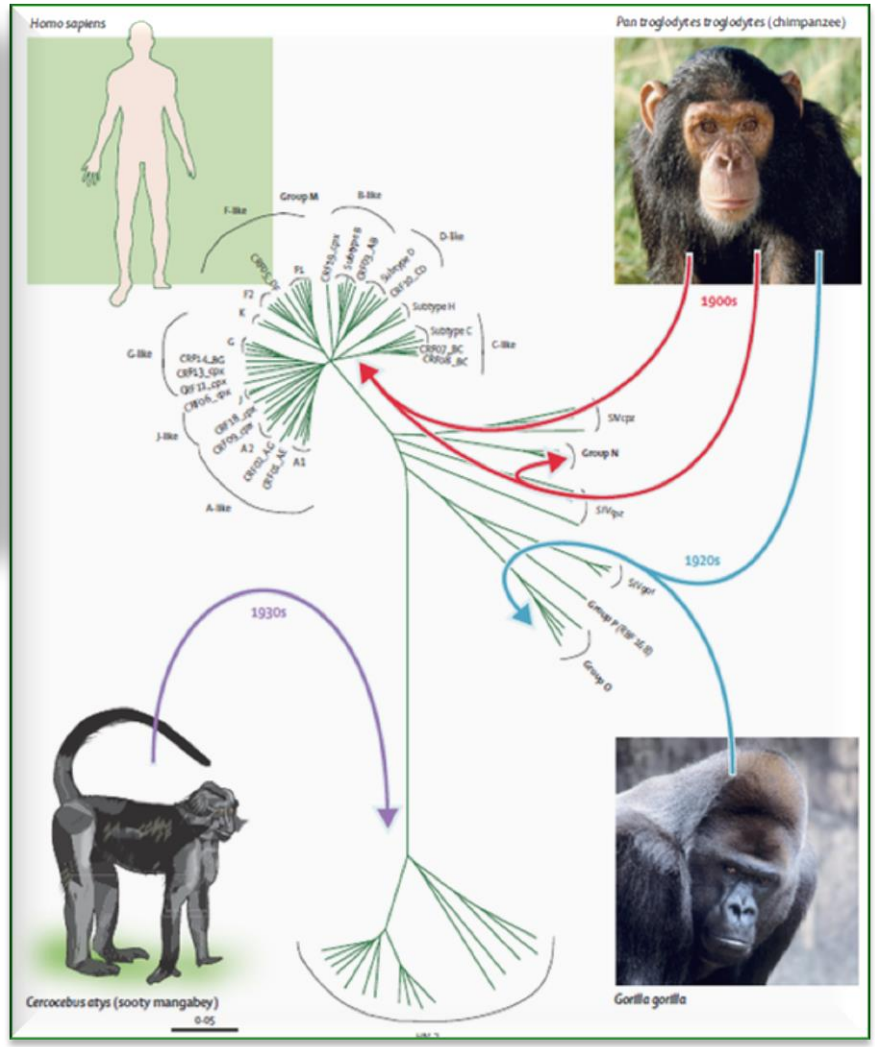
" It all started as a rumour- then we realized we are dealing with a disease- then we realized that it was an epidemic and now we have accepted it as a tragedy"

-Anonymous Ugandan epidemiologist 1992

HIV & ITS ORIGINS

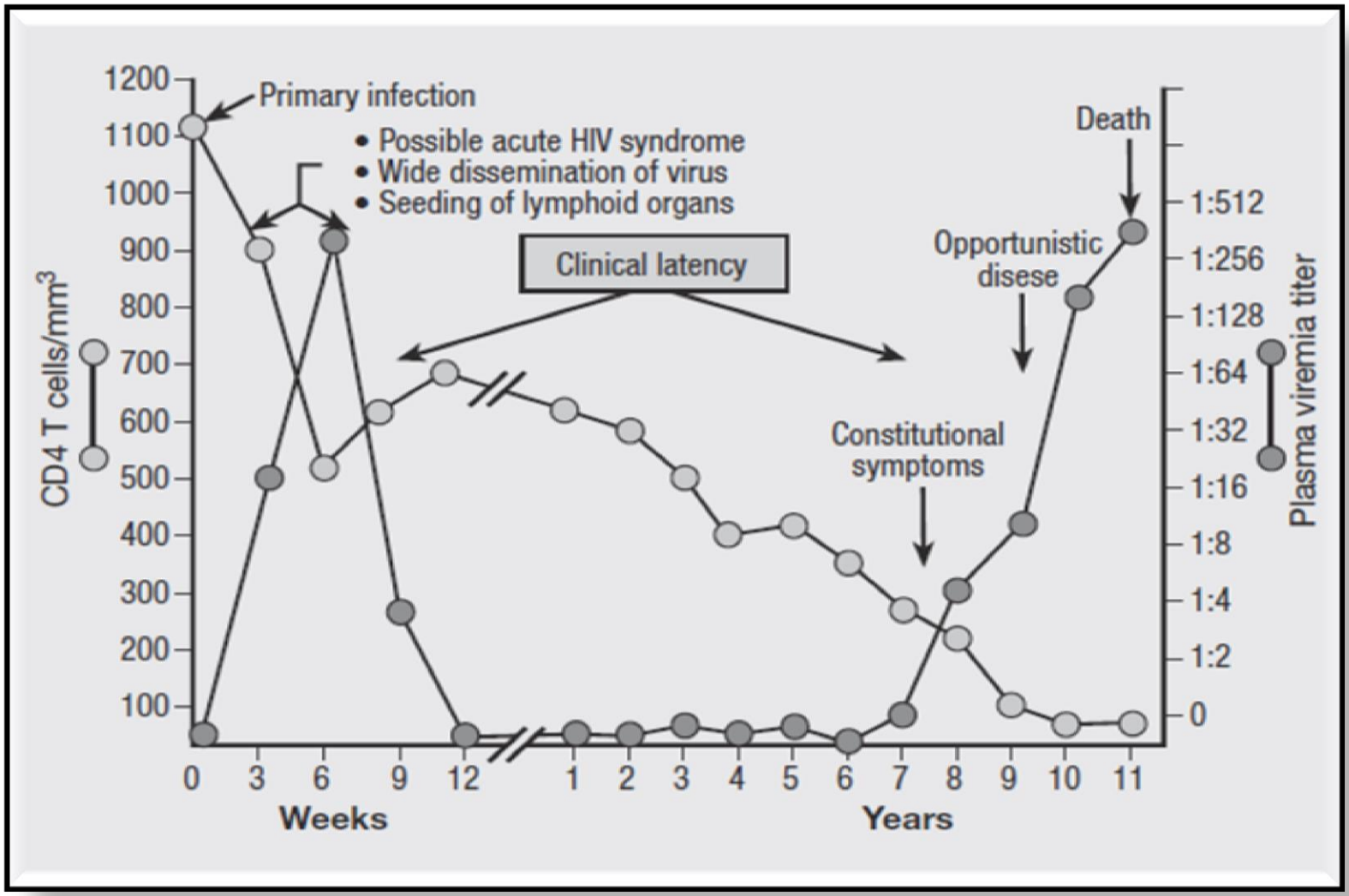
- HIV is a zoonotic disease transmitted from animal (non-human) to humans
- HIV- "lentivirus" a subgroup of retroviruses
  - Lentivirus is a genus of viruses of the Retroviridae family (long intervals between infection and onset of serious symptoms)





Ref: Tebit DM, Arts EJ. Tracking a century of global expansion and evolution of HIV to drive understanding and to combat disease. Lancet Infect Dis 2011; 11: 45-56

