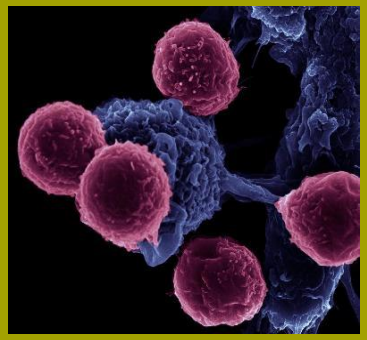


Update on HIV

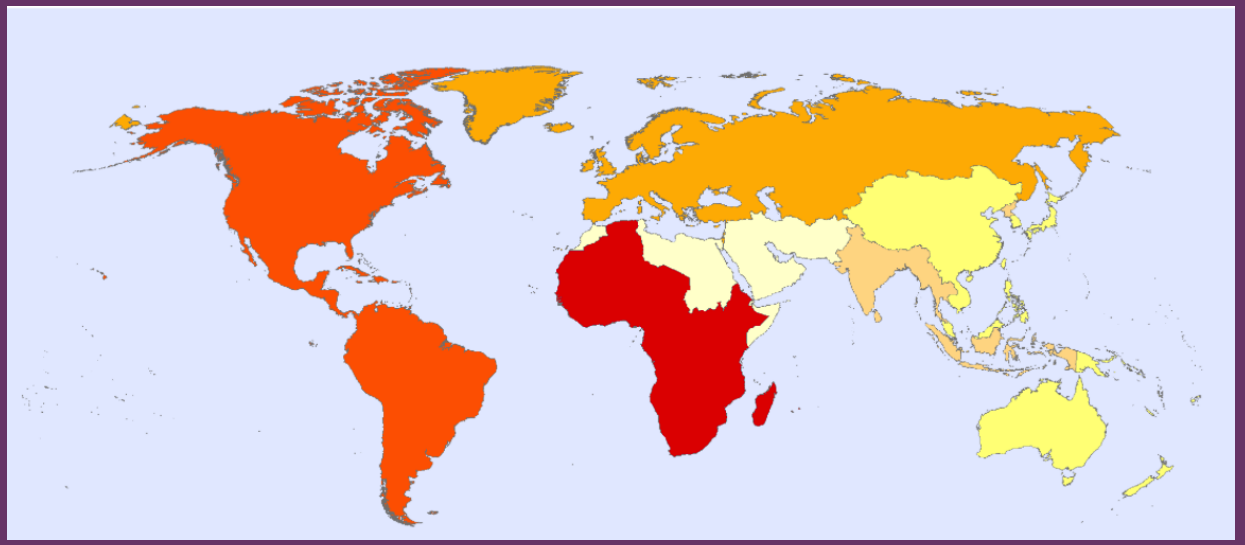
Prof Theresa Rossouw

University of Pretoria

Outline

- Update on epidemiology
- Key populations & drivers
- Opportunistic infections – what to watch out for
- ART – now & upcoming
- Hepatic injury on ART
- Treatment failure
- PrEP and prevention

Update on the Epidemic



FACT SHEET – JULY 2018

2017 GLOBAL HIV STATISTICS

36.9 million [31.1 million–43.9 million] people globally were living with HIV in 2017.

21.7 million [19.1 million–22.6 million] million people were accessing antiretroviral therapy in 2017.

1.8 million [1.4 million–2.4 million] people became newly infected with HIV in 2017.

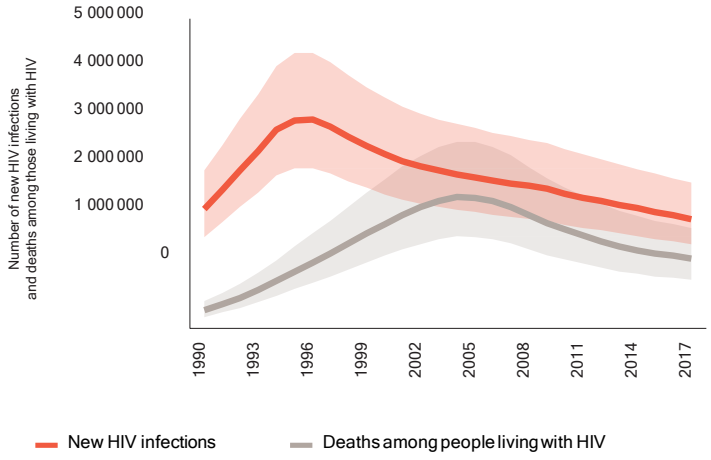
940 000 [670 000–1.3 million] people died from AIDS-related illnesses in 2017.

77.3 million [59.9 million–100 million] people have become infected with HIV since the start of the epidemic.

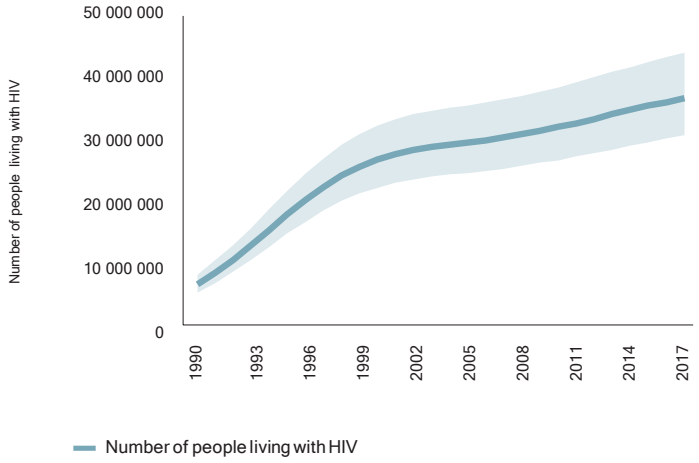
35.4 million [25.0 million–49.9 million] people have died from AIDS-related illnesses since the start of the epidemic.

Rising numbers of people living with HIV

Number of new HIV infections and deaths among the HIV population (all causes), global, 1990-2017

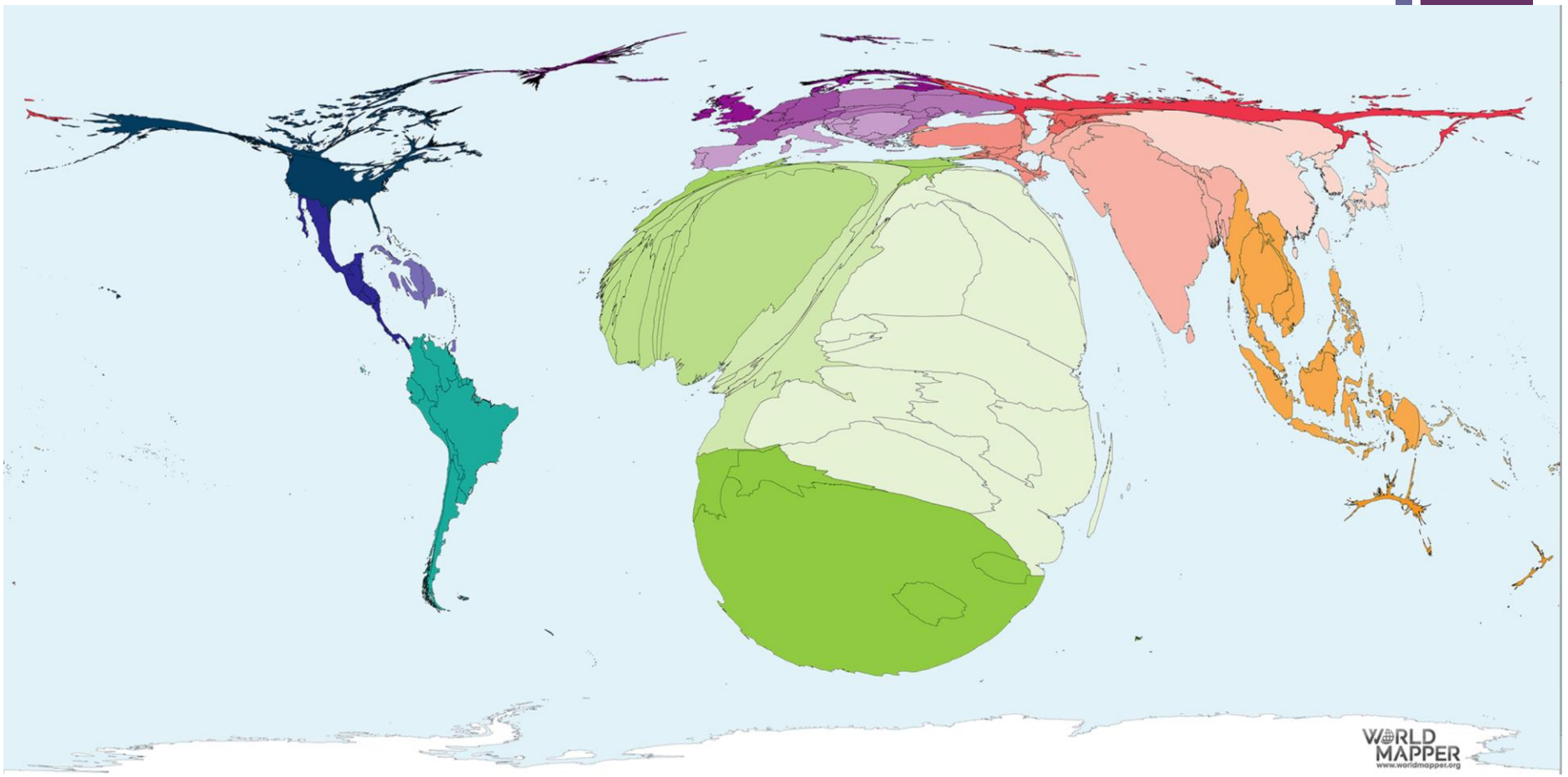


Number people living with HIV, global, 1990-2017



Source: 2018 Global AIDS Monitoring.

Global HIV Prevalence




... IN THE 'LEADING CAUSE OF DEATH' EVENT, THE CONTINENT'S NEW NUMBER ONE!..
ALL AFRICA
AIDS
WAR
MALARIA
1
2
3
ZAPIRO

HIV: South Africa (2016)

- 7.1 million infected – 11.2%
- Adults (15 - 49 y) – 18.3%
  - 55% in KwaZulu Natal & Gauteng
  - 29% pregnant women
    - ~12 000 (9600 - 22 000) children infected by MTCT
- 270 000 (240 000 - 290 000) new HIV infections
  - ~1 new infection every 2 minutes
  - Women 15-24 y account for 90%
- 110 000 (88 000 - 140 000) AIDS-related deaths
  - ~1 every 5 minutes
  - >1.8 million died since the epidemic began

spotlight

A print and online publication monitoring South Africa's response to TB and HIV, the state of our health systems and the people that use it and keep it going.

3. HIV mortality: How many people die of AIDS-related causes in South Africa per year?

According to the Thembisa model around 123 000 people in South Africa died of AIDS-related causes in 2017. This is down from a peak of around 270 000 in 2005.

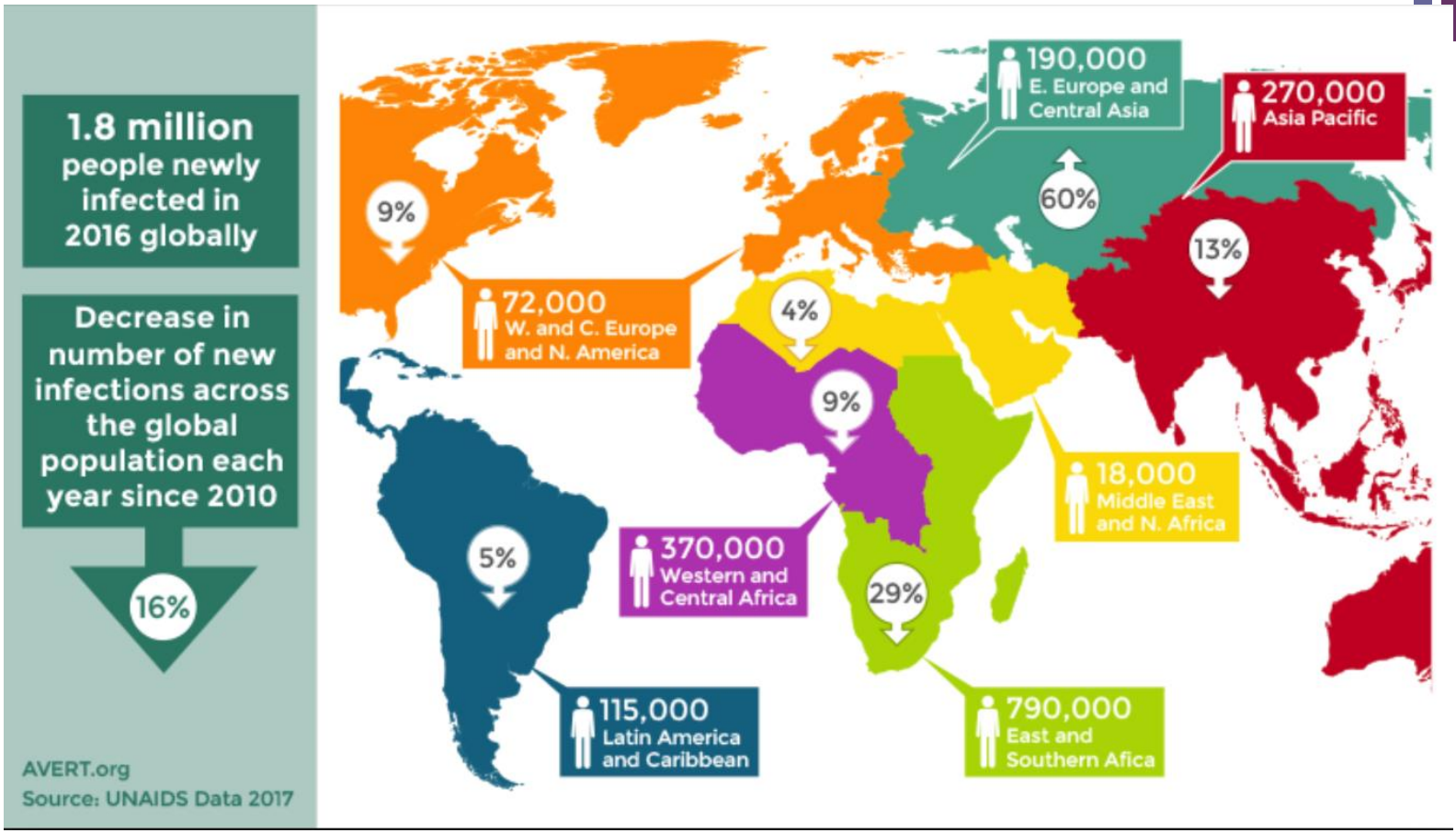
The Bad News & the Good News

- **South Africa has the largest HIV epidemic in the world**
  - 19% of the global number of people living with HIV
  - 15% of new infections
  - 11% of AIDS-related deaths

- **South Africa has the largest treatment programme in the world**
  - 20% of people on ART globally

- One of the largest domestically funded programmes
  - ~80% of AIDS response funded by the government

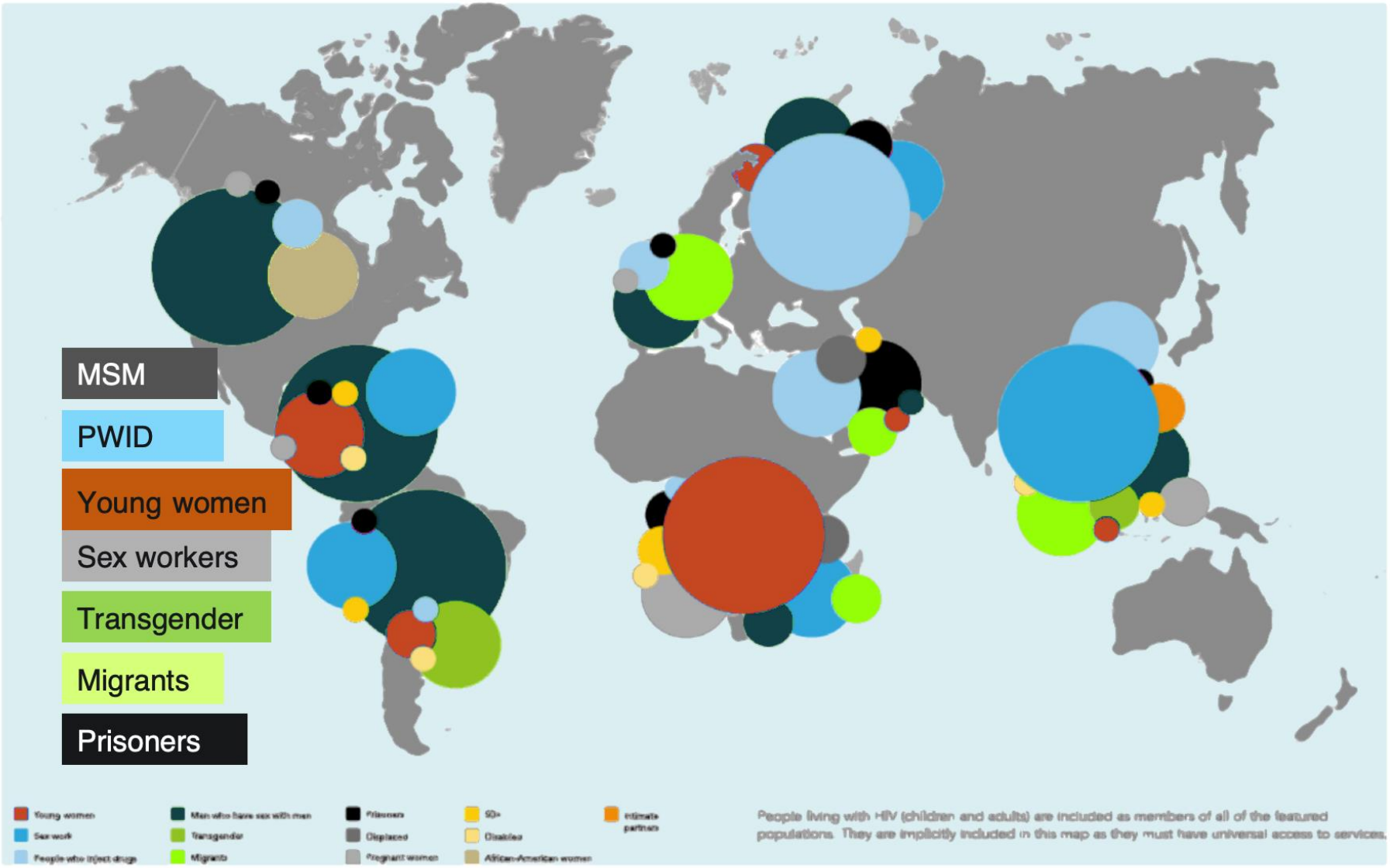
Progress in HIV Incidence




SABSSM V
#SABSSMV2017
South Africa's 5th National HIV/AIDS Household Survey results
231,000 new HIV infections
7.9 million people living with HIV (14% prevalence)
4.4 million people on treatment (60%)
Incidence down 44% since 2012