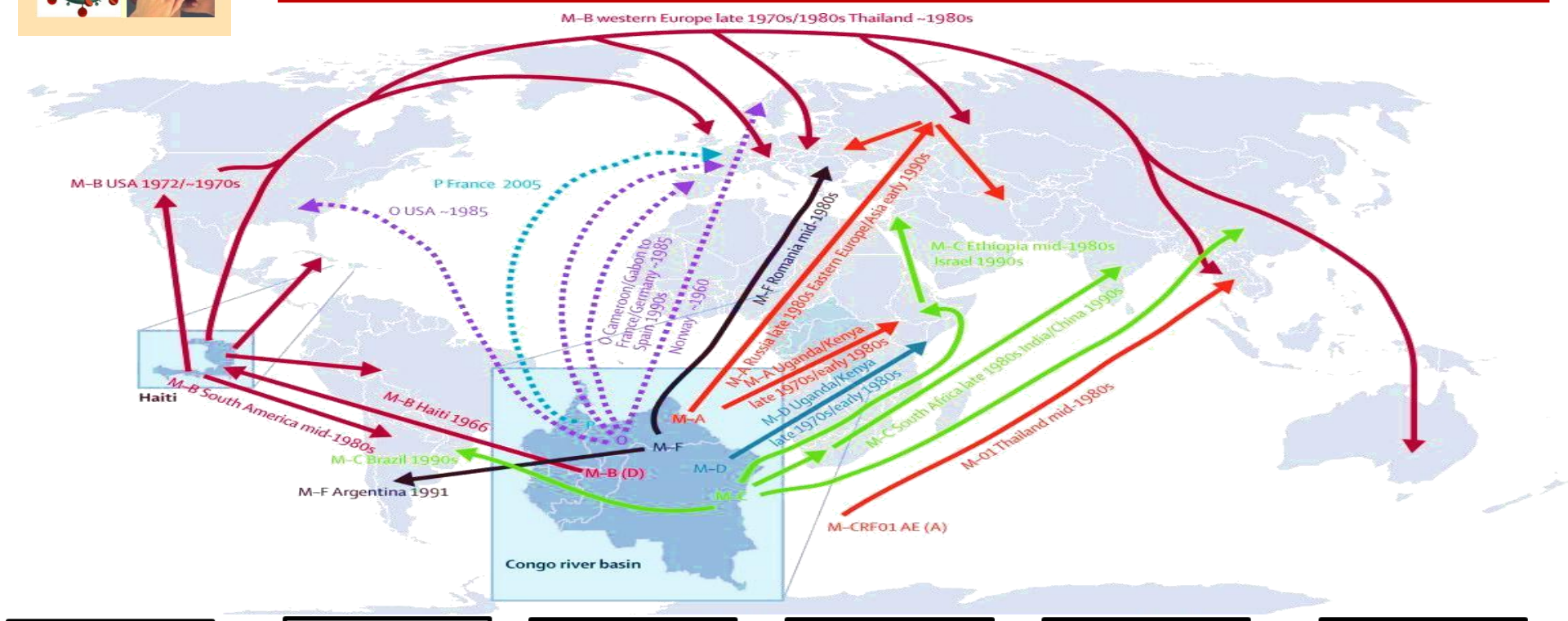
THE NATURAL HISTORY OF HIV INFECTION: TYPICAL OF LENTIVIRUSES

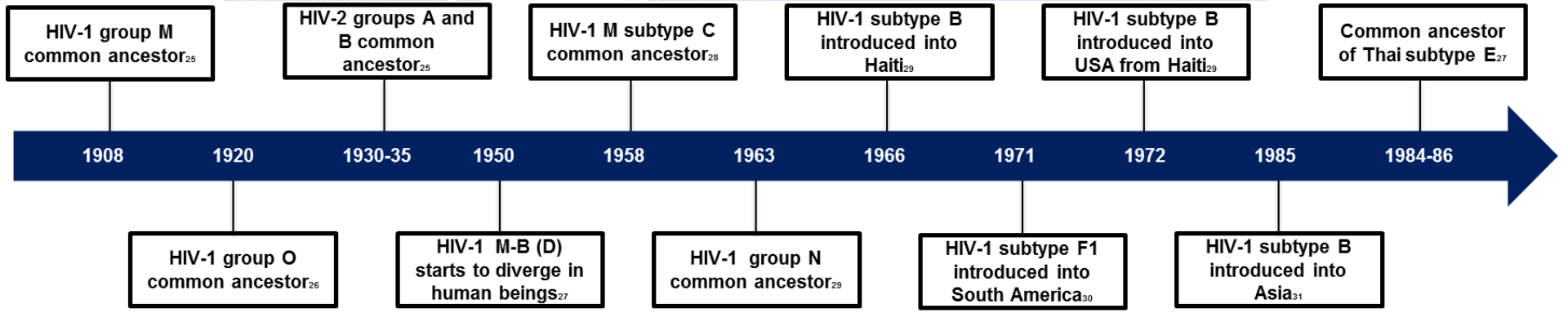


HIV-1 is now a clinical disease

Ref: Lucia Palmisano and Stefano Vella. A brief history of antiretroviral therapy of HIV infection: success and challenges. 2011.

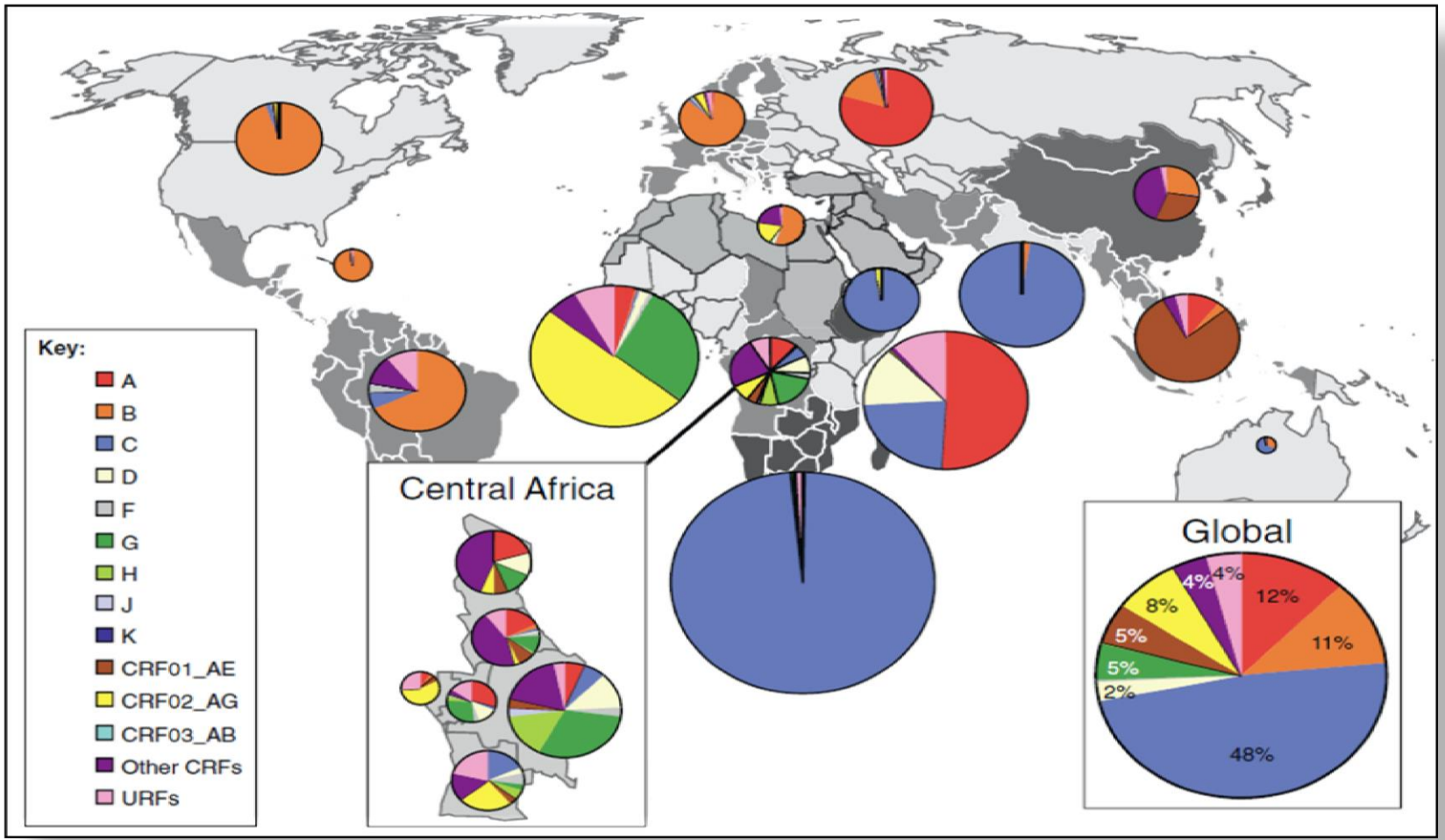
SPREAD OF HIV FROM CONGO BASIN TO THE REST OF THE WORLD & GLOBAL EVOLUTION





Ref: Tebit DM, Arts EJ. Tracking a century of global expansion and evolution of HIV to drive understanding and to combat disease. Lancet Infect Dis 2011; 11: 45-56

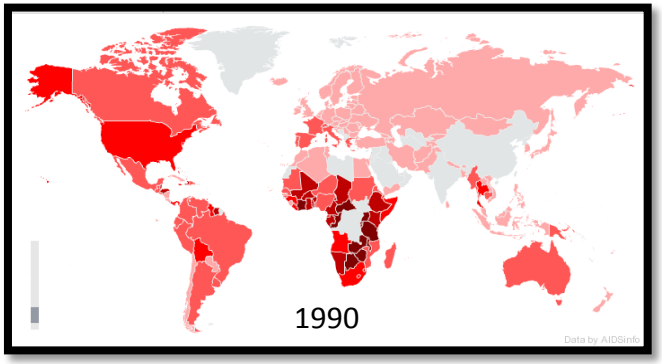
GLOBAL DISTRIBUTION OF HIV-1 SUBTYPES AND RECOMBINANTS

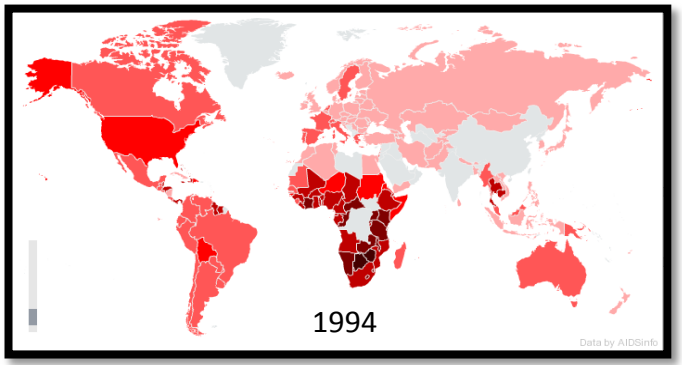


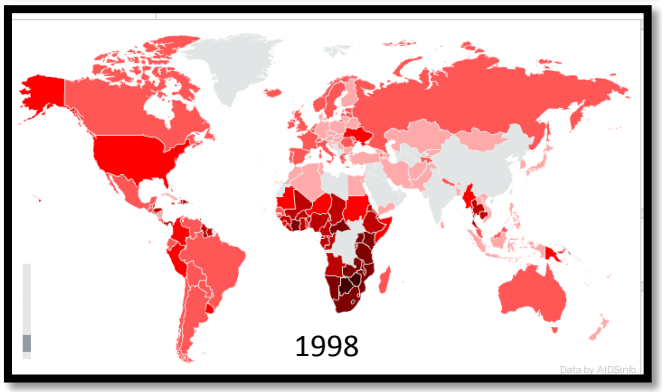
Ref: Joris Hemelaar,.The origin and diversity of the HIV-1 pandemic .2012

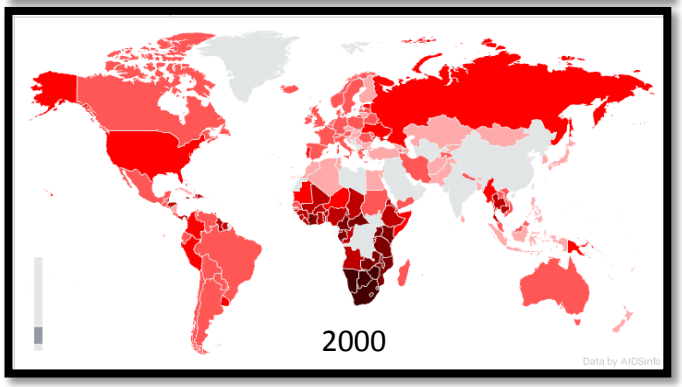
GLOBAL HIV EPIDEMIC (1990 – 2011)

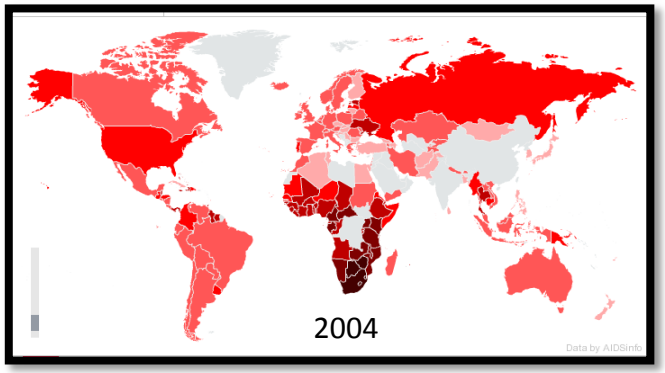
Ref: http://www.unaids.org/en/dataanalysis/datatools/aidsinfo/