Key Populations & Drivers

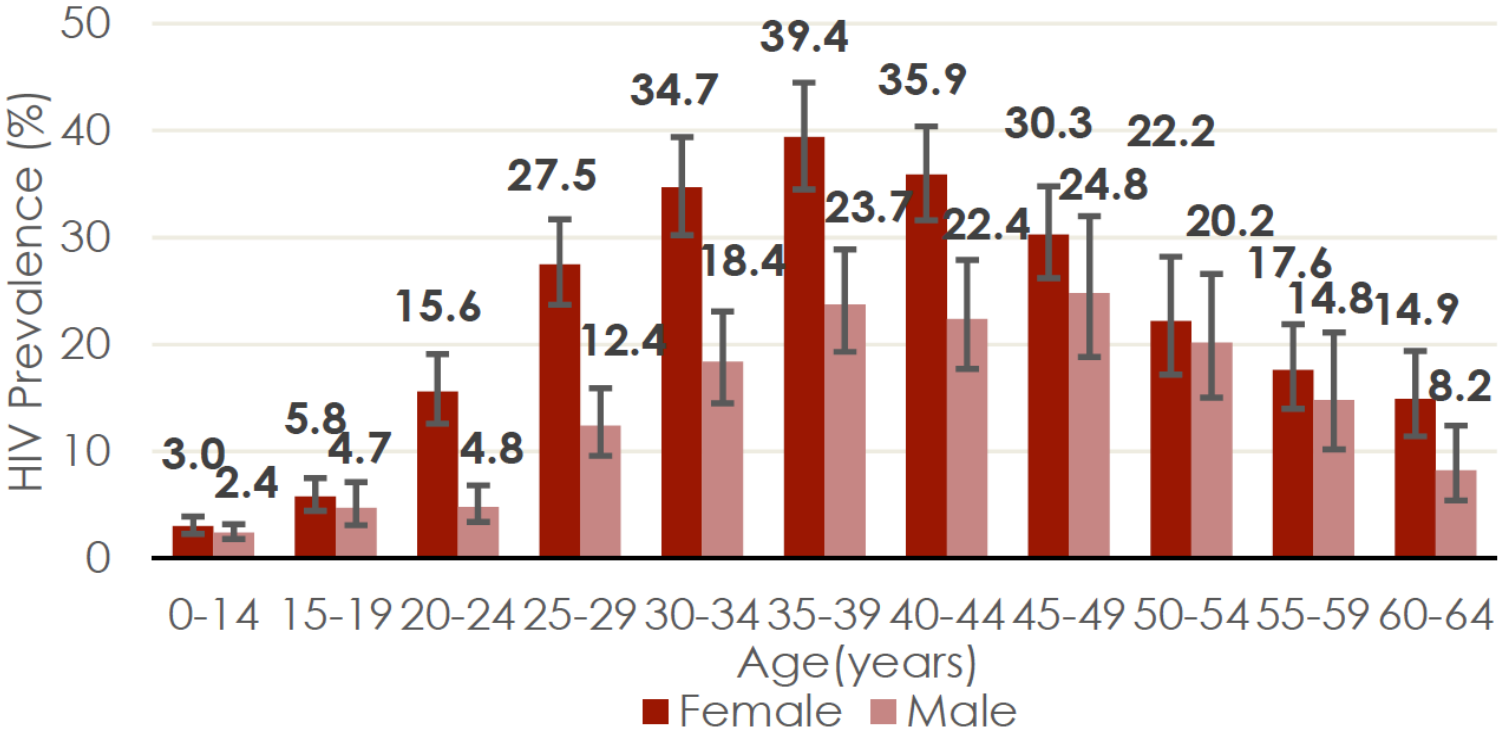
Key Populations vary by location

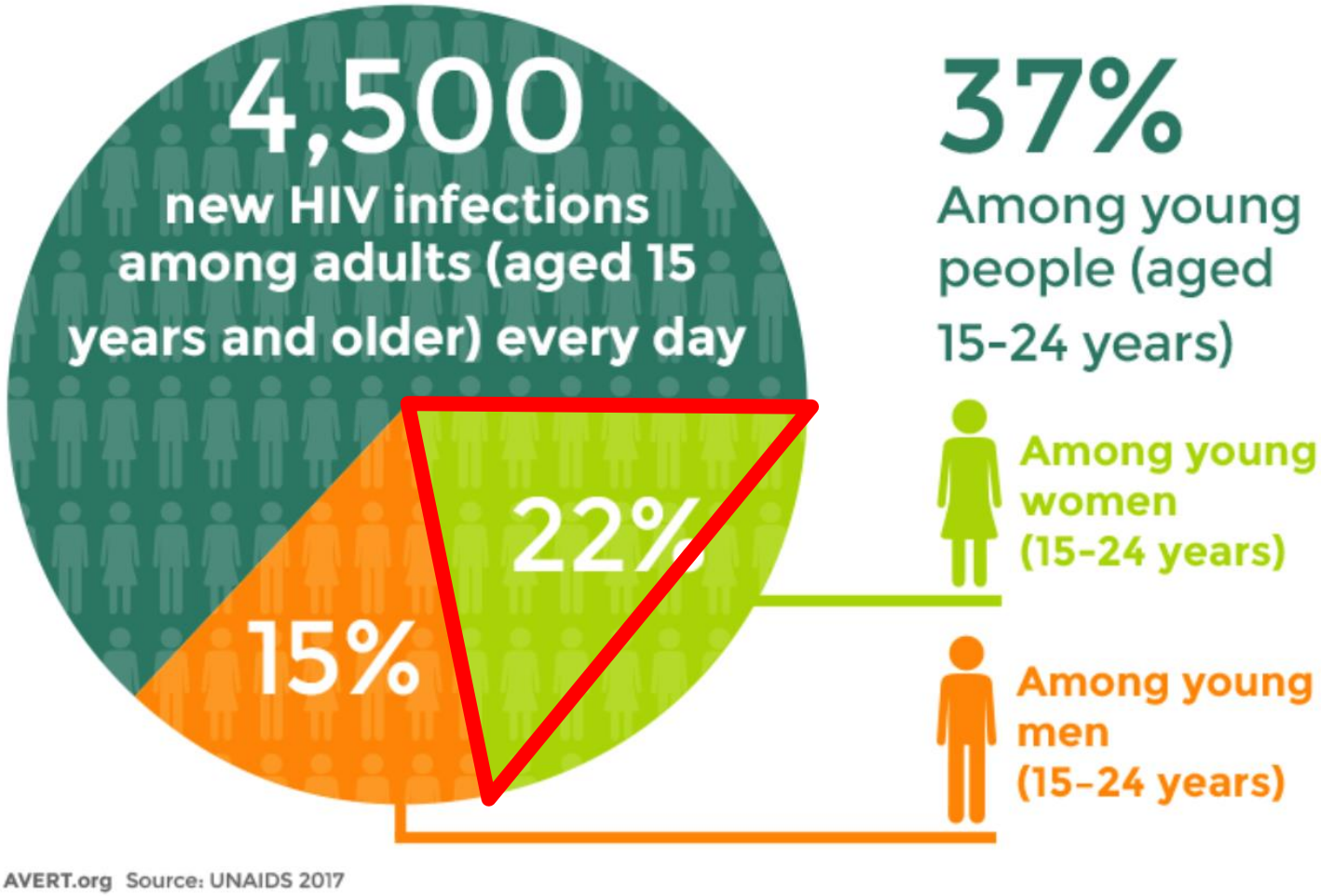


PEPFAR
U.S. President's Emergency Plan for AIDS Relief

Source: UNAIDS, 2014

THE FIFTH SOUTH AFRICAN NATIONAL HIV PREVALENCE, INCIDENCE, BEHAVIOUR AND COMMUNICATION SURVEY, 2017 (SABSSM V[1])



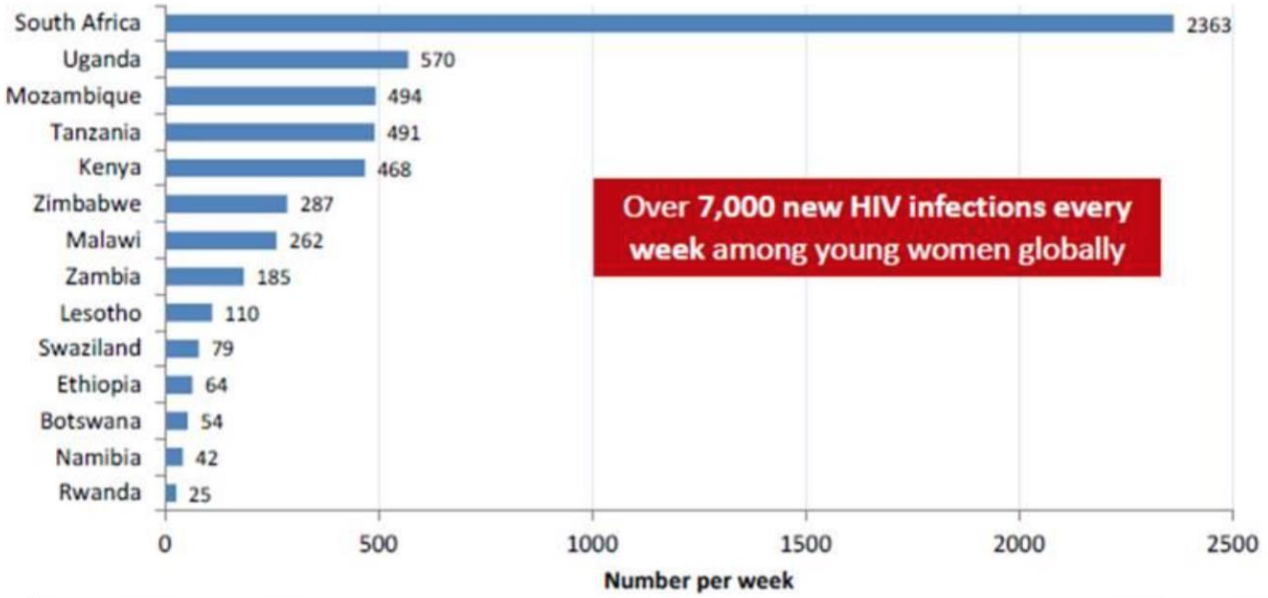

4,500
new HIV infections among adults (aged 15 years and older) every day
22%
15%
37%
Among young people (aged 15-24 years)
Among young women (15-24 years)
Among young men (15-24 years)
AVERT.org Source: UNAIDS 2017

HIV Incidence among Young Women

More than 1/3 New HIV Infections Globally Occur among Young Women in Africa

Estimated number of new HIV infections *per week* among young women aged 15-24 years in East and Southern Africa, 2012

Data source: UNAIDS 2013



Over 7,000 new HIV infections every week among young women globally

One of every 3 HIV infections in young women occurs in SA

HIV prevalence in school boys & girls in rural South Africa (Grades 9 & 10)

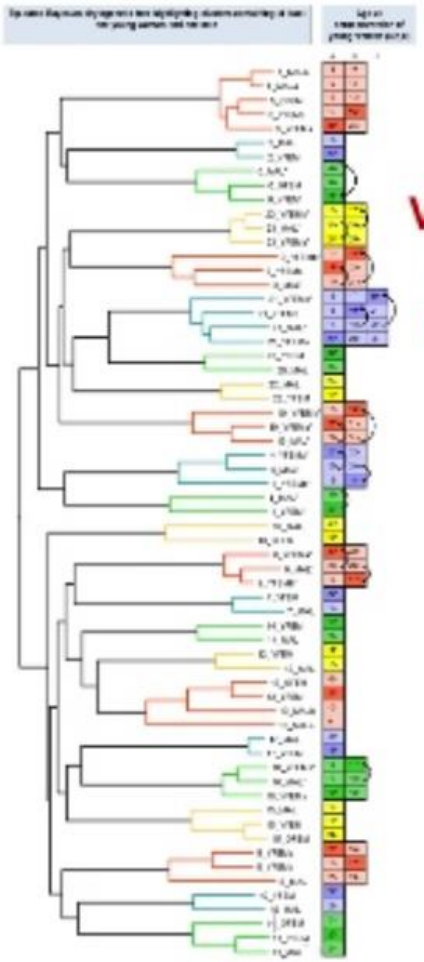
Age Group (years)	HIV Prevalence (2010) % (95% Confidence Interval)	
	Male (n=1252)	Female (n= 1423)
≤15	**1.0** (0.0 - 2.2)	**2.6** (1.2 - 4.0)
16-17	**1.1** (0.2 - 2.0)	**6.1** (2.6 - 9.6)
18-19	**1.5** (0 - 3.7)	**13.6** (9.0 - 18.1)
≥20	**1.8** (0 - 3.9)	**24.7** (6.3 - 43.1)

Source: Abdool Karim Q, et al Sex Transm Infect 2014

CAPRISA

Who is infecting who?

Africa Centre identified phylogenetically linked HIV transmission networks in Hlabisa



High HIV incidence men
mean age 27 years (range 23-35 years)

Very young women acquire HIV from men, on average, 8 years older

Men and women > 24 years usually acquire HIV from similarly aged partners

High HIV risk women
Mean age 18 years
(range 16-23 years)

High HIV prevalence women
Mean age 26 years
(range 24-29 years)

When teen women reach mid-20s they continue the cycle

CAPRISA

Source: *Dellar R, et al. Manuscript in preparation*

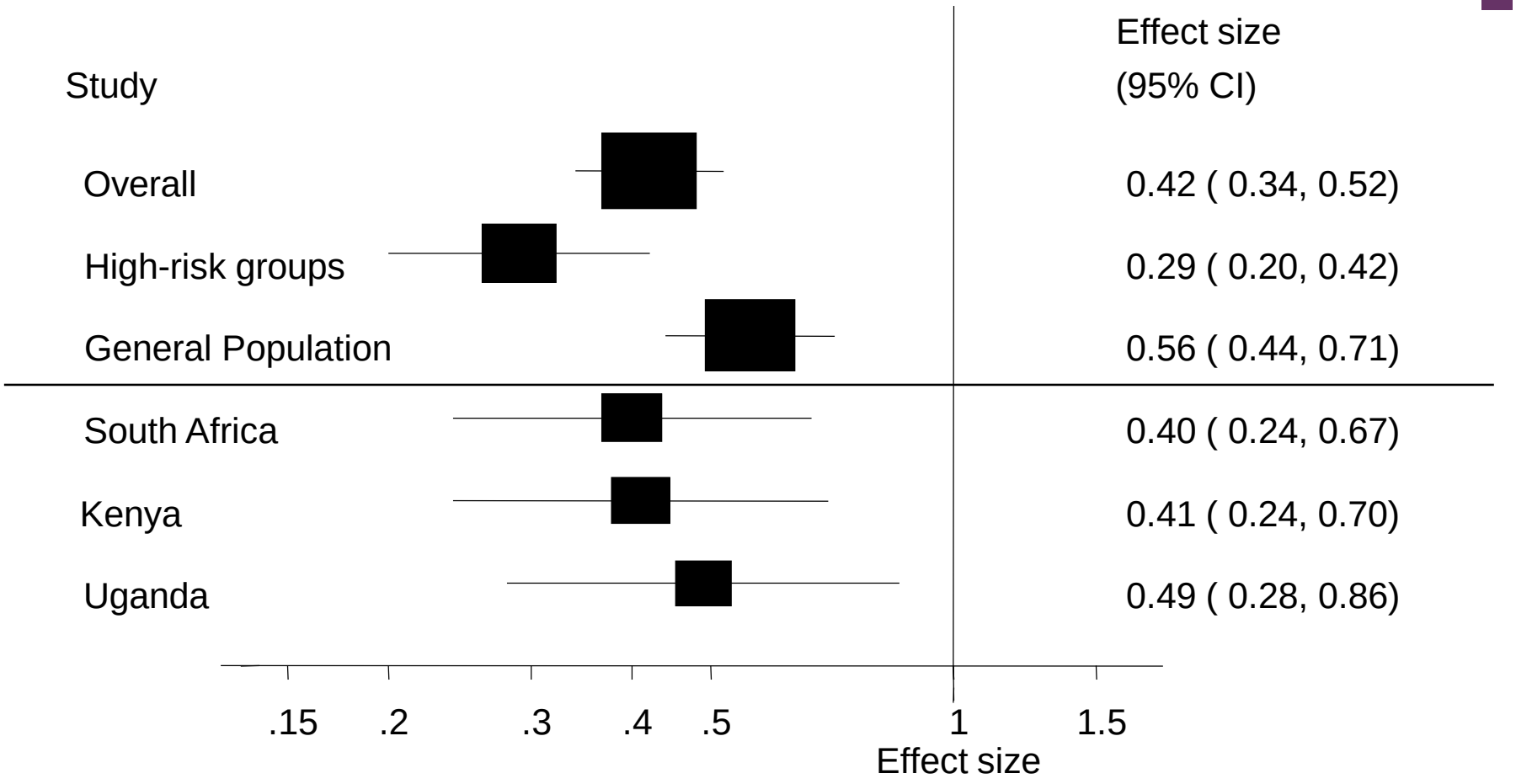
Key Drivers

- Concurrent sexual partnerships
- Inter-generational sex
- Sexual coercion – gender norms
- Late or no male circumcision
- Stigma & vulnerability

Sexual behaviour

Circumcision & HIV Prevalence

Impact on HIV incidence: Evidence from observational studies and RCTs



Evidence from RCTs

Site	Population	Effect
Orange Farm, SA	18 – 24	60% ↓
Rakai, Uganda	15 – 49	48% ↓
Kisumu, Kenya	18 – 24	53% ↓


hiv & aids
discrimination
and stigma

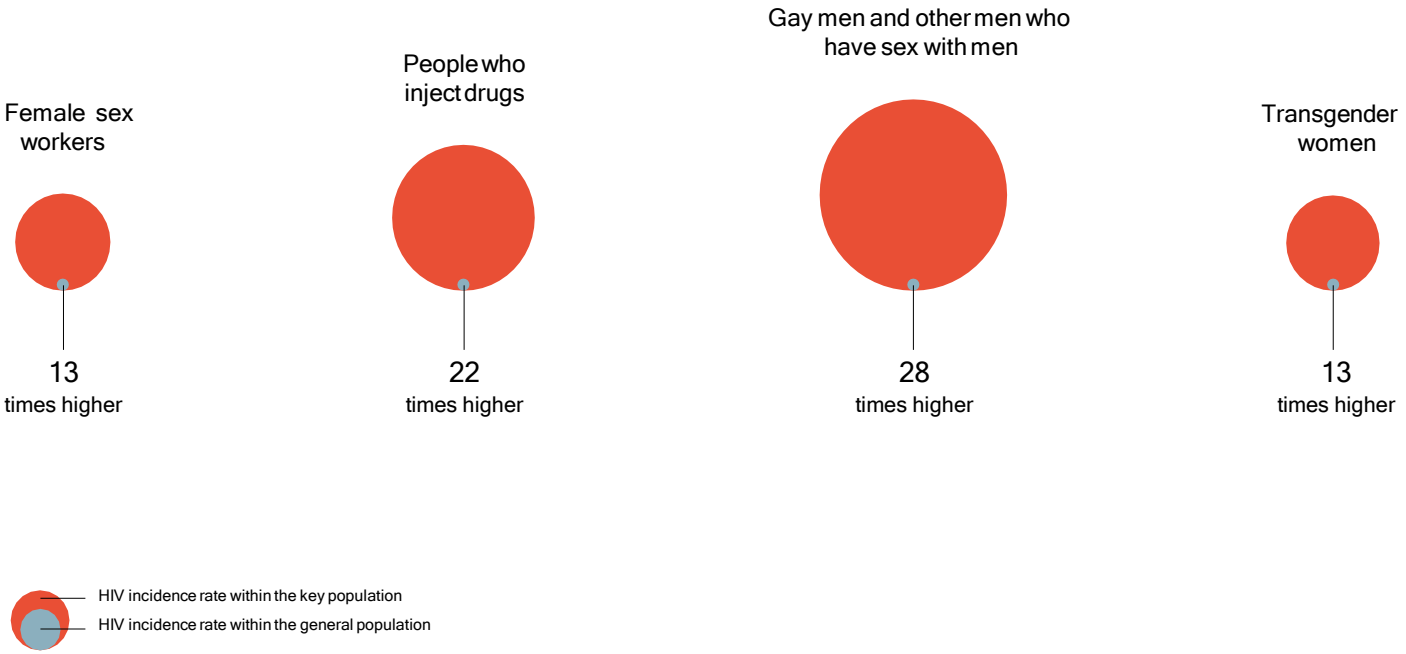
The Grim Reaper (Australia AIDS campaign -1987)

Powerful Images

- Represent 'ready-made' but inaccurate explanations
- Provide powerful basis for stigma & discrimination
- These stereotypes enable some people to deny that they personally are likely to be infected or affected

Key populations at higher risk of infection

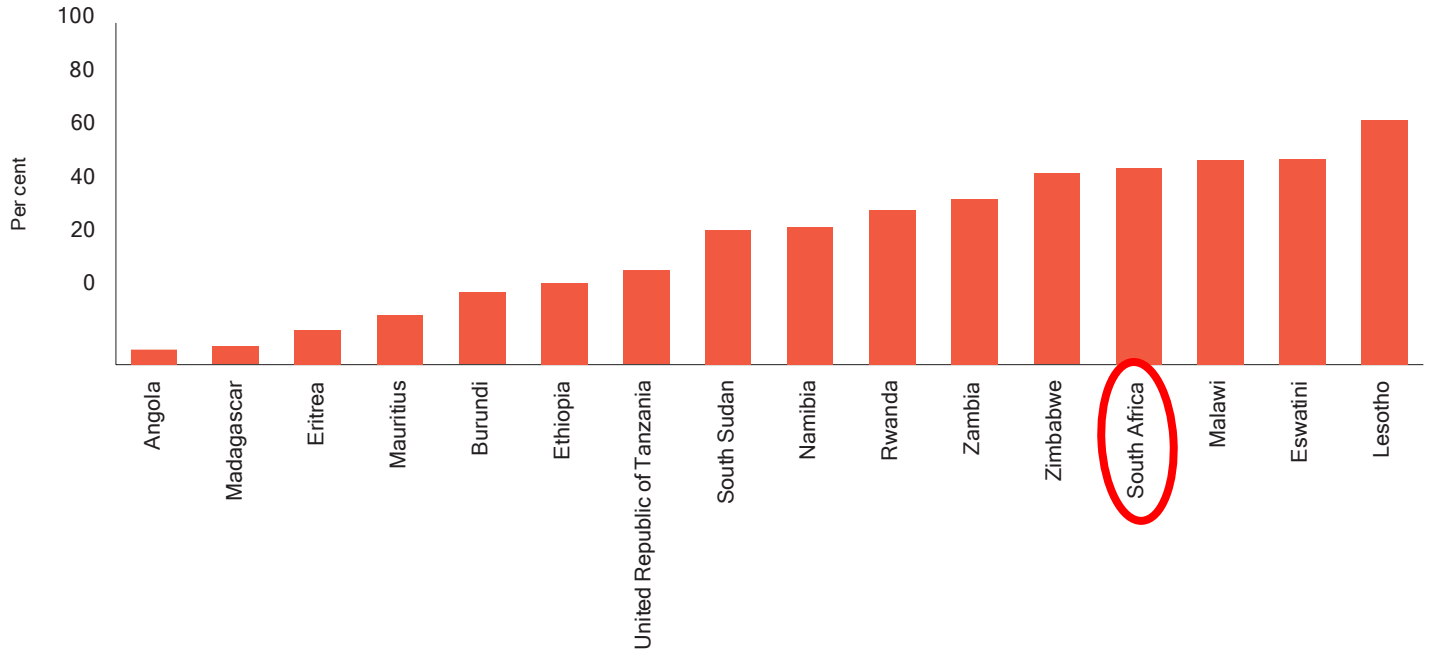
Relative risk of HIV acquisition, by population group compared to the general population, global, 2017



Source: 2018 Global AIDS Monitoring.

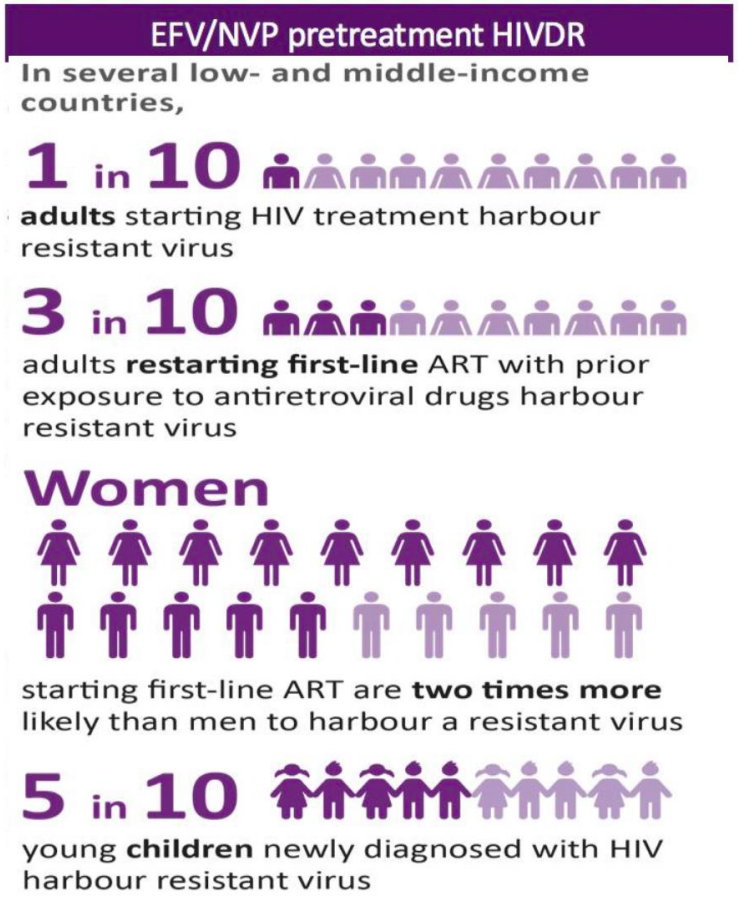
High HIV burden among sex workers in eastern and southern Africa

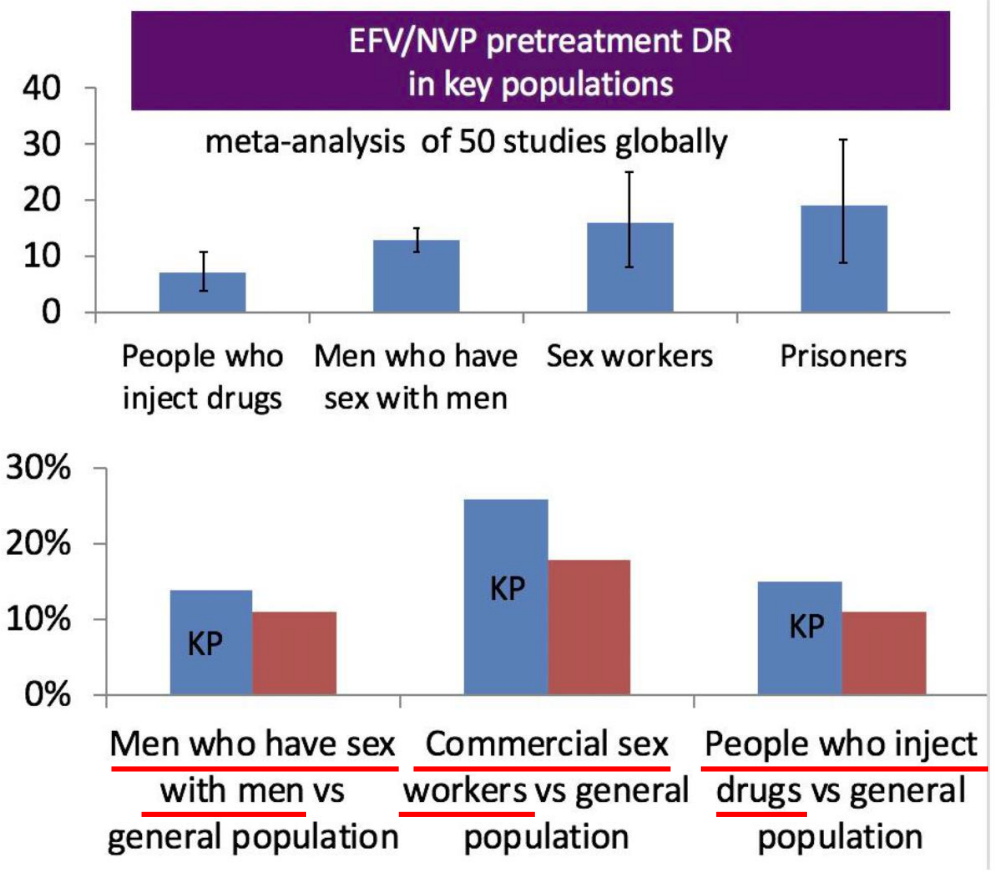
HIV prevalence among female sex workers, eastern and southern Africa, most recent data, 2014-2017



Source: 2018 Global AIDS Monitoring.

Levels of pretreatment HIVDR (PDR)



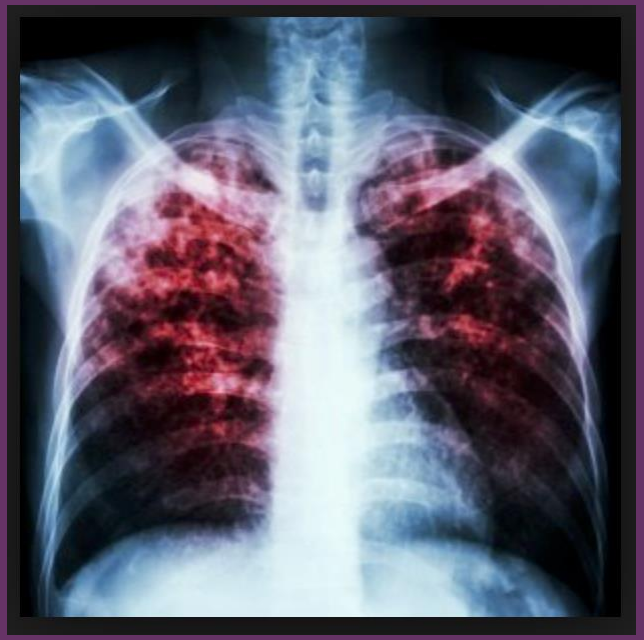


Thanks: Silvia B (WHO)

Increased Risk of HIV Infection in People who use Drugs

- IV
- Sharing needles
- Behavioural disinhibition
- Chem-sex

Opportunistic Infections



HIV-TB Co-Infection

HIV/TB Co-Infection

- At least 1/3 of people living with HIV is infected with latent TB
  - People co-infected with TB and HIV are 21–34 times more likely to develop active TB disease than people without HIV
- TB is the leading cause of death among people with HIV living in the developing world
  - ¼ HIV-related deaths
  - ~430,000 people die of HIV-associated TB/year
- Mortality among HIV+ ~30% within first 2/12 of TB treatment if ART is withheld
  - The timing for starting ART in patients with TB has been widely debated

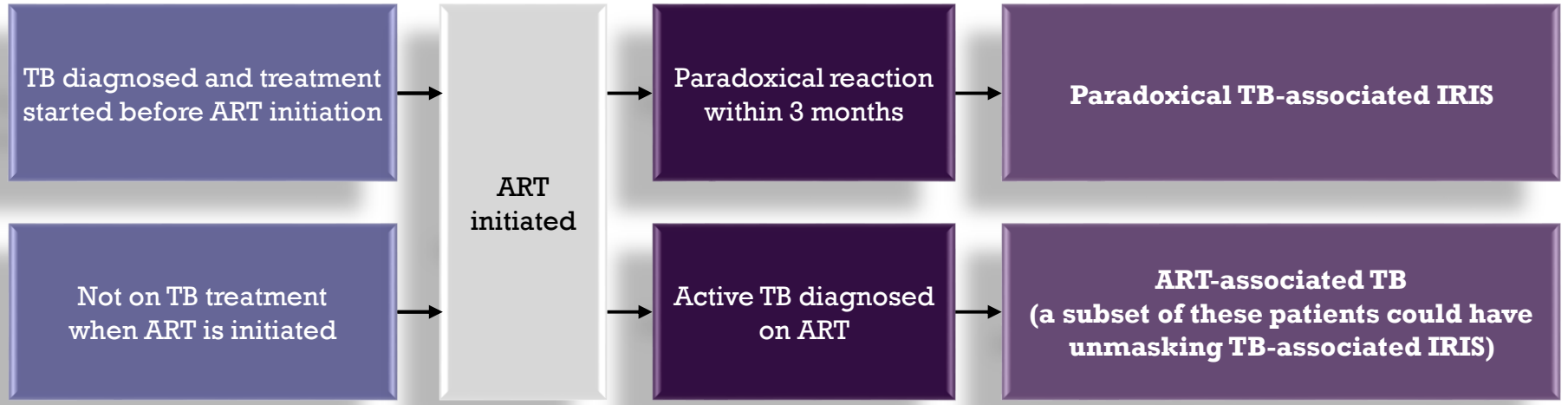
- 25. WHO HIV/TB Facts 2012–2013. Available at: http://www.who.int/tb/publications/factsheet_tbhiv.pdf. Accessed January 2014;
  26. Blanc FX, et al. N Engl J Med 2011;365:1471–81