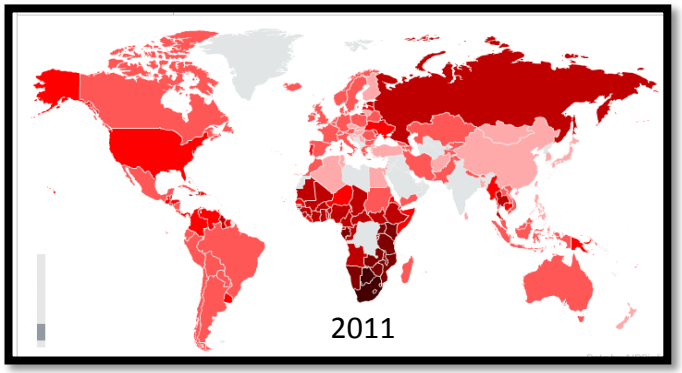


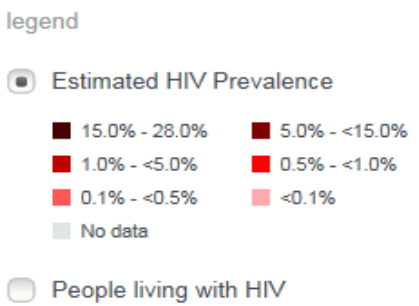






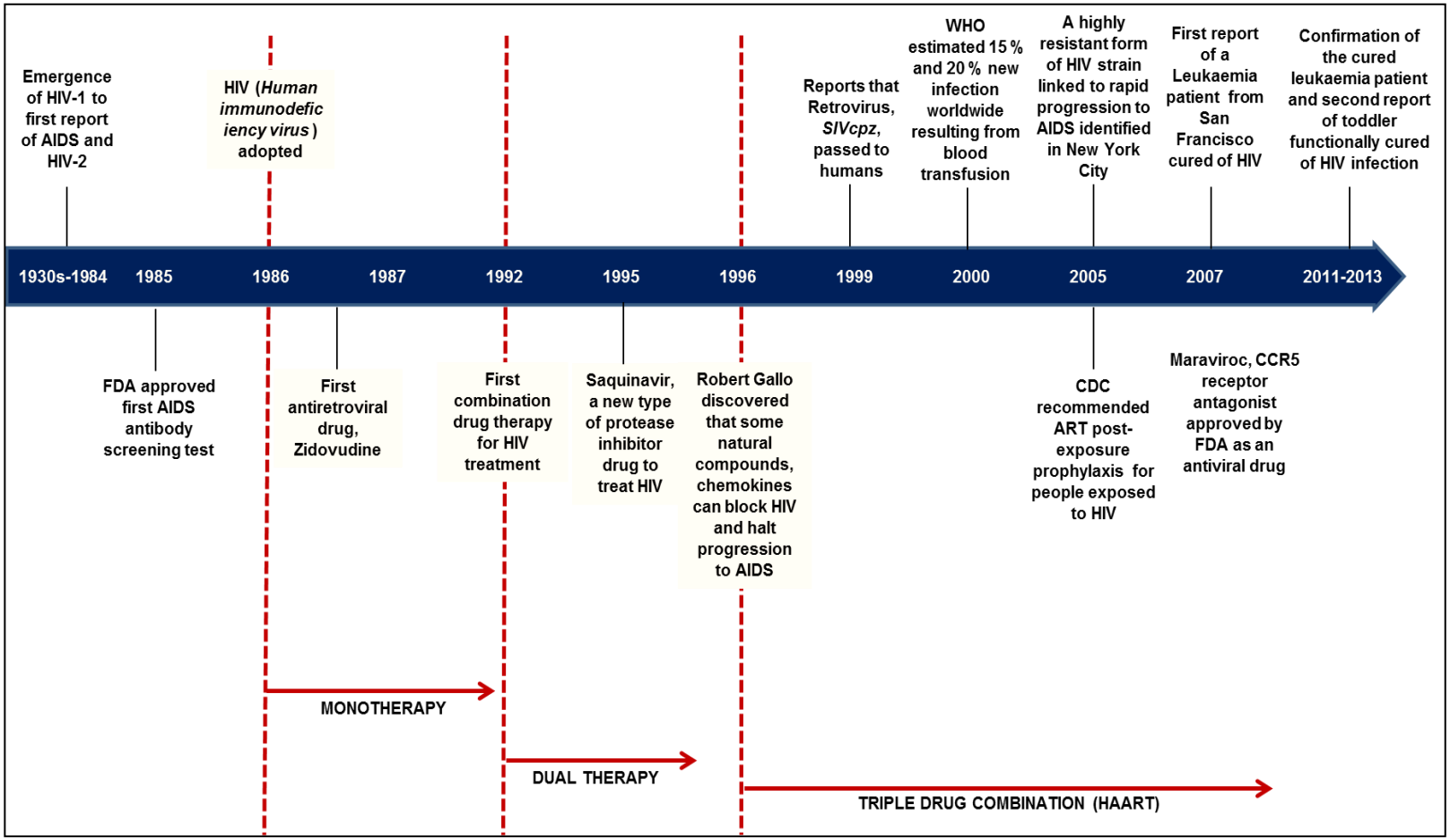






HIV TREATMENT

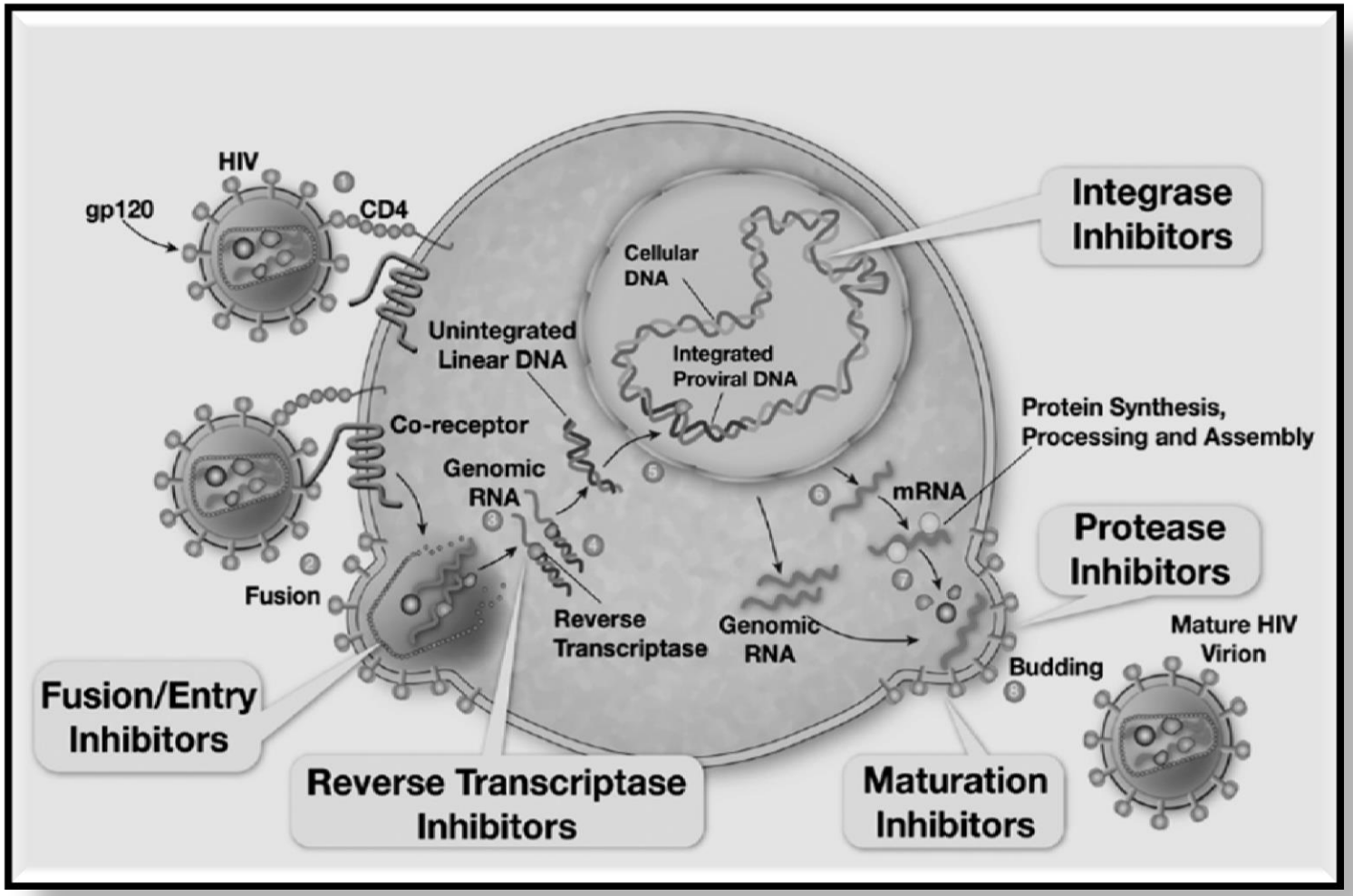
TIMELINE



Ref:

1. *Pickrell, J., Timeline: HIV & AIDS, New Scientist, September 4, 2006; U.S. Food and Drug Administration, March 2, 1985*
2. *Jacques , P. 2011. The Origins of AIDS. Cambridge University Press.*
3. *Antiretroviral Post-exposure Prophylaxis after sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV , CDC guideline - retrieved 2011*
4. *Robert C. Gallo, M.D.". bio. The Institute of Human Virology. Retrieved 2009-12-30*
5. *Toddler 'Functionally Cured' of HIV Infection, NIH-Supported Investigators Report. National Institute of Allergy and Infectious Diseases.*
6. *Sa´ez-Cirio´n et al., 2013. PlosPathogen: 9(3): e1003211*

TARGET SITES FOR ANTIRETROVIRAL DRUGS IN THE HIV LIFE CYCLE



Ref:Lucia Palmisano and Stefano Vella. A brief history of antiretroviral therapy of HIV infection: success and challenges. 2011.

ARV DRUG DEVELOPMENT
Targeting specific enzymes in the HIV life cycle

2. Attachment Inhibitors

KD-247, Griffithsin

3. Fusion Inhibitors

Maraviroc, Enfuvirtide

4. Reverse Transcription Inhibitors

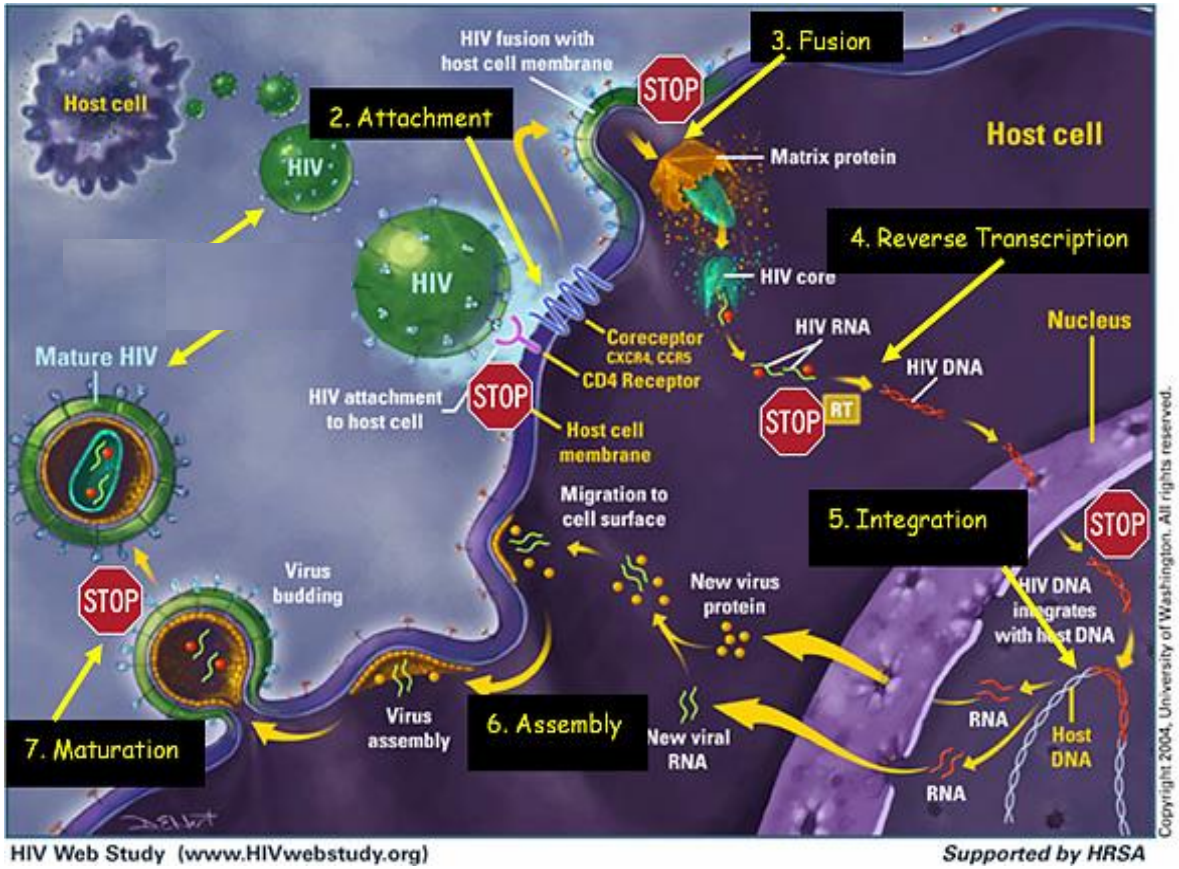
NNRTI	NRTI	
Atevirdine	***Abacavir***	***Amivudine***
Delavirens	Amdoxovir	Lodenosine
Efavirens	Apricitabine	Racivir
Emivirine	***Didansine***	Stampidine
Etravirine	***Elcuvitabine***	Stavudine
Nevirapine	***Entecavir***	***Tenofovir***
Rilpivirine		***Zalcitabine***
		zidovudine

5. Integrase Inhibitors

Elvitegravir, ***Raltegravir,*** GSK1349572, MK-2048

7. Maturation Inhibitors

Atazanavir, Fosamprenavir, Daruavir, Ritonavir
Lopinavir, Nelfinavir, Squinavir, Tipranavir,
Indinavir



From 1987 (Zidovudine) to 2008-30 HIV therapeutic single or combination drugs were approved by the FDA- targeting 5 HIV enzymes.

Critical in the HIV replication cycle

WHEN TO START THERAPY:

Balance now favours earlier ARV therapy

- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

- ↑ Potency, durability, simplicity, safety of current regimens
- ↓ Emergence of resistance
- ↓ Toxicity with earlier therapy
- ↑ Subsequent treatment options
- Risk of uncontrolled viremia at all CD4+ cell count levels
- ↓ Transmission

Delayed ART **Early ART**

Ref: Practical strategies to engage HIV patients in timely care. www.clinicaloptions.com/hiv

DRUG RESISTANCE

REASONS: Poor adherence to treatment or infected with mutant virus Result

- High rate of viral replication (10^9 to 10^{10} virons /person/day)
- Errors in HIV due to high rate of replication- HIV Polymerase
- Selective pressure and mutant viral strains

RESISTANCE:
ABILITY OF HIV TO ENTER CELL AND REPLICATE DESPITE PRESENCE OF ARV DRUGS

OUTCOME

- Increase in viral load
- On-going damage to immune system
- Single or multiple-class drug resistance- limited access to therapy
- Progression of HIV disease

COMBINATION OF FACTORS MAY CONTRIBUTE TO POOR ADHERENCE

Socio-demographics
- Economics
- Education
- Cultural beliefs, values and practises