IRIS: Definitions

Excessive inflammatory response to a preexisting antigen or pathogen and a paradoxical deterioration in clinical status *after initiation* of ART

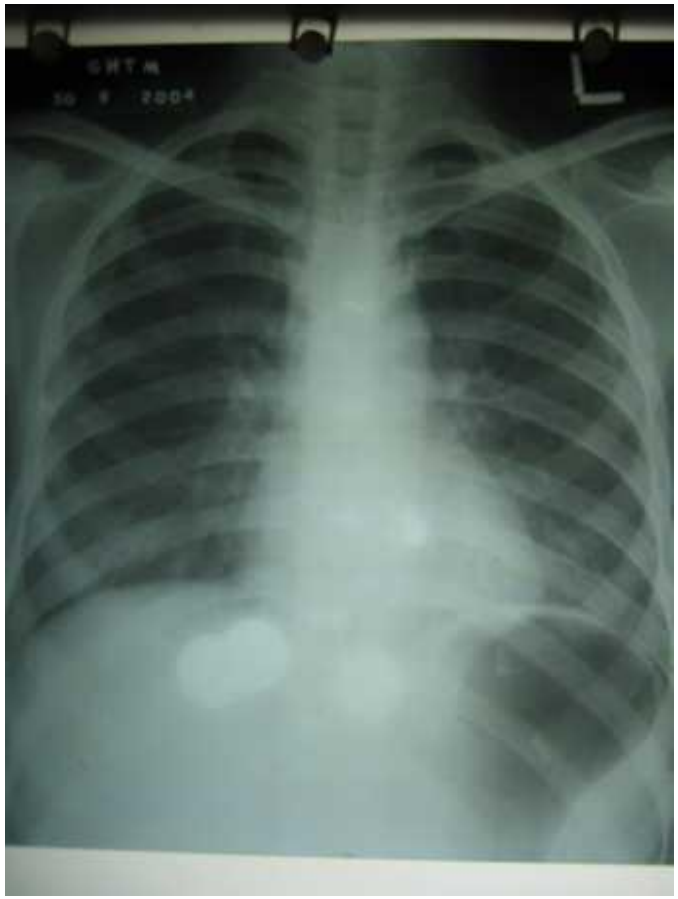
- **Paradoxical IRIS**: worsening of symptoms of a *known disease*, either at a new body site or at the original body site

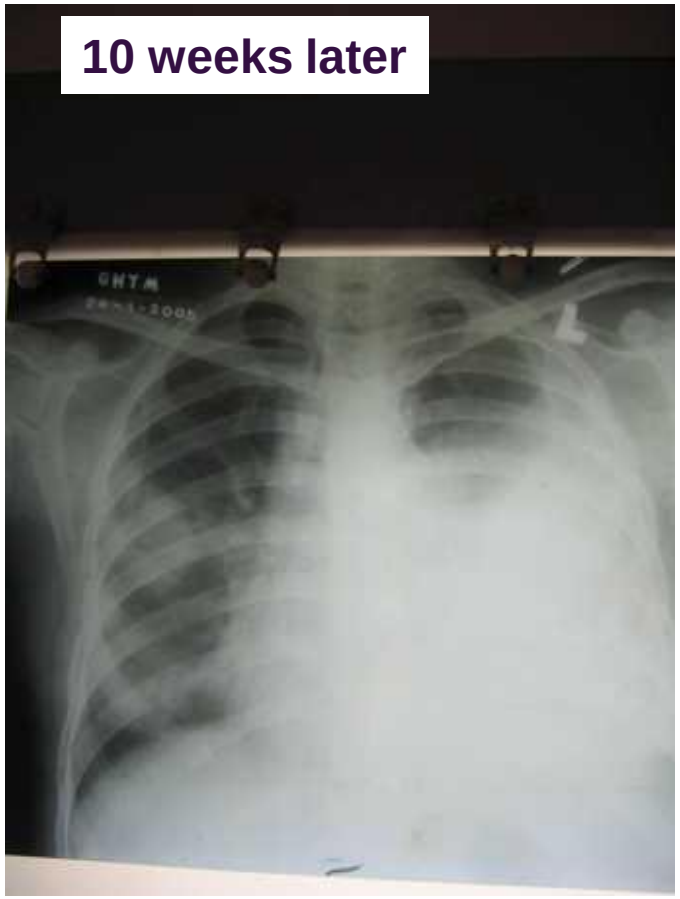
- **Unmasking IRIS**: an *occult* opportunistic infection not clinically apparent prior to ART



Haddow LJ, et al. Clin Infect Dis 2009;49:1424–32

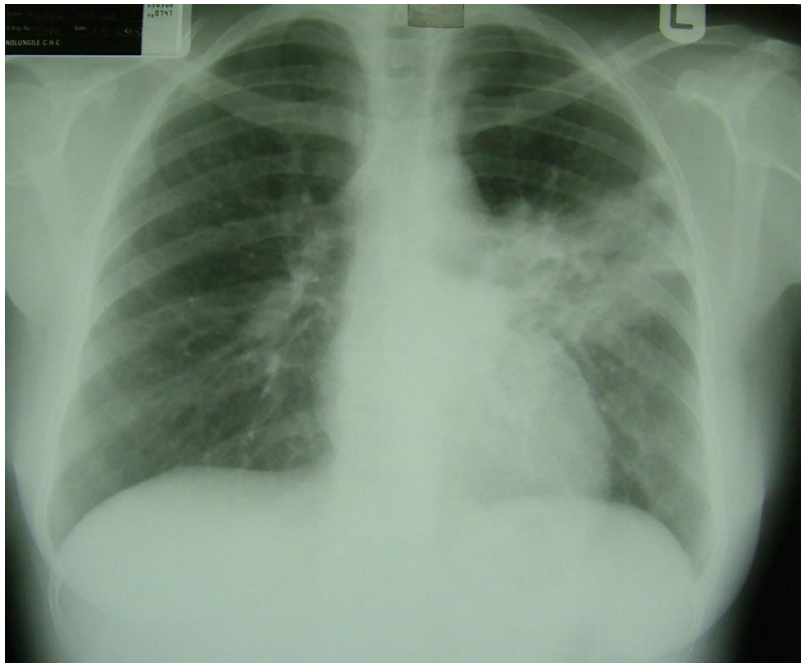
Unmasking IRIS

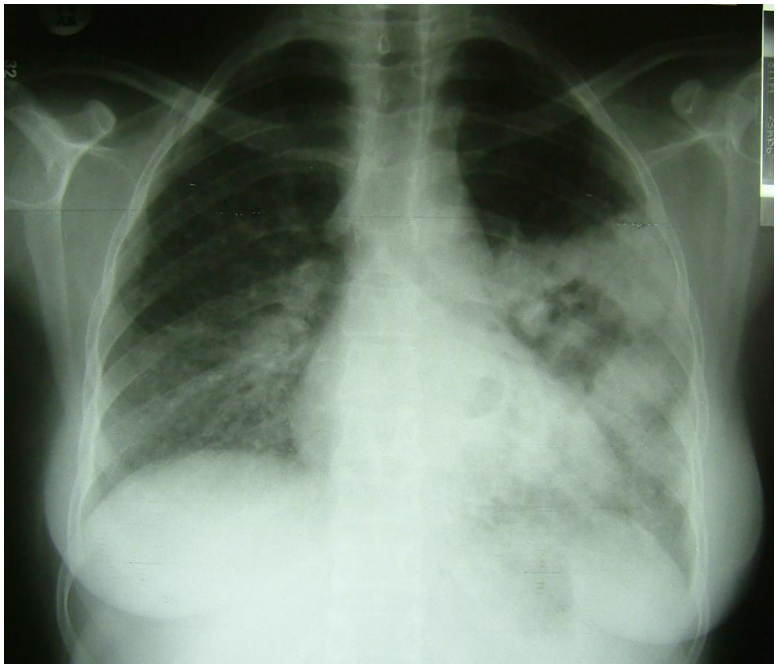




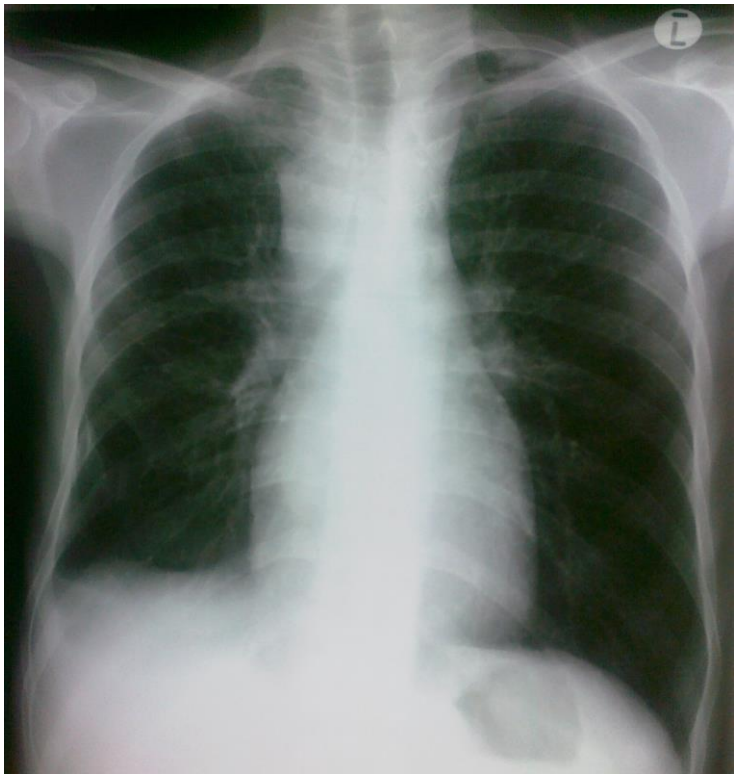
Source: Dr.Rajasekaran, Superintendent, GHTM,Chennai

Worsening pulmonary infiltrate and cavitation due to TB-IRIS

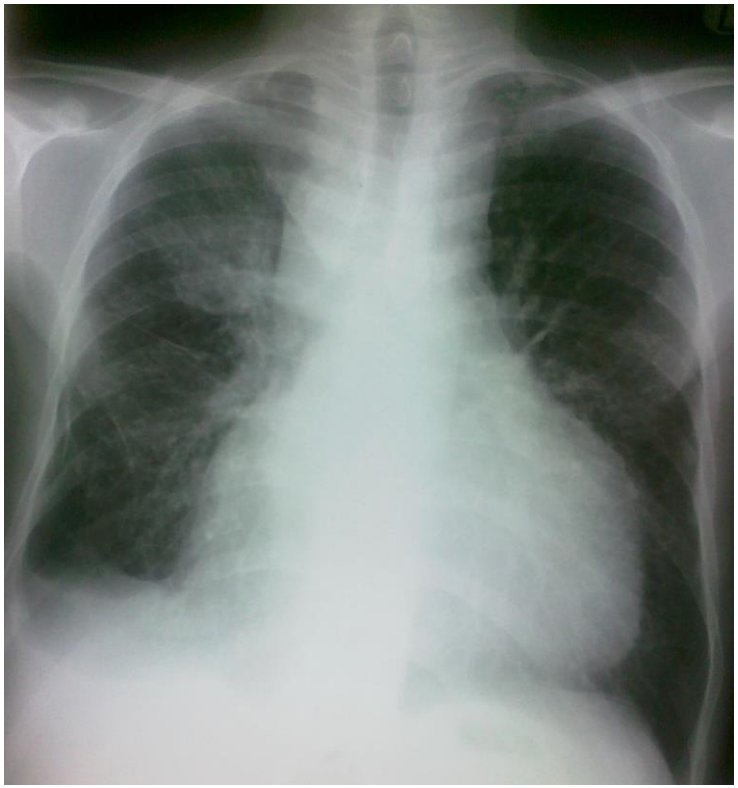




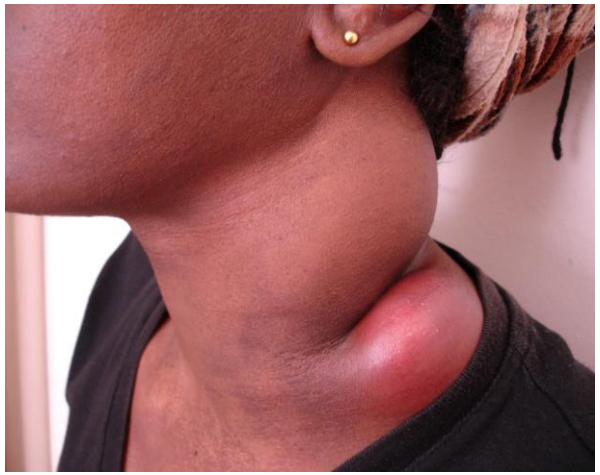
Pericardial tamponade due to paradoxical TB-IRIS

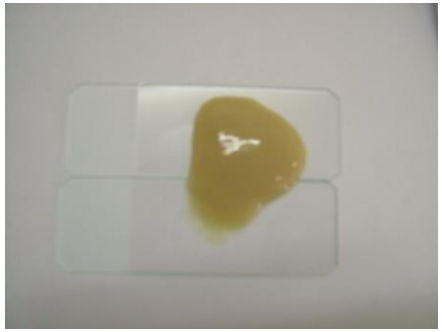


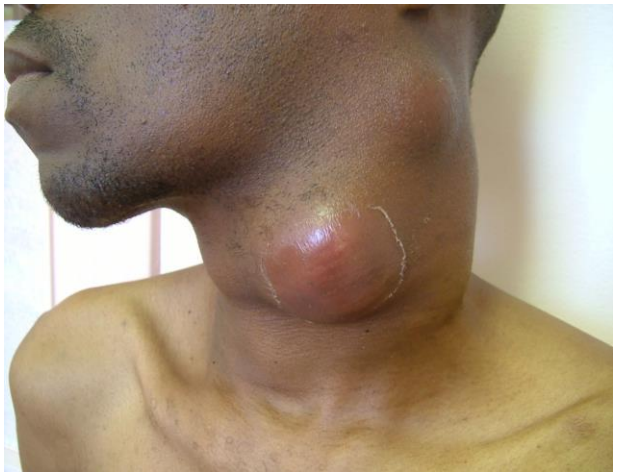
On TB treatment prior to ART

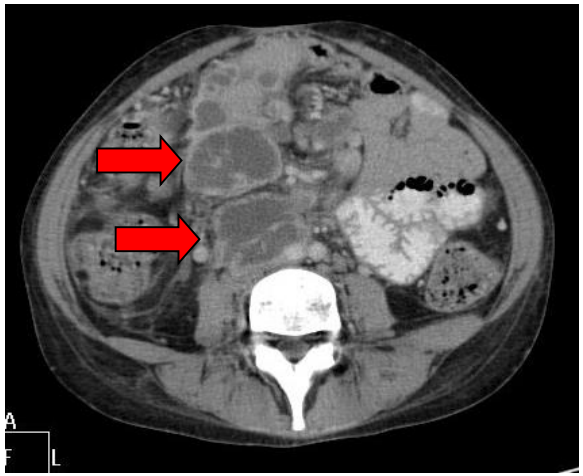


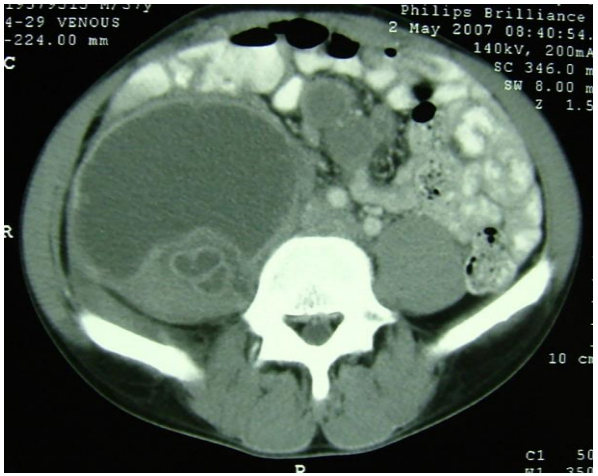
3 weeks on ART
(1 liter drained at pericardiocentesis)

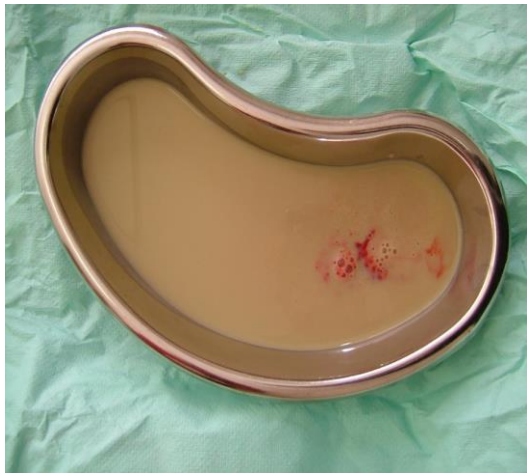






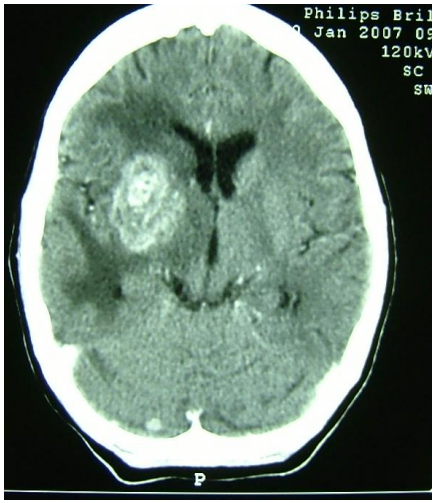



4-29 VENOUS
-224.00 mm
Philips Brilliance
2 May 2007 08:40:54
140kV, 200mA
SC 346.0
SW 8.00
10 cm



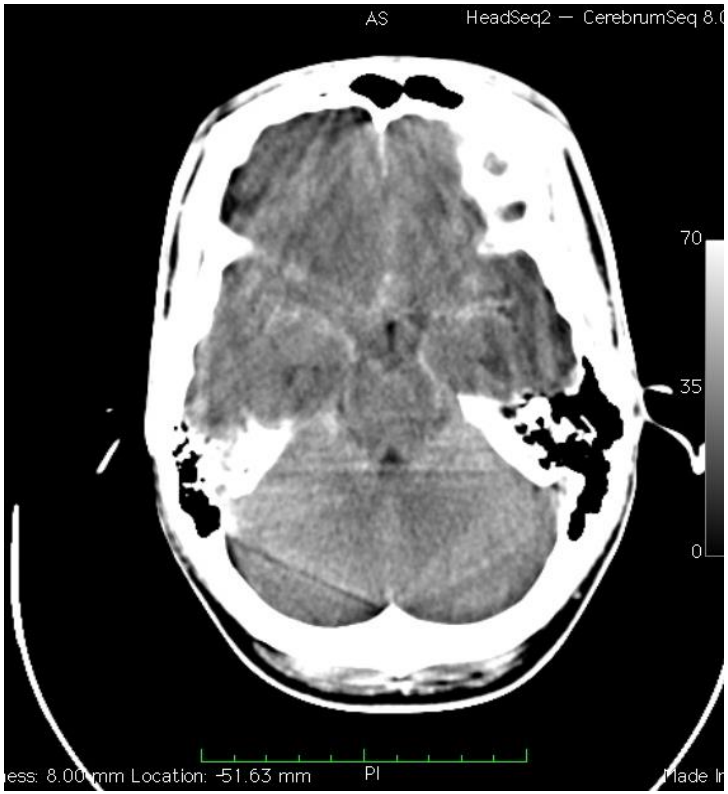
Neurological TB-IRIS

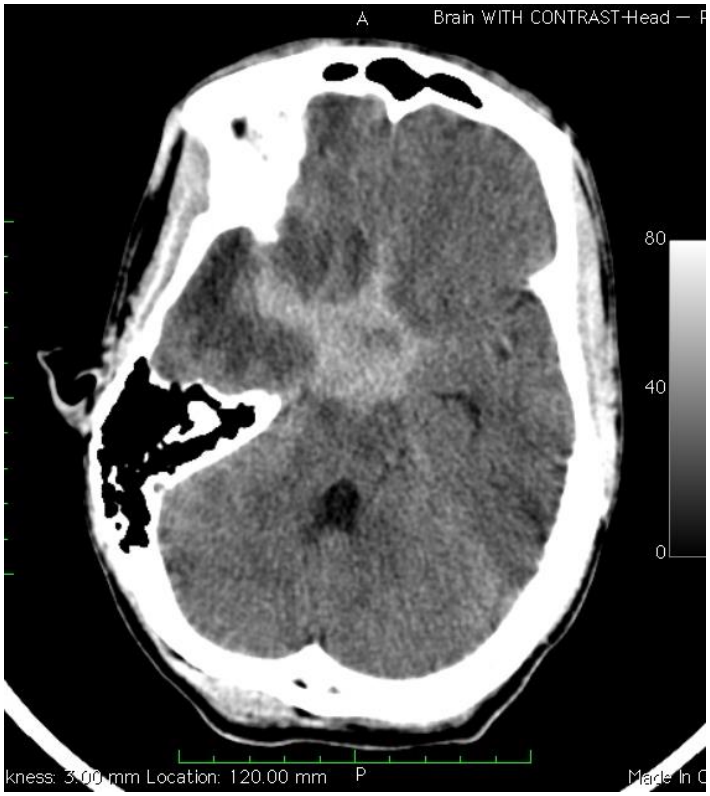
- 12% with paradoxical TB-IRIS have CNS involvement
- Up to 47% of TBM patients starting ART develop IRIS
- Features
  - Meningitis
  - Tuberculoma/s
  - Radiculomyelopathy
- Occurs in patients with or without CNS TB prior to ART
- Outcomes
  - 13% mortality and 18% loss to follow-up in one series
  - 25% and 75% mortality in other series
  - Neurological disability



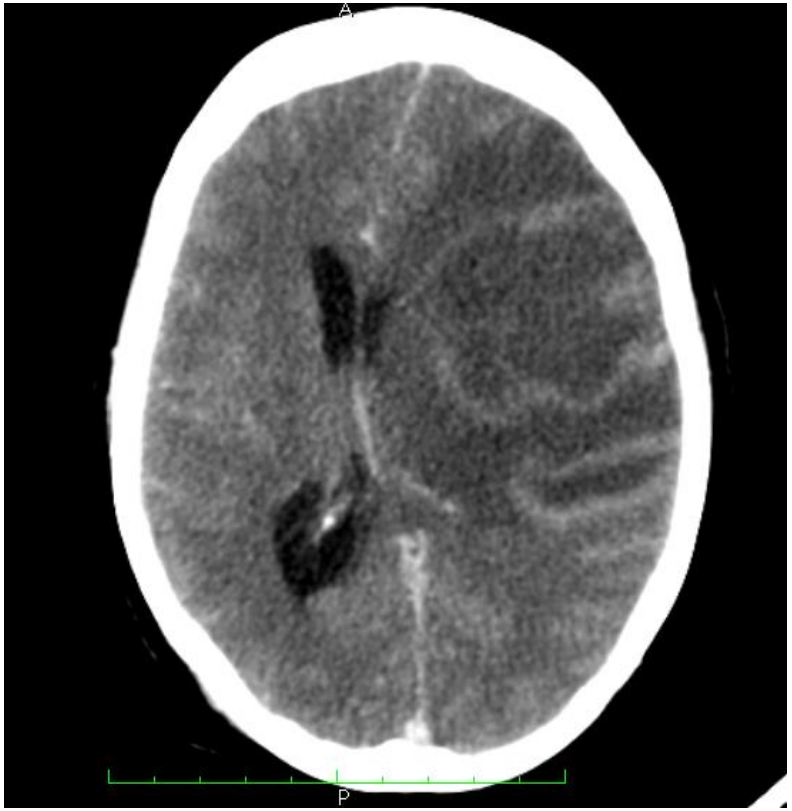
Pepper et al, Clin Infect Dis 2009
Marais et al, Clin Infect Dis 2012
Agarwal et al, AIDS Res Ther 2012

TBM-IRIS


AS
HeadSeq2 — CerebrumSeq 8.0
70
35
0
ness: 8.00 mm Location: -51.63 mm
PI


A
Brain WITH CONTRAST-Head — P
80
40
0
kness: 3.00 mm Location: 120.00 mm
P

TB-IRIS with enlarging mass lesion/cerebral oedema

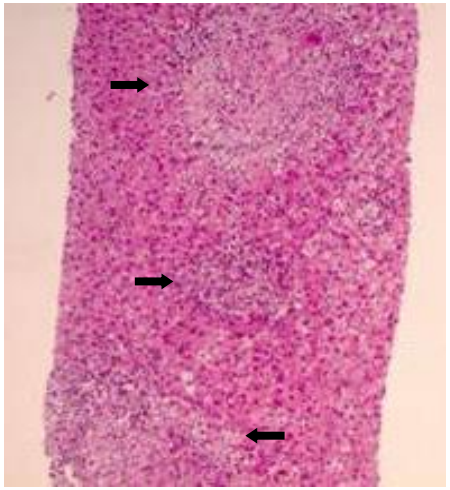


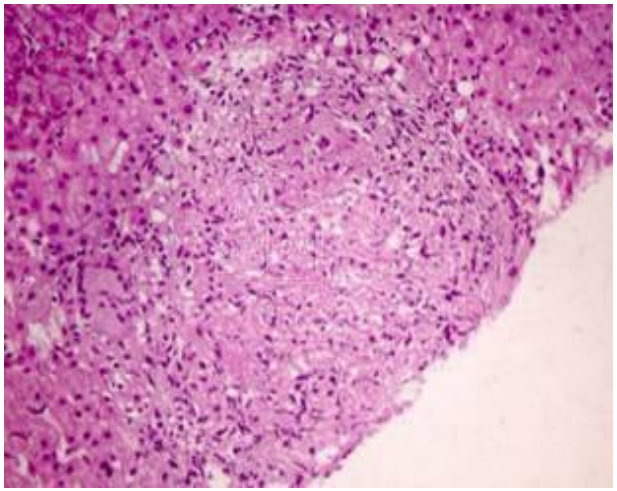
TBM and PTB prior to ART
Patient died

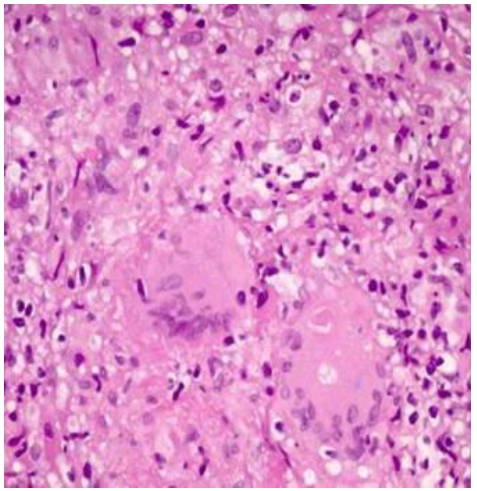
Hepatic TB-IRIS is characterised by which of the following?

1. Severe jaundice on clinical examination
2. Elevation in transaminases more then 10x ULN
3. Non-tender hepatomegaly
4. Elevation of ALP and GGT

Hepatic TB-IRIS case







- 4 months treatment for drug-sensitive pericardial TB
- Clinically improved, then started ART
- 3 weeks later presented with fever and hepatomegaly
- LFT: Bil 52, CBil 31, ALP 1081, GGT 1468, ALT 82, AST 88
- CD4 rise from 64 to 221
- Biopsy AFB- and TB culture -

What is the typical time of onset of paradoxical TB-IRIS after ART start?

1. 3 -10 days
2. 1- 4 weeks
3. 4 - 8 weeks
4. Around 3 months

Onset of IRIS

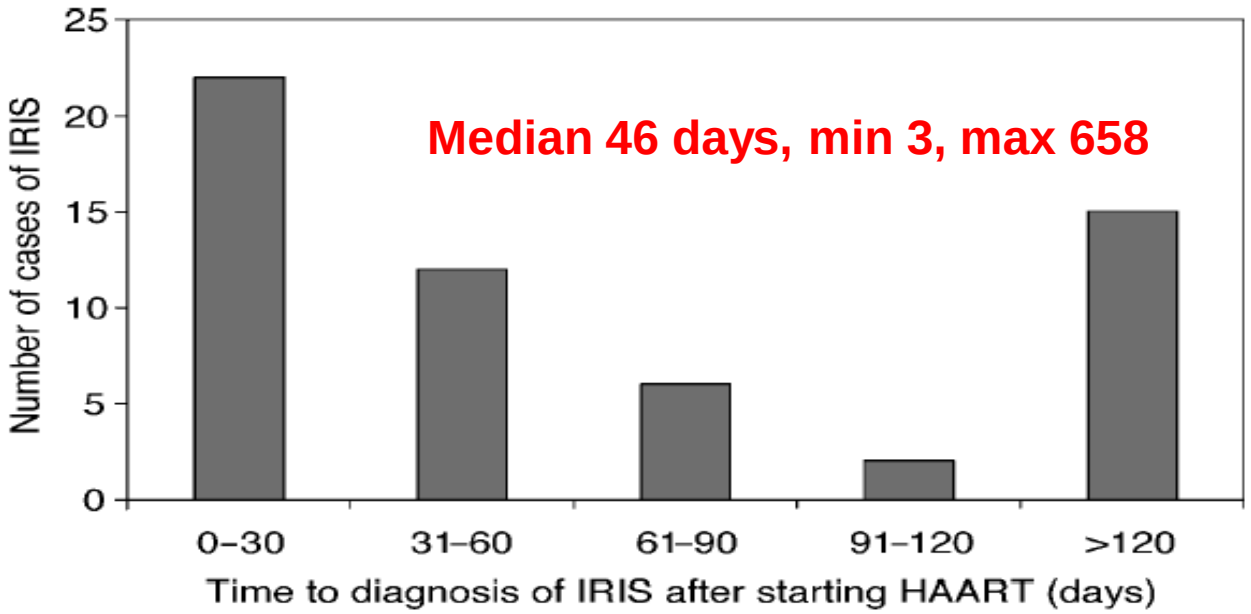
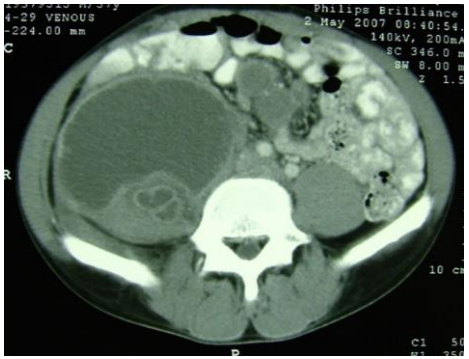


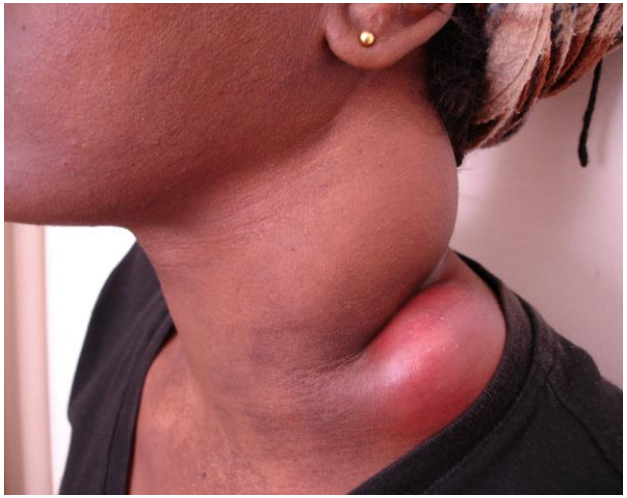
Fig. 1. Time to diagnosis of IRIS after starting HAART. IRIS, immune reconstitution inflammatory syndrome; HAART, highly active antiretroviral therapy.

Source: AIDS 2005, Vol 19 No4 ;399-406, Samuel A. Shelburne et al

Prolonged TB-IRIS

- Typically suppurative lymphadenitis & abscesses
  - Systemically well
- Tuberculomas & cerebral abscesses
- TB-IRIS duration (n = 172)
  - Median: 71 days
  - IQR: 41-113 days
  - IRIS >90 days: 40%





BMC Infect Dis. 2016; 16: 518.

Prolonged TB-IRIS: Management

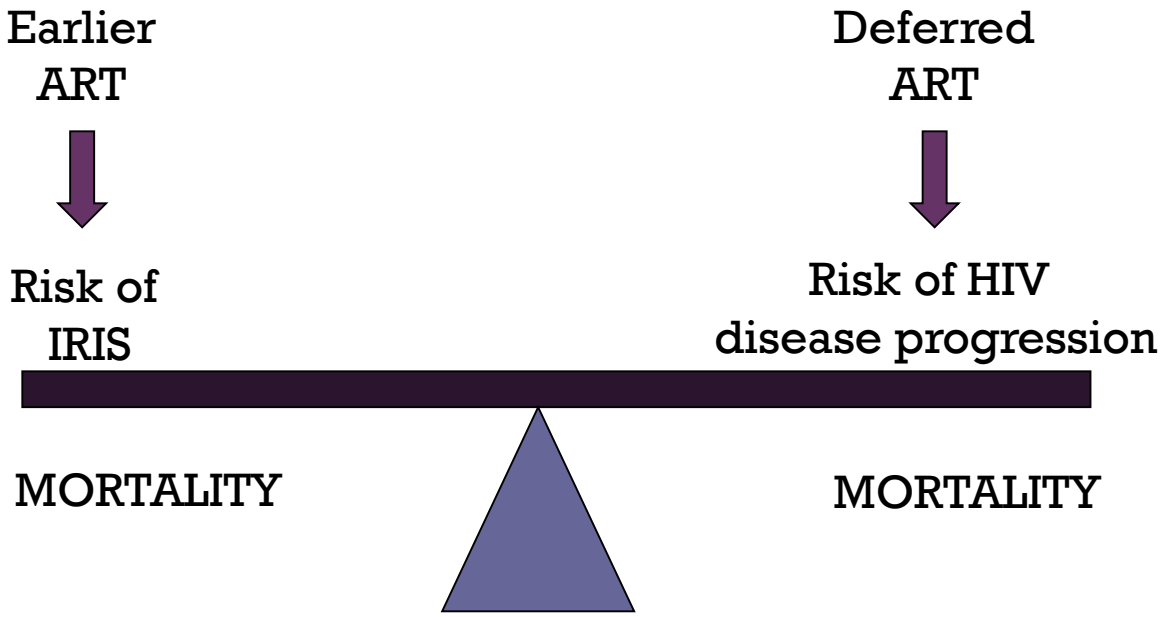
- Often repeated aspirations required
- Avoid surgical drainage
- Repeat TB culture and susceptibility testing
- Corticosteroids for >4 months questionable unless CNS
- Experimental therapies
  - TNF-α blockers
    - Infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), etanercept (Enbrel)
    - Thalidomide, LSD
- Consider prolonging TB treatment
  - How adequate is drug penetration?