Social support
- status disclosure, friends, partner & family support

Cognitive Factors
- cognitive impairment,
- forgetfulness

Psychological Factors
- Depression, anxiety

Substance Abuse
- Alcohol

State of disease

INDIVIDUAL FACTORS

HEALTH SYSTEMS

ADHERENCE

ART REGIMEN & TREATMENT EXPERIENCE

Adequate education & counselling

Effective linkage to care

Effective communication & decision making with patient

Access- insurance, transport

Convenience/ confidentiality

Adherence counselling & follow -up

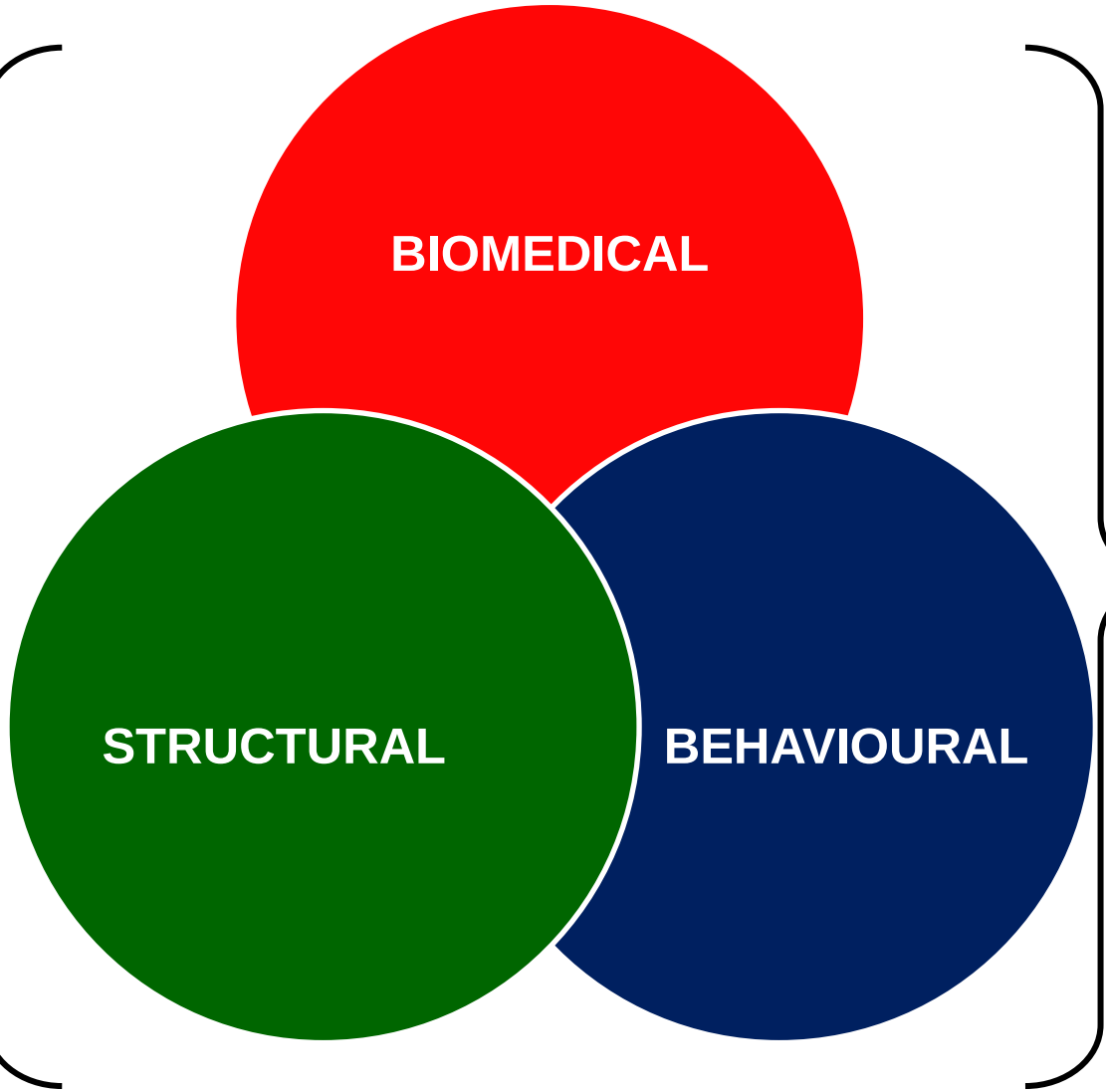
Complexity of regimen | **Toxicity** | **Side effects**

Every effort required to mitigate risks of developing ARV resistance

HIV PREVENTION INTERVENTIONS

Community & Policy Makers:

- Support commitment in addressing the epidemic
- HIV Prevention adequate support & resources
- Focused program for key populations
- Address stigma & gender-based violence
- Integrating HIV & reproductive health care for women
- Health Systems strengthening
- Address stigma



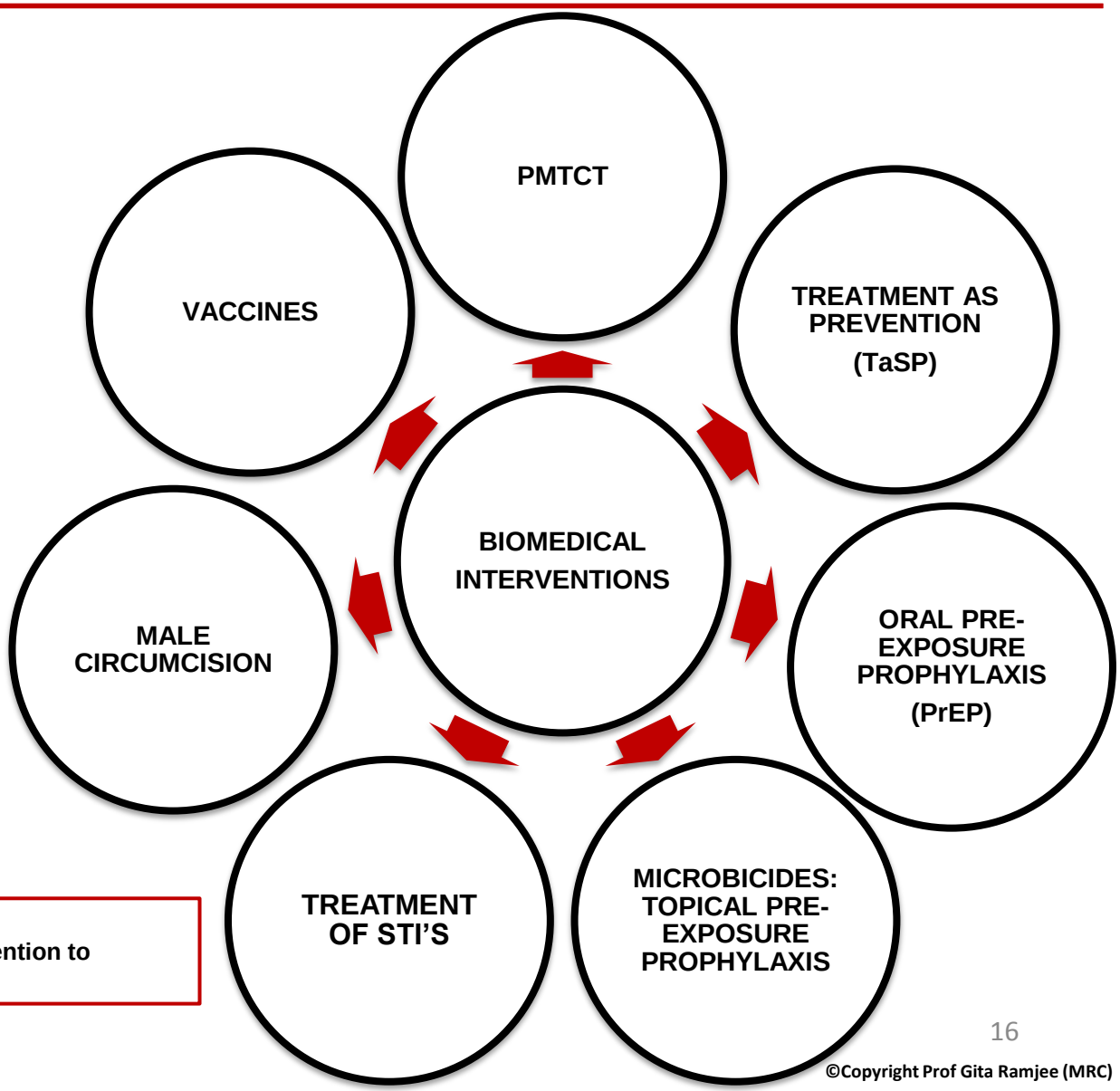
Individual:

- Commitment
- Adherence & acceptability of intervention
- VCT
- HIV status disclosure
- Reduce Stigma

BIOMEDICAL PREVENTION STRATEGIES

- Reduces HIV acquisition by 50-60%.
- Extensively rolled out
- High rate of effectiveness in reducing community HIV incidence 73% (Gray et al AIDS, 2012).
- SA: MMC increase 36.0%(2008)-40.5(2012)

- Overwhelming biological evidence
- Remain important for public health intervention to prevent HIV