Risk Factors for IRIS*

- Male sex?
- Younger age
- Lower CD4+ cell count at ART initiation
- Higher HIV RNA at ART initiation
- Lower CD4+ cell count percentage at ART initiation
- Lower CD4:CD8 ratio at ART initiation
- More rapid initial fall in HIV RNA on ART
- ART-naïve at time of OI diagnosis
- Shorter interval between OI therapy initiation and ART initiation

* Derived from cohorts where IRIS due to multiple pathogens were reported, (i.e. cohorts which examined only TB-IRIS were excluded)

Murdoch DM, et al. AIDS Research and Therapy 2007;4:1–10



When to start ART after recent diagnosis of TB?

3 large RCTs (SAPIT, STRIDE, CAMELIA)

Impact of Earlier vs. Later ART Initiation: IRIS

- Results strongly favour beginning ART earlier despite an increased risk of IRIS
  - More frequent & earlier IRIS did not lead to worse overall outcomes
- For patients with CD4+ count ≥50 cells/mm^3 waiting 8 to 12 weeks after initiation of TB therapy to start ART was associated with fewer cases of IRIS. This brief delay in starting ART may simplify the management of TB

Diagnostic Considerations

No diagnostic test

Alternative diagnosis
Bacterial infection
Fungal infection
PCP
NTM
Lymphoma
Kaposi's sarcoma

?

Drug-resistant TB

Drug reaction
Drug fever vs TB-IRIS fever
Hepatic involvement

Important Differential Diagnoses

Manifestation	Differential diagnoses
Pulmonary infiltrate	Bacterial pneumonia PCP Kaposi's sarcoma
Pleural effusion	Bacterial empyema Kaposi's sarcoma
Meningitis	Bacterial Cryptococcal
Space-occupying lesion	Toxoplasmosis Cryptococcoma Primary CNS lymphoma
Fever with general deterioration	Bacterial sepsis NTM Kaposi's or lymphoma

Consider and investigate for DR-TB in all scenarios

Medicine is a science of uncertainty and an art of probability.

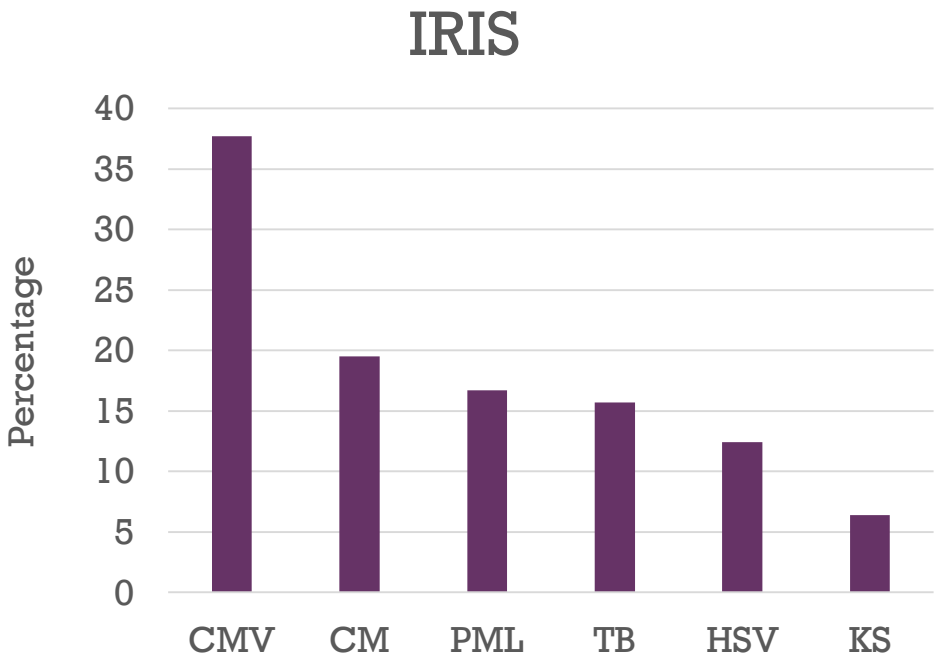
Sir William Osler
1849-1919

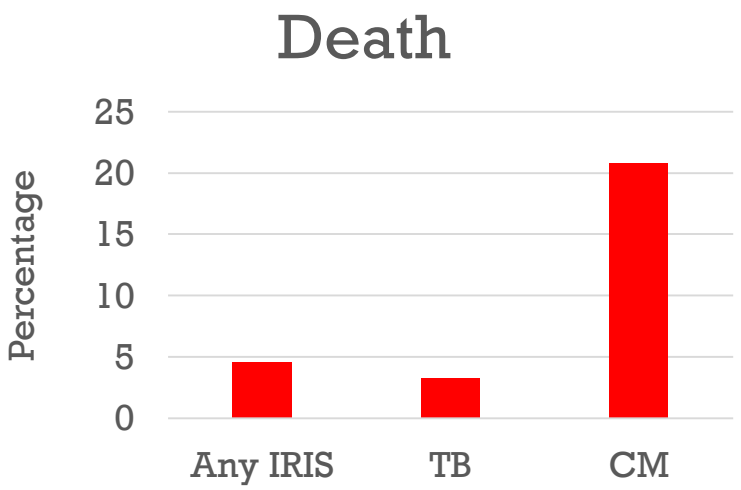
WHO: TB-IRIS Alert

- IRIS is not a reason to switch patients to second-line ART
- ART regimen may need to be adjusted to ensure compatibility with the TB treatment

WHO. Treatment of Tuberculosis Guidelines. Fourth edition. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf

Significance of IRIS





Lancet ID 2010, 10:251-261

Management of IRIS after ART

- ART should be continued wherever possible:
  - Unless IRIS causes severe and/or life threatening illness
  - ART interruption could lead to increased risk of additional OIs and re-occurrence of IRIS
- Treatment modalities have included:
  - NSAIDs in mild disease
  - Corticosteroids in moderate-to-severe disease
- Management on an individual patient basis

WHO. Treatment of Tuberculosis Guidelines. Fourth edition. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf; Elston JW. and Thacker H. Int J STD & AIDS 2009;20:221–24

Prednisone for Paradoxical TB-IRIS

- **Design:** A randomized, double-blind, placebo-controlled trial of prednisone; N=110.
  - Patients with immediately life-threatening TB-IRIS manifestations excluded
  - Prednisone arm (N=55): **1.5 mg/kg per day for 2 weeks then 0.75 mg/kg per day for 2 weeks** *vs.* placebo (N=55)
- **Primary combined endpoint:** Days of hospitalization & outpatient therapeutic procedures (counted as 1 hospital day)

RESULTS	PREDNISONE ARM (N=55)	PLACEBO ARM (N=55)
Median hospital days (*P*=0.04)	282	463
Karnofsky symptom score	Improvement at Weeks 2 & 4	-
Chest x-rays (*P*=0.002 & 0.02)	Significant improvement at Weeks 2 & 4	-
Infections (*P*=0.05)	27 (49%)	17 (31%)
Severe infections (*P*=0.40)	2 (4%)	4 (7%)

Isolates from 10 participants were found to be resistant

15% steroid side effects: BP >140/90, oedema, hyperglycaemia, hypomania, acne, Cushing-like features, gastritis symptoms

Conclusions:

- Prednisone reduced hospitalization & therapeutic procedures; hastened improvements in symptoms, performance & quality of life
- Important to investigate for drug-resistant TB and other causes for deterioration before administering glucocorticoids

Watch out for

- Kaposi's sarcoma
- Herpes virus reactivations
- Candidiasis
- *Strongyloides* hyper-infection

Cryptococcal Meningitis

Global Incidence of Cryptococcal Meningitis

More than 1 in 10 HIV-related deaths are as a result of cryptococcal meningitis.

Three quarters of deaths from cryptococcal meningitis are in sub-Saharan Africa.

Early ART initiation is the most important and cost-effective preventive strategy to reduce the incidence and high mortality associated with CM

Park BJ, et al. AIDS 2009;23:525–30; WHO. Rapid Advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. December 2011. Available at: http://whqlibdoc.who.int/publications/2011/9789241502979_eng.pdf; Accessed January 2014

In the **BRAIN** (cryptococcal meningitis)

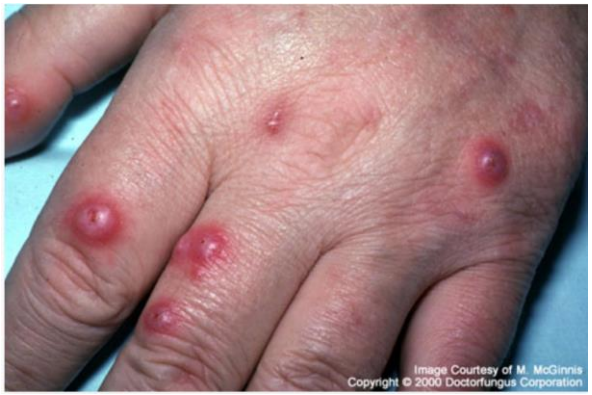
Cryptococcal meningitis is an infection caused by the fungus Cryptococcus after it spreads from the lungs to the brain. The symptoms of cryptococcal meningitis include:

- Headache
- Fever
- Neck pain; neck rigidity
- Nausea and vomiting, lethargy, personality change, memory loss
- Sensitivity to light
- Confusion or changes in behavior

- The duration of symptoms before presentation is likely to be longer in non-AIDS patients, with a history of more than 2 weeks in only 25% of HIV positive patients.

Presentation

- In patients with meningoencephalitis, lethargy, mental status changes and memory loss (usually secondary to increased intracranial pressure) can occur
- In HIV-infected patients with CM, extraneuronal involvement is common
- Common sites of infection include:
  - lungs; bone marrow; genitourinary tract
  - osseous involvement (~ 5%)
  - cutaneous dissemination
    - typically described as molluscum-like skin lesions(~10%)



Warkentien T, Crum-Cianflone N F. International Journal of STD & AIDS 2010;21:679–84; Baradkar V, et al. Indian Journal of Sexually Transmitted Diseases and AIDS 2009;30:19–22; AIDSMAP. Managing meningitis in people with HIV in resource-limited settings: a clinical review. HATiP. 2007;98:2–16. Available at: http://www.aidsmap.com/pdf/HATIP-98-21st-December-2007/page/1256394/. Accessed June 2011

Key Recommendations (WHO): Diagnosis

Guiding principles:

- Early diagnosis and treatment are key to improving mortality from cryptococcal disease
  - Healthcare professionals need to have a low threshold for suspecting CM

Diagnosis:

- In HIV+ patients with suspected first episode of CM, prompt lumbar puncture with measurement of CSF opening pressure and rapid CSF CrAg assay or rapid serum or plasma CrAg (either LA or LFA) are recommended as the preferred diagnostic approach

- In HIV+ patients with suspected non-meningeal cryptococcal disease, use of a serum or plasma CrAg assay is recommended, in conjunction with histopathological and/or culture examination of appropriate tissue or fluid samples where possible, and exclusion of other competing diagnoses
  - India ink microscopy examination or a CrAg assay in appropriate tissue or fluid samples may also be used

WHO. Rapid Advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. December 2011. Available at: http://whqlibdoc.who.int/publications/2011/9789241502979_eng.pdf; Accessed January 2014

Key Recommendations (WHO): Treatment

Drugs available	Pre-hydration + electrolyte replacement + toxicity monitoring/ management	Induction phase options 2 weeks	Consolidation phase options 8 weeks	Maintenance/ secondary prophylaxis options
Amphotericin B ± flucytosine	Available	Amphotericin 0.7–1 mg/kg/day + flucytosine 100 mg/kg/day Amphotericin 0.7–1 mg/kg/day + fluconazole 800 mg/day	Fluconazole 400–800 mg/day	Fluconazole 200 mg daily
Amphotericin B	Not available for full 2 week induction period	Amphotericin 0.7–1 mg/kg/day short course (5–7 days) + fluconazole 800 mg/day (2 weeks)	Fluconazole 800 mg/day	
Amphotericin B Not available	Not available	Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day Fluconazole 1200 mg/day alone	Fluconazole 800 mg/day	

WHO. Rapid Advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. December 2011. Available at: http://whqlibdoc.who.int/publications/2011/9789241502979_eng.pdf; Accessed January 2014

Timing of ART in HIV+ Patients with CM - Delayed

- ART-naïve HIV+ patients with CM were randomized to compare effects of:
  - Early ART (within 72 hours after CM diagnosis; n=28) vs.
  - Delayed ART (after 10 weeks of treatment with fluconazole alone; n=26)
- Risk of mortality was almost three times as great in the early ART vs. delayed ART

- ART-naïve HIV+ patients initiating amphotericin B for CM were randomized:
  - ART with 7 days (intervention, n=13) vs.
  - ART after 28 days (control, n=14)
- Estimated rate of CSF clearance did not differ significantly between arms

	ART		*P*-value
	Early	Delayed	
3-year mortality rate, %	88%	54%	<0.006
Median survival, days	28	637	0.031

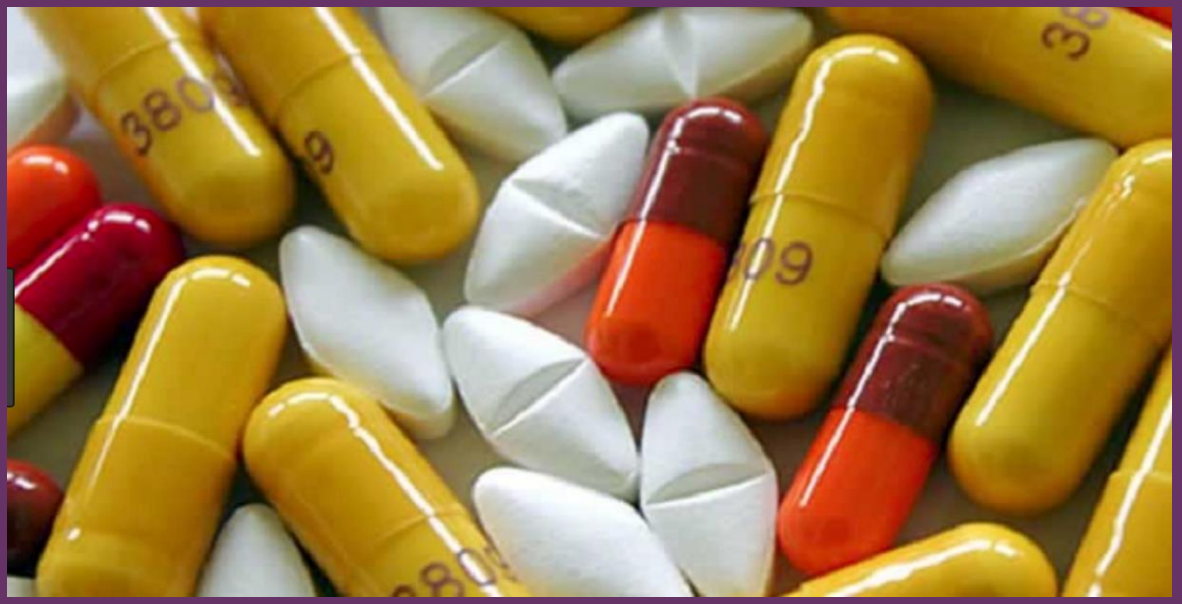
- In resource-limited settings where CM management may be suboptimal, when compared with a delay of 10 weeks after a CM diagnosis, early initiation of ART results in increased mortality

	ART		*P*-value
	Early	Delayed	
Death	2/13 (15%)	5/14 (36%)	0.39
CM-IRIS	7/13 (54%)	0/14 (0%)	0.002

- Early ART was not associated with improved CSF fungal clearance, but resulted in a high risk of CM-IRIS. Further research on optimal incorporation of ART into CM care is needed

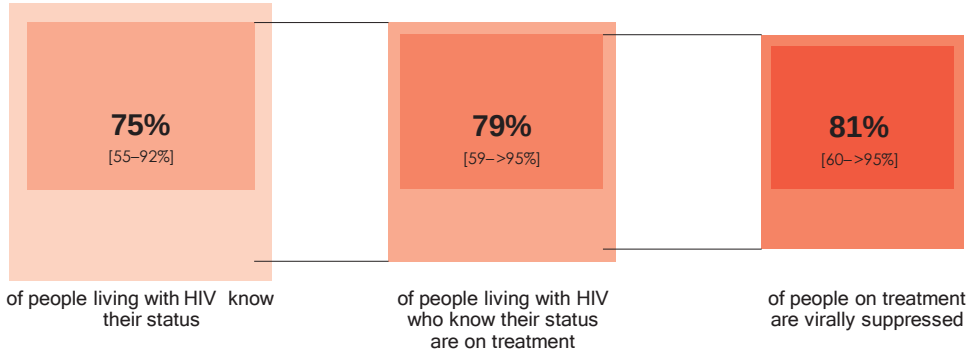
45. Makadzange AT, et al. Clin Infect Dis 2010;50:1532–8; 46. Bisson G, et al. Clin Infect dis 2013;56:1165–73

Antiretroviral Therapy

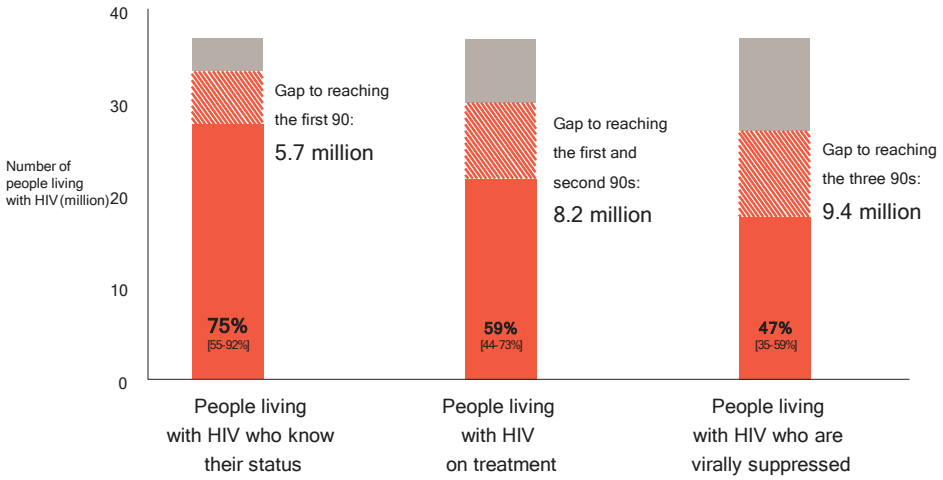


Remarkable progress on HIV testing & treatment

Progress towards 90-90-90, global, 2017

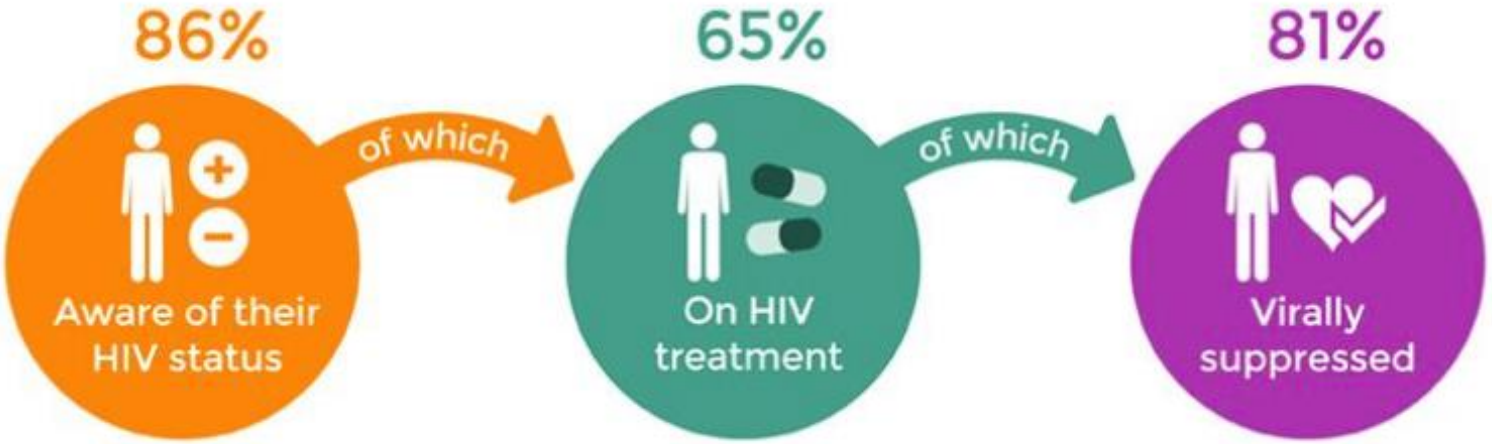


HIV testing and treatment cascade, global, 2017



Source: UNAIDS special analysis, 2018; see annex on methods for more details.

SOUTH AFRICA Progress towards 90/90/90 targets among adults aged 15-59



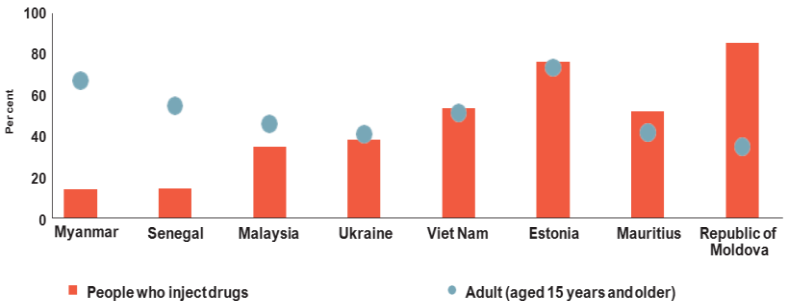
Source: UAIDS data 2017

Avert www.avert.org

Treatment access often lower among key populations

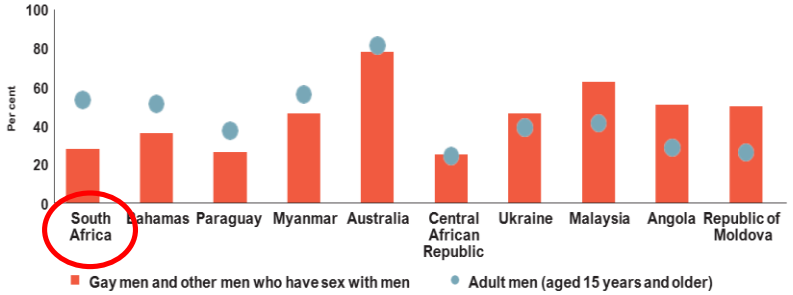
Antiretroviral therapy coverage, by population, select countries, 2014–2017

People who inject drugs and all adults (aged 15 years and older), 2014-2017

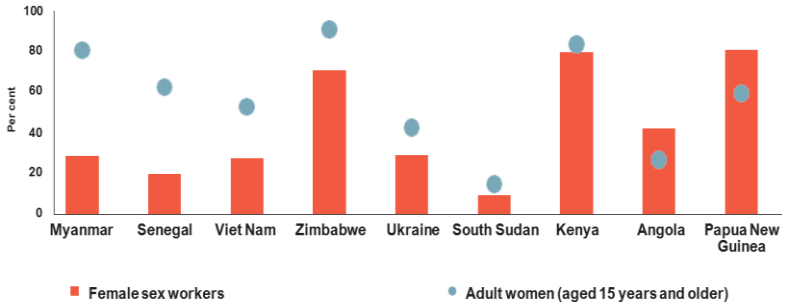


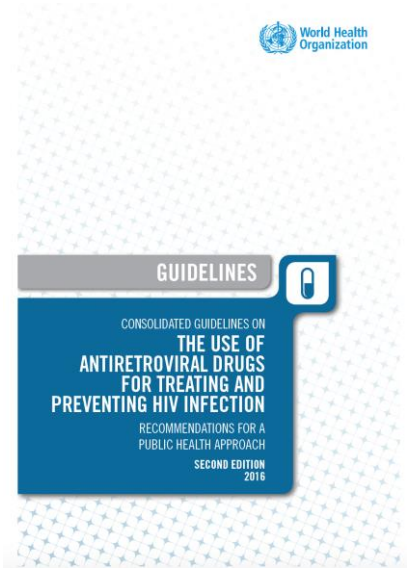
Source: Global AIDS Monitoring, 2018

Gay men and other men who have sex with men and adult men (aged 15 years and older), 2016-2017



Female sex workers and adult women (aged 15 years and older), 2016-2017





4. CLINICAL GUIDELINES: ANTIRETROVIRAL THERAPY	
4.3 When to start ART	
NEW 4.3.1 When to start ART in adults (>19 years old)	ART should be initiated in all adults living 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 in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a CD4 count ≤350 cells/mm^3 (strong recommendation, moderate-quality evidence).
NEW 4.3.2 When to start ART in 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).
NEW 4.3.3 When to start ART in adolescents (10–19 years of age)	ART should be initiated in all adolescents living with HIV, regardless of WHO clinical stage and at any CD4 cell count (conditional recommendation, low-quality evidence). As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with a CD4 count ≤350 cells/mm^3 (strong recommendation, moderate-quality evidence).
4.3.4 When to start ART in children younger than 10 years of age	NEW ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count:
	• Infants diagnosed in the first year of life (strong recommendation, moderate-quality evidence).
	NEW • Children living with HIV 1 year old to less than 10 years old (conditional recommendation, low-quality evidence).
	As a priority, ART should be initiated in all children <2 years of age or children younger than 5 years of age with WHO clinical stage 3 or 4 or CD4 count ≤750 cells/mm^3 or CD4 percentage <25% and children 5 years of age and older with WHO clinical stage 3 or 4 or CD4 count ≤350 cells/mm^3 (strong recommendation, moderate-quality evidence).

ONCE STARTED, ART SHOULD NOT BE INTERRUPTED

South African Experience

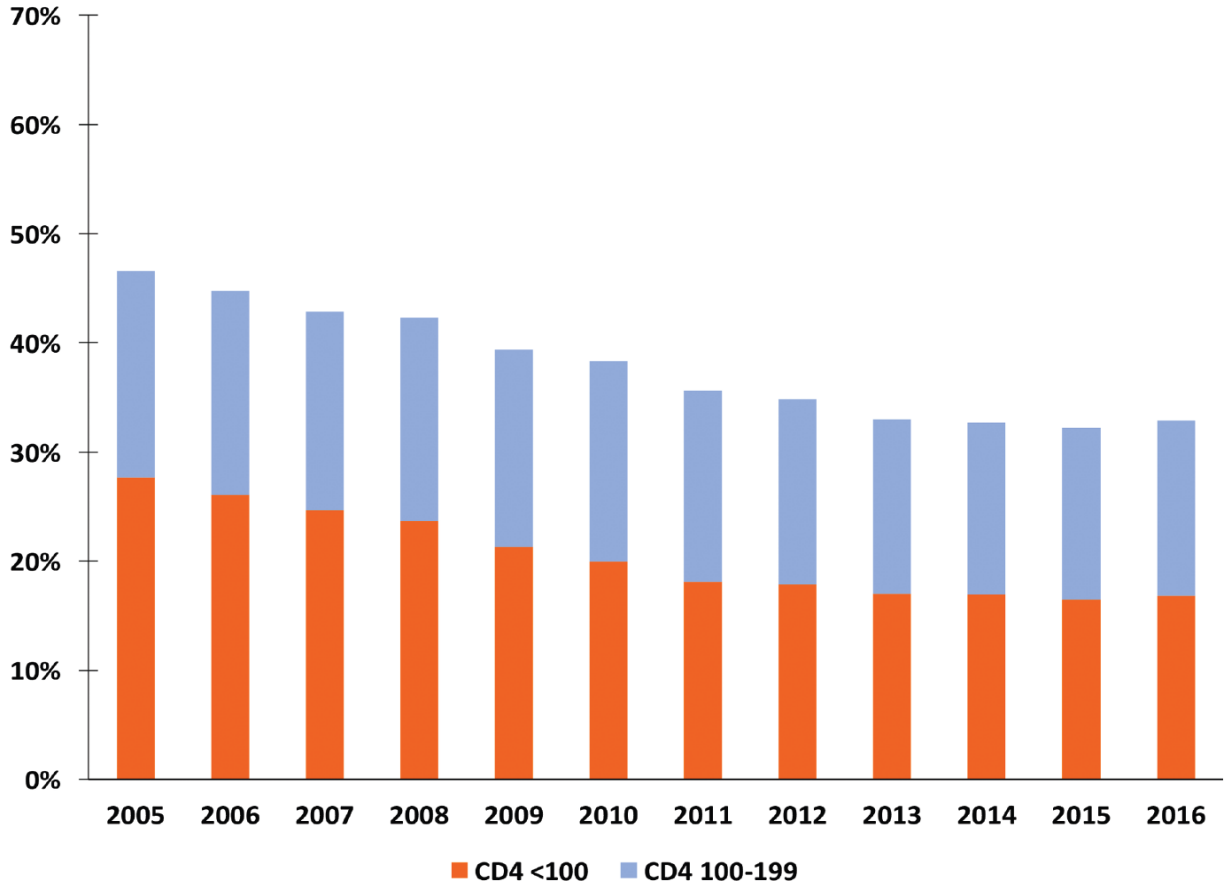


Figure 1. Proportion of patients entering care with advanced and very advanced HIV disease (first CD4 count test <100 and 100–199 cells/μL).

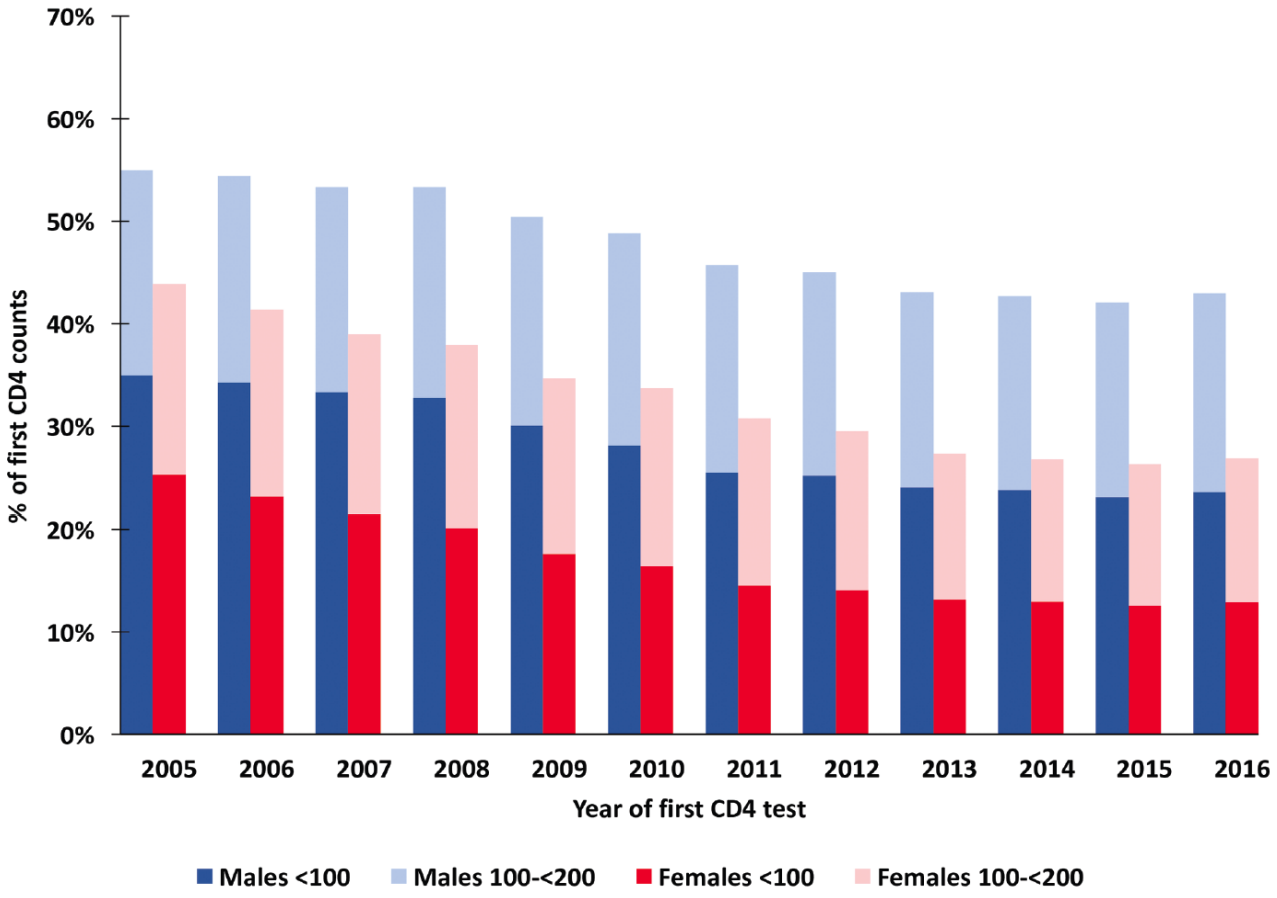
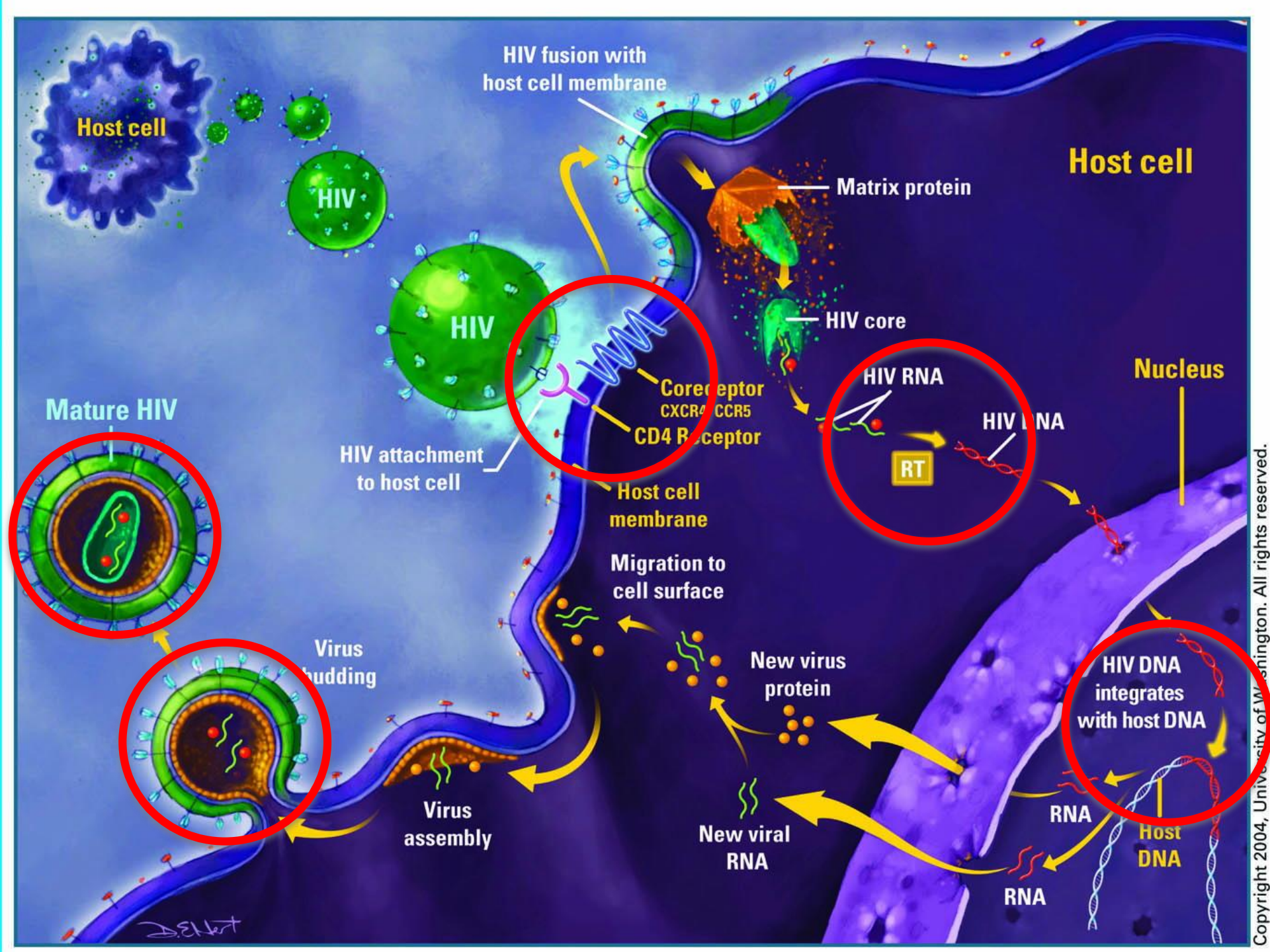