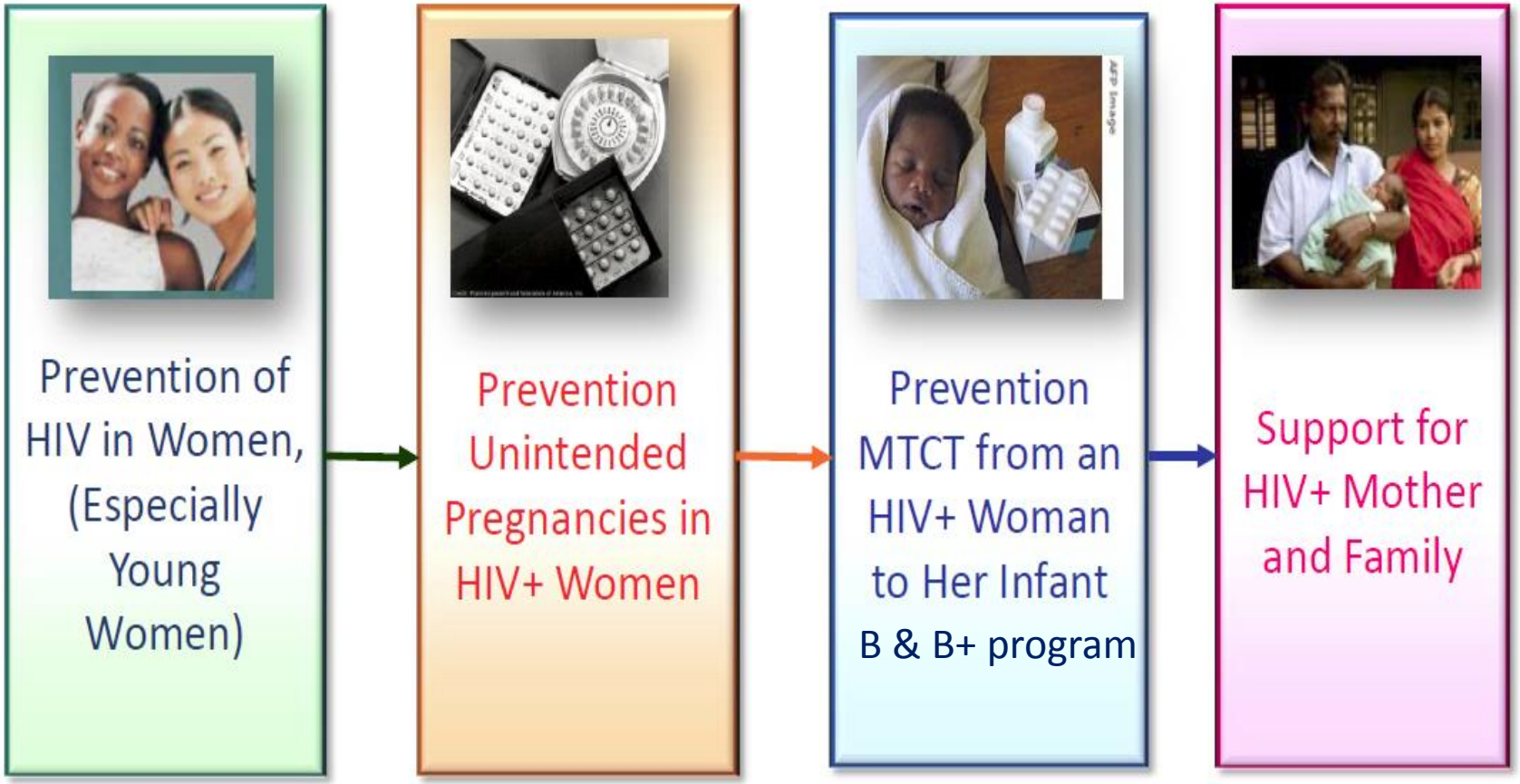


GLOBAL PROGRESS IN REDUCING PMTCT

- In 2011, 330 000 [280 000–390 000] children acquired HIV infection
  - a 43% decline since 2003 (560 000)
  - a 24% drop since 2009 (430 000)
- More than 90% of the children who acquired HIV infection in 2011 live in sub-Saharan Africa
- In sub-Saharan Africa, the number of children newly infected fell by 24% from 2009 to 2011

Ref: UNAIDS 2012

FOUR-PRONGED STRATEGY FOR PREVENTION OF MOTHER TO CHILD HIV TRANSMISSION



Research Priority- implementation & sustainability of B & B+ PMTCT programs (WHO) in resource poor settings

Ref: James McIntyre (On the road to) zero vertical transmission, 6th SA AIDS Conference 2013

HIV TREATMENT AS PREVENTION (TaSP)

- High HIV viral load is the single greatest risk factor for all modes of HIV transmission
- Treatment as prevention is based on the fact that ARV treatment can reduce plasma and genital viral loads to undetectable levels
- Reduced viral loads results in reduced infectiousness

HPTN 095

CONCEPT:

- Provision of early ARV Treatment to HIV infected partner in an HIV discordant relationship in order to reduce viral load and therefore infectiousness (Cohen et al, 2011)

1763 discordant couples in Africa & America effect of ART (HIV +ve) on HIV –ve: 96% (CI: 73%- 99%)

Cohen et al 2011, NEJM

ORAL PRE-EXPOSURE PROPHYLAXIS (PrEP)

CONCEPT: Use of oral Antiretroviral Therapy (ART) in HIV negative individuals prior to sex to prevent HIV Infection

SUCCESSES:

- **Daily use of oral combination prophylaxis with Tenofovir (TDF)and Truvada (TDF/FTC) among HIV –ve MSM. (iPrEx Study)**

2499 Men who have sex with men.
Effect of Daily TDF-FTC on HIV: 42% (CI: 15%-63%)
Grant et al,2010 NEJM

- **Daily use of oral Tenofovir or Truvada reduced HIV infection among uninfected partners of HIV-discordant couples. (Partners in PrEP study)**

4,758 HIV discordant couples in Kenya & Uganda
Effect of TDF on HIV: 67% (CI: 44%-81%)
Effect of FTC/TDF on HIV: 75% (CI: 55%-87%)
Baeten et al, 2012, NEJM

ORAL PRE-EXPOSURE PROPHYLAXIS

- **Daily use of Truvada reduced HIV infection among young heterosexuals in Botswana. (CDC)**

1219 heterosexual men &women in Botswana. Effect of TDF-FCT on HIV: 63 % (CI: 21.5 - 83.4)
Thigpen et al, 2012, NEJM

- **Daily use of oral Tenofovir in IDU's in Thailand. (CDC)**

2411 men and women IDU's.
Effect of TDF on HIV: 49 % (CI: 9.6-72.2)
Lancet on line : 12 June 2013

- **FDA approved Truvada for use in HIV negative MSM with pre-conditions on eligibility and safety (http://www.fda.gov/newsevents/312210.htm)**

- **CDC Interim guidance on PrEP for Injecting drug users.**

Ref: *http://www.cdc.gov/mmWr/preview/mmwrhtml/mm6223a2.htm?s_cid=mm6223a2_w*

ORAL PRE-EXPOSURE PROPHYLAXIS (WOMEN IN SUB-SAHARAN AFRICA)

CONFLICTING RESULTS WITH THOSE IN OTHER HIGH-RISK POPULATIONS

- Use of daily oral Truvada among women in Sub- Saharan Africa showed no effect on HIV incidence (Lut van Damme, et al 2012, NEJM)
- Use of daily oral Tenofovir or Truvada among young women show no effect on HIV incidence in VOICE Trial 2012 (MTN 003) (Marrazzo JM, Ramjee G et al) CROI 2013.

LESSONS LEARNT

- ARVs do not work for HIV treatment or prevention unless taken as prescribed.
- High Adherence is key
- Individual risk perception is critical
- Important to understand the cultural context in which new biomedical strategies are used
- For young women greater understanding of biological risk factors is critical. Genital tract inflammation is likely to play a critical role

Ref: Jo Anne Passmore , SA AIDS 19th June 2013

RISK FACTORS: CONTRACEPTION & HIV

- Hormonal contraception- oral pills, injectables, patches, rings, implants- effective methods of pregnancy prevention

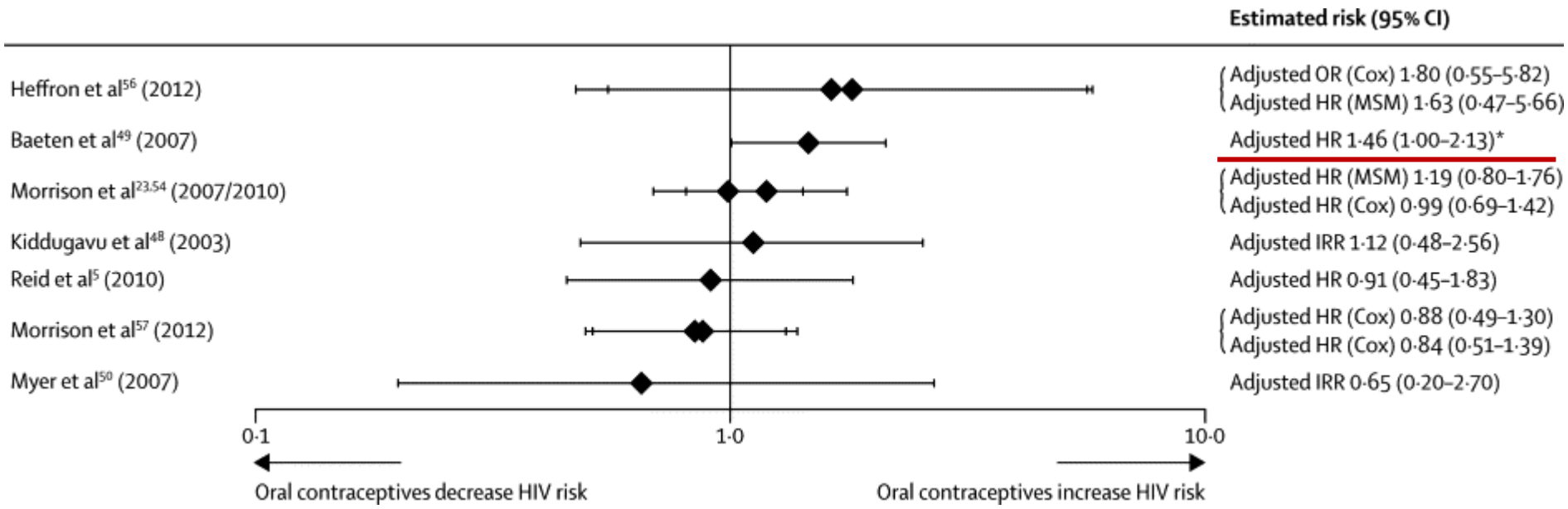
- Recent conflicting evidence from observational studies suggests that progesterone- only injectable contraception use increases risk of HIV acquisition

- Risk could be attributable to changes in immune function or changes in genital tract environment. Different forms of contraceptives may change immune functions in different ways

Ref: *http://www.who.int/reproductivehealth/publications/family_planning/hc_hiv/en/index.html*

CONTRACEPTION AND HIV: CURRENT DATA

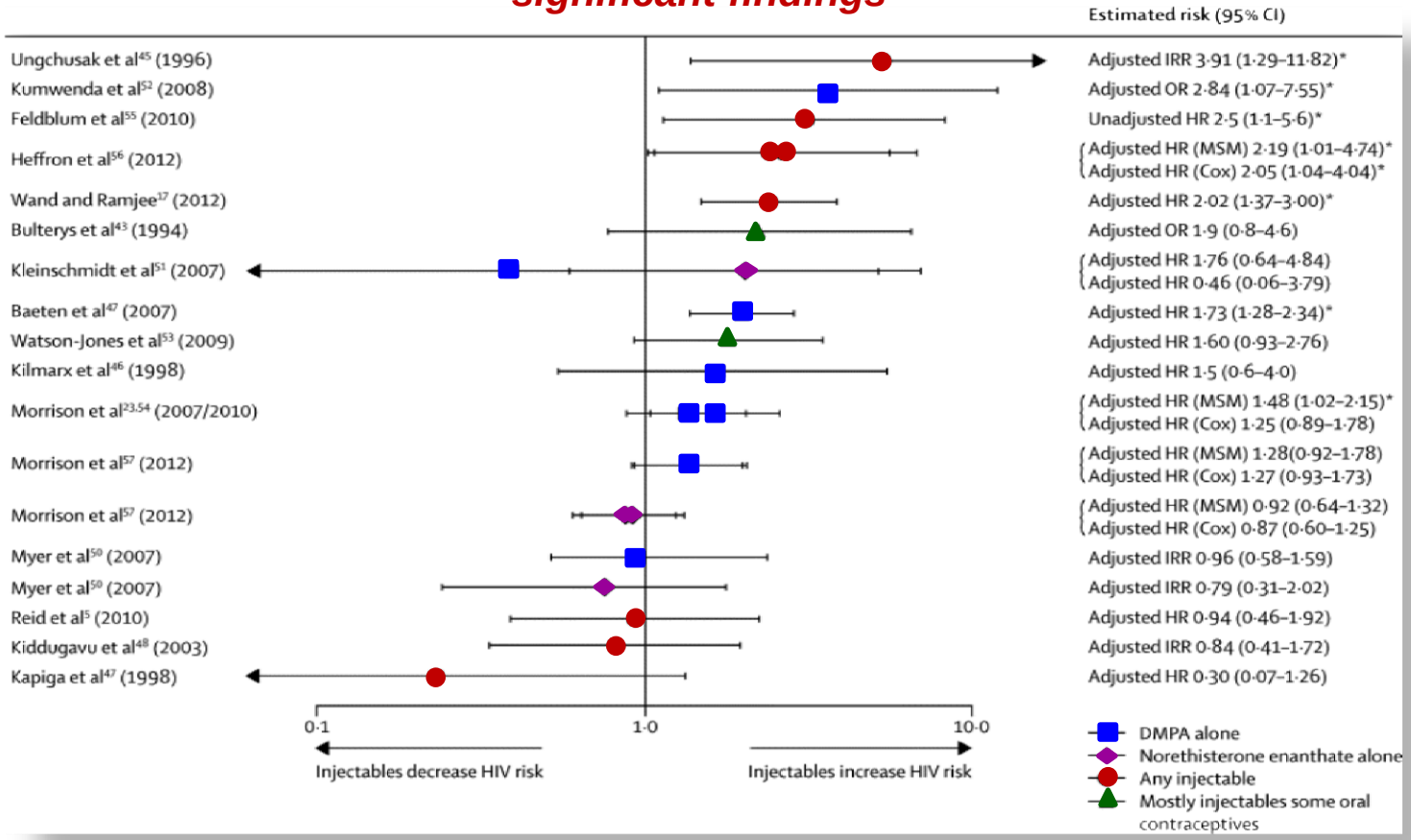
Use of oral contraceptive pills and HIV acquisition (seven studies that met minimum quality criteria only)For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are shown. Error bars show 95% CIs. OR=odds ratio. HR=hazard ratio. IRR=incidence risk ratio. *Analysis showed significant findings.



Ref: Chelsea Polis, **Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence, 2013**

CONTRACEPTION AND HIV: CURRENT DATA

Use of injectable contraceptives and HIV acquisition (all 16 studies)For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are shown. Error bars show 95% CIs. IRR=incidence risk ratio. OR=odds ratio. HR=hazard ratio. DMPA=depot-medroxyprogesterone acetate. *Analysis showed significant findings



***Ref: Chelsea Polis,* Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence, 2013**

CONTRACEPTION & HIV: WAY FORWARD

- **Observational studies- inconclusive results.**
- **Need for RCT to determine whether progestin-only injectable contraceptives do indeed increase risk of HIV-1 acquisition.**
- **Population attributable risk of Depo Provera suggest that removing Depo Provera without substantial evidence may increase unintended pregnancy rates which could result in other complications.**
- **Integration of HIV prevention and Reproductive Health Services for women is critical.**

MICROBICIDE RESEARCH: 1992 – 2012

Microbicides- Products designed for vaginal or rectal administration to prevent HIV acquisition

CAPRISA 004 (2007-2010)
Tenofovir gel
39% EFFECTIVE

MTN003 –VOICE (2009-2013)
Daily use
Tenofovir gel & tablet

FACTS 001 (2011-2014)
Tenofovir gel
SA study to confirm CAP004
on-going

MTN 020 (2012 – 2015)
Intravaginal
Dapivirine ring
on-going

ARV BASED PRODUCTS
Prevents establishment of HIV infection

SURFACTANTS
(disrupts membrane)

POLYANIONS
(prevents attachment of virus)

N-9 sponge (1987-1990)
NIH

N-9 fi -1996)

COL-1 6-2000)
A

SAVVY (2004-2006)
FHI

N9 INCREASED RISK

Carragu d (20 2008)
P Cou

HPTN03 -2009),
MDP301 6-2009)
PF 0

CONR (20 007)
FHI Co ose S hate

SAFE, NOT EFFECTIVE

1992-2012
10 Products in large scale clinical trails

- 1 proof of concept
- Further evidence needed for licensure

Adherence is critical for efficacy

VACCINES

Year Completed	Product/Clade/Trial Name	Countries	Number of participants	Results
2003	AIDSVAX B/B VAX003	Canada, Netherlands, Puerto Rico, US	5,417	No effect
2003	AIDSVAX B/E VAX004	Thailand	2,546	No effect
2007	MRK-Ad5 B Step	Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US	3,000	Immunizations halted early for futility; subsequent data analysis found potential for increased risk of HIV infection among Ad5-seropositive, uncircumcised men.
2007	MRK-Ad5 B Phambili	South Africa	801	Immunizations halted based on Step result; additional data presented in May 2013.
2009	ALVAC-HIV (vCP1521) and AIDSVAX B/E Thai Prime-Boost/RV 144	Thailand	16,402	Modest effect (31.2%) Not licensure trial
2013	DNA and Ad5 A/B/C HVTN 505	US	2,500	Immunizations halted early for futility; vaccine regimen did not prevent HIV infection nor reduce viral load among vaccine recipients who became infected with HIV; follow-up continues.

Ref: AVAC Report 2012: Achieving the End – One year and counting. www.avac.org/report2012.

FOLLOW-ON TRIALS BASED ON RV144: STRATEGY INCLUDES DEVELOPMENT AND RESEARCH TRACKS

RV144 FOLLOW-UP: Thailand

Research Studies:

- **RV144i immune correlates studies**
- **RV305 protein boost in volunteer-subset from RV144**
- **RV306 expanded immunogenicity of RV144 regimen**
- **RV328 AIDSVAX B/E study**

Partners/Funders:
US Army, Thai government, NIH, Sanofi Pasteur, BMGF

RESEARCH TRIAL

Population: **Heterosexual, high-risk**

Products: **DNA + NYVAC (Sanofi Pasteur) + protein/adjuvant (such as MF59) vs. NYVAC (Sanofi Pasteur) +protein/adjuvant**

Partners/Funders: **NIH, HVTN, Sanofi Pasteur, Novartis, BMGF**

LICENSURE TRIAL: Thailand

Population: **MSM, high-risk**

Products: **ALVAC (Sanofi Pasteur) + gp120/adjuvant (such as MF59)**

Partners/Funders: **US Army, Thai government, NIH, Sanofi Pasteur, BMGF, Novartis**

LICENSURE TRIAL: South Africa

Population: **Heterosexual, high-risk**

Products: **ALVAC (Sanofi Pasteur) + gp120/MF59 (Novartis)**

Partners/Funders: **NIH, HVTN, Sanofi Pasteur, Novartis, BMGF**

Ref: This schematic comes from the Pox-Protein Public Private Partnership (P5), a collaboration spanning four continents established in 2010 to build on the results of RV144. P5 partners include the US NIAID, the Bill & Melinda Gates Foundation, the HIV Vaccine Trials Network, the US Military HIV Research Program, Sanofi Pasteur and Novartis Vaccines and Diagnostics.

SUMMARY OF EVIDENCE: BIOMEDICAL HIV PREVENTION

Treatment for prevention (discordant couples)
96 % (CI: 73,99)

Oral Pre- Exposure Prophylaxis (discordant couples) (Tenofovir and Truvada)
Truvada: 73% (CI: 49,85) & Tenofovir: 62% (CI: 34-78)

Oral PrEP (heterosexual couples) (Truvada)
63 % (CI: 21,98)

Medical Male Circumcision
54% (CI:38,66)

Oral Pre-Exposure Prophylaxis for IDU's
49 %(CI: 9.6-72.2)

Oral Pre-Exposure Prophylaxis for MSM
44% (CI:15,63)

STD Treatment (Random cohort of 1000 adults)
42% (CI:21,58)

Topical Microbicide (heterosexual women)
39 %(CI:16,60)

HIV Vaccine (Thai RV 144)
31% (CI:1,51)

- The search for the most effective HIV prevention prophylaxis for all is still elusive
- Effect size is directly proportional to adherence

BEHAVIOURAL HIV PREVENTION STRATEGIES

HPTN 043:
- A four-fold increase in testing was observed in HIV mobile voluntary counseling and testing
- Data suggests- knowing the status- decreases risky behaviour

HIV Counselling & Testing

- Evidence suggests that clean needle syringe exchange program can reduce HIV transmission among IDU's
- HIV sero-prevalence declined by a mean annual 18.6% for 36 cities with NSPs compared to an 8.1% increase in 67 cities without NSPs (Wodak, 2005)

- Highest seroconversion rate was observed among women who had reported to have had sex at 15 years or younger (12.0 per 100 person-years, 95% CI 8.0 to 18.0) (Wand and Ramjee et al 2012).

Delaying Sexual Debut

BEHAVIOURAL INTERVENTIONS

Clean Needle Exchange Programs

Eliminating Stigma

Development of the AIDS-Related Stigma Scale (Kalichman et al 2005)
- Disclosure of HIV testing may eliminate stigma

Barrier Methods (Male & Female Condoms)

- Correct and consistent use of male condom use can reduce HIV acquisition by up to 97 % (Pinkerton & Abramson, 1997)
- HIV incidence in consistent condom users: 0.9 per 100 person-years (95% CI, 0.4-1.8)
- HIV incidence in non consistent condoms users: 6.8 per 100 person-years (95% CI, 4.4-10.1)(Davis and Weller, 1999)

STRUCTURAL HIV PREVENTION STRATEGIES

- Intervention more effective between partner (Lurie et al, 2003)
- Comprehensive HIV prevention package for Migrants (William set al, 2003)

- Microfinance is one of the few interventions that can both mitigate AIDS impact and prevent new infections (Pronyk et al 2005)
- A South African based study provided evidence for the effect of a microfinance based structural intervention on the prevention on HIV infection and intimate-partner violence (Pronyk et al 2006)

Micro Financing Programs

Migration

STRUCTURAL INTERVENTIONS

Health Systems Strengthening Linkage and Retention in Care

- Decentralizing and integrating HIV health services with effective linkage to care are shown to contribute to improved health outcomes (Pfeiffer et al 2010)

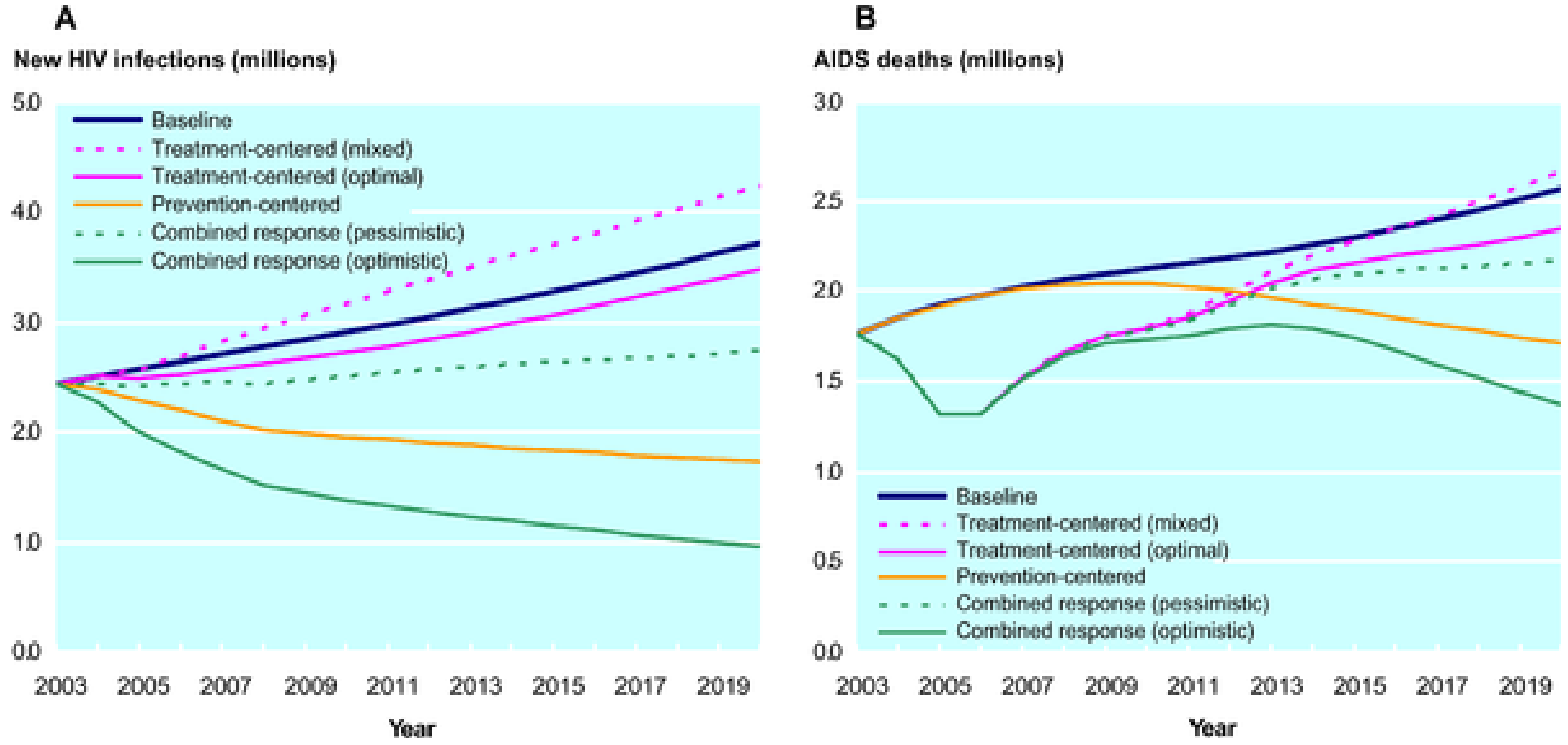
Poverty

- Poor access to health care
- High risk behaviour for economic survival e.g. sex workers or transactional sex (Baba-Djara et al 2013)

Gender Inequality & Gender Violence

- Stepping Stones : a participatory HIV prevention programme to improve sexual health through building stronger, more gender equitable relationships (Jewkes et al 2006)
- Women who had participated in this study had 15% fewer new HIV infections and a change in men's gender-related behaviour was observed (Jewkes et al 2008)

HIV INCIDENCE AND AIDS MORTALITY AMONG ADULTS IN SUB-SAHARAN AFRICA, 2003–2020, UNDER DIFFERENT INTERVENTION SCENARIOS (MODELING)



Integration of HIV prevention & care activities for long-term reduction in HIV incidence & significant decline in AIDs mortality

Ref: Salomon JA, Hogan DR, Stover J, Stanecki KA, et al. (2005) Integrating HIV Prevention and Treatment: From Slogans to Impact. PLoS Med 2(1): e16. doi:10.1371/journal.pmed.0020016 http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0020016

EDCTP: RESEARCH PRIORITIES FOR HIV PREVENTION, TREATMENT & CARE IN AFRICA

IMPLEMENTATION RESEARCH

- Capacity development to enhance quality of care, retention and adherence
- Novel models of delivery of proven interventions

OPERATIONAL RESEARCH

- To optimize care
- Optimize health delivery models

HUMAN RESOURCES

- Scientific & health care capacity development

THERAPEUTICS DRUG DEVELOPMENT

- Novel therapeutics & alternative use of current therapeutics (to address drug resistance)
- Therapeutic trials

PREVENTION

- New biomedical interventions e.g. vaccines, microbicides, Novel PrEP formulations
- Combination prevention strategies

European & Developing Countries Partnerships to prevent & treat HIV & related co-morbidities through an integrated and a multidisciplinary research program including development of world class African scientists

THANK YOU