Figure 2. Proportion of males and females presenting to care with advanced and very advanced HIV disease from 2005 to 2016 (CD4 values presented as cells/μL).

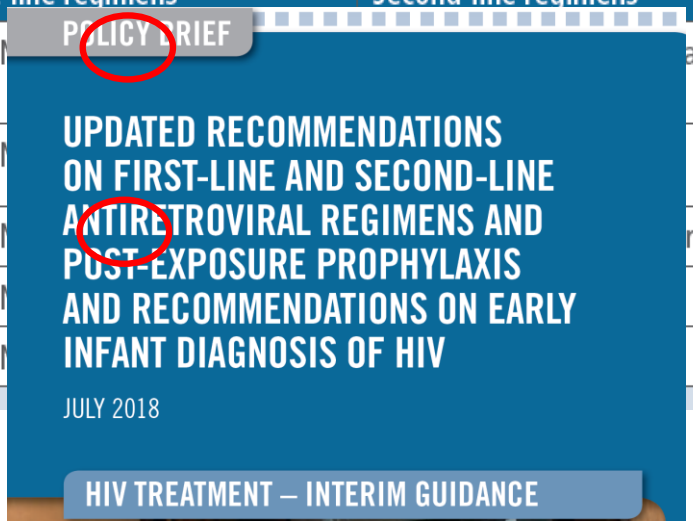


National ART regimen – 1st line

All new patients	TDF + 3TC/FTC + EFV	Fixed-dose combination (Atripla/ Tribuss)
Contraindications to EFV: psychosis, severe depression	TDF+ 3TC/FTC + NVP	Careful with NVP in: - Women CD4>250 - Men CD4>400
Contraindication to TDF: renal disease	AZT + 3TC + EFV ABC + 3TC + EFV	Monitor FBC Hypersensitivity reaction

TABLE 1. SUMMARY OF SEQUENCING OPTIONS FOR FIRST-, SECOND- AND THIRD-LINE ART REGIMENS FOR ADULTS (INCLUDING PREGNANT WOMEN AND ADOLESCENTS) AND CHILDREN

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (including women and adolescent girls who are of childbearing potential or are pregnant)[a]	Two N	avir/	Darunavir/ritonavir (DRV/r)[g,h] + DTG[i] + 1–2 NRTIs (if possible, consider optimization using genotyping)
	Two N		
Children	Two N	r)	
	Two N		
	Two N		



Adult antiretroviral therapy guidelines 2017

TABLE 4: Preferred first-line regimen options.

Options	Preferred	Alternative	One of
NRTI backbone	TDF + FTC/3TC	ABC† + 3TC	–
	–	AZT‡ + 3TC	–
	–	d4T§ + 3TC	–
Third drug	–	–	EFV
	–	–	DTG
	–	–	RPV¶

NRTI, nucleoside reverse transcriptase inhibitor; tenofovir; FTC, emtricitabine; 3TC, lamivudine; ABC, abacavir; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; DTG, dolutegravir; RPV, rilpivirine.

†, If creatinine clearance < 50 mL/min; ‡, Only if both TDF and ABC contraindicated or unavailable AND haemoglobin > 8 g/dL; §, Only for short-term use in patients with contraindications to all other NRTIs – we advise against using d4T for longer than 3 months; ¶, Only if VL < 100 000 copies/mL.

National ART regimen – 2nd line

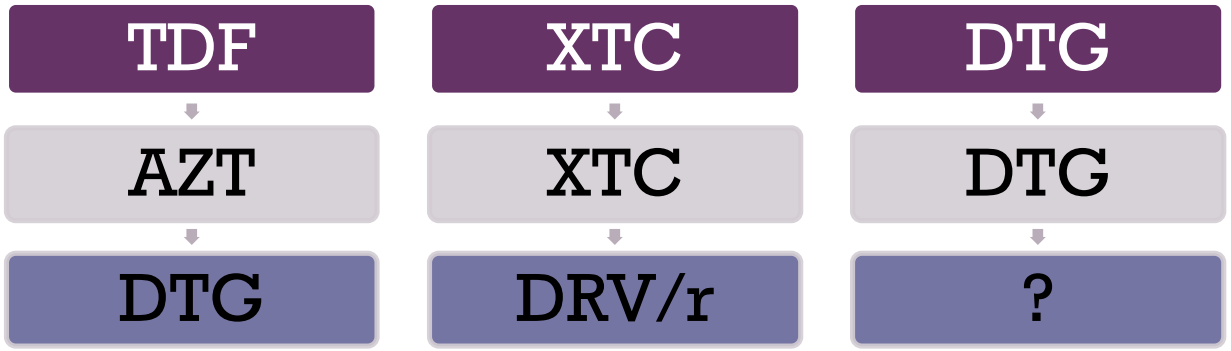
Failing on d4T or AZT-based regimen	TDF + 3TC/FTC + LPV/r	
Failing on TDF-based regimen	AZT + 3TC + LPV/r	Keep on TDF if HepB+ If unable to tolerate LPV or toxicity → ATV

- Virological failure:
  - Intensive adherence management
  - Repeat VL 3 months
  - If remains > 1000 → switch
  - Failing second line → HIV drug resistance test

National ART regimen – 3rd line

- Drug resistance testing
- Third-line committee application
- Use available drugs from NRTI class
- Added new drugs/ classes
  - INSTI: Raltegravir/ Dolutegravir
  - 2nd generation NNRTI: Etravirine
  - 2nd generation PI: Darunavir/r

Possible Future SA Guidelines



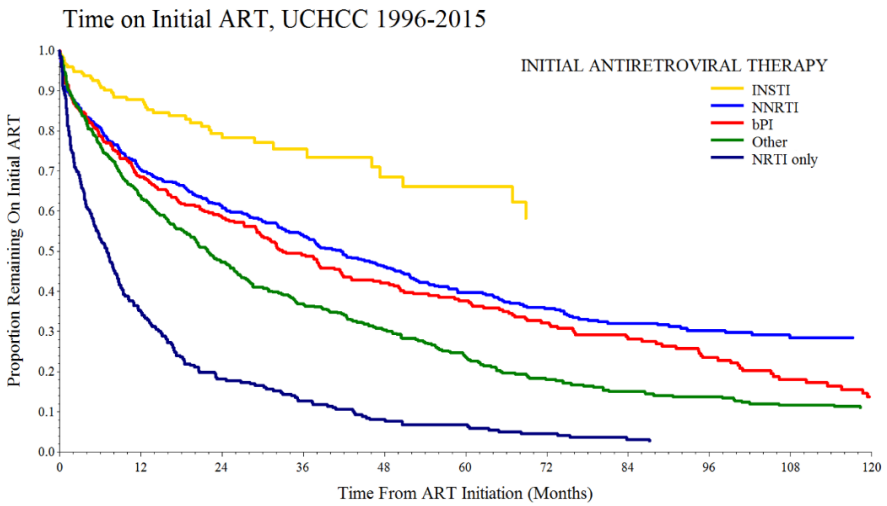
Efavirenz

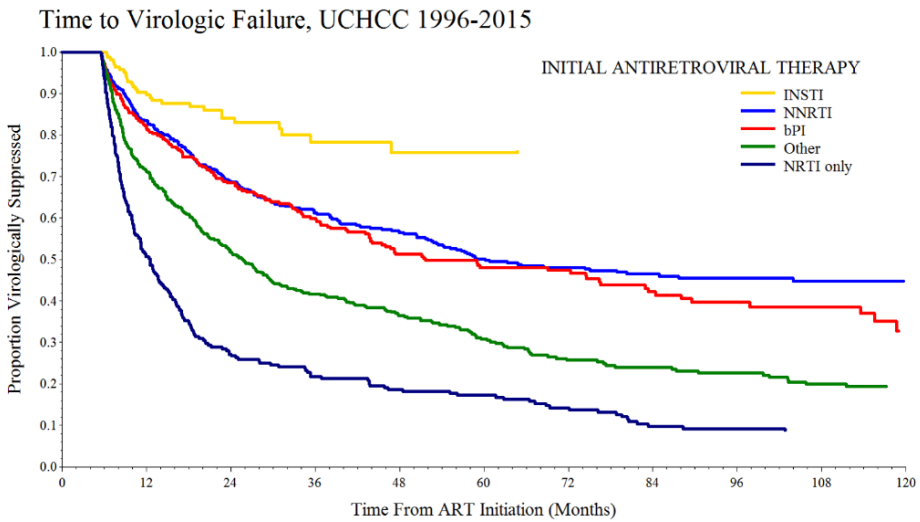
- Lots of clinical experience with its use
- Can be used in pregnancy and with TB treatment
- Cheap
- Available as FDC
- Once daily dosing
- BUT
- Increasing concern over CNS side effects
- Hepatotoxicity – can be persistent & fatal
- Gynaecomastia, lipid abnormalities

Dolutegravir

- Cheaper
- Suitable for co-formulation, but currently only co-formulated with ABC, 3TC
- 50mg once daily (INSTI-naive)
- Very good efficacy
- Better side effect profile
- Very high barrier to resistance
- BUT
- Still concerns about CNS side effects
  - insomnia
- Double dose needed with TB treatment

Increased Persistence Of Initial ART With INSTI-containing Regimens





	Discontinuation	Virologic failure
	HR (95% CI)	HR (95% CI)
INSTI	0.49 (0.35, 0.69)	0.70 (0.46, 1.06)
bPI	1.24 (1.05, 1.47)	1.24 (1.01, 1.53)
Other	1.47 (1.24, 1.75)	1.21 (0.99, 1.46)
NRTI	2.98 (2.38, 3.74)	1.72 (1.35, 2.19)
NNRTI	Ref.	Ref.

From JJ Eron, Jr, MD at San Antonio, Texas, August 21-23, 2017, Ryan White HIV/AIDS Program Clinical Conference, IAS–USA.

Safety and Efficacy of INSTIs and EFV_{400} in 1st line ART (network metanalysis)

Major outcomes	INSTI vs EFV_{600}	DTG vs other INSTI	DTG vs EFV_{60}	DTG vs EFV_{40}	EFV_{400} vs EFV_{600}	QUALITY OF EVIDENCE
Viral suppressin	INSTI better	DTG better	DTG better	comparable [1]	comparable	moderate
CD4 recovery	INSTI better	DTG better	DTG better	comparable	EFV_{400} better	moderate
Treatment discontinuation	INSTI better	DTG better	DTG better	comparable	EFV_{400} better	moderate
Mortality	comparable	comparable	comparable	comparable	comparable	low
AIDS progression	comparable	comparable	comparable	comparable	comparable	low
SAE	comparable	comparable	comparable	comparable	comparable	moderate

TSEPAMO: BIRTH OUTCOMES WITH ART IN BOTSWANA

Observational study birth outcome data

Started on August 15, 2014

8 of the largest maternity wards in Botswana
~45% of the total births in the country

Research assistants abstract data from the obstetric cards for all in-hospital deliveries

c/o Rebecca Zash

Tsepamo: EARLY RESULTS

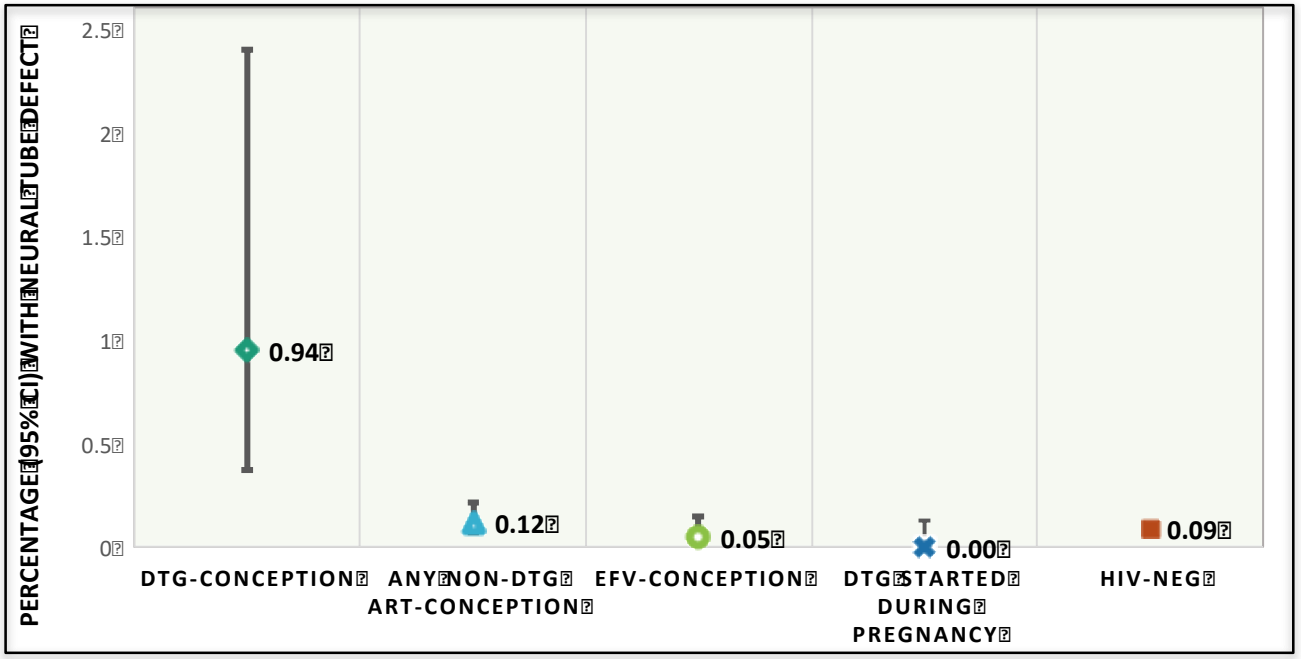
- Prospective cohort study in HIV-infected women initiating ART with EFV/FTC/TDF vs DTG/FTC/TDF while pregnant (N = 5438)

Adverse Birth Outcomes (ABO), n (%)	DTG (n = 845)	EFV (n = 4593)	aRR* (95% CI)
Any	291 (34.4)	1606 (35.0)	1.0 (0.9-1.1)
▪ Severe	92 (10.9)	519 (11.3)	1.0 (0.8-1.2)
Stillbirth	18 (2.1)	105 (2.3)	0.9 (0.6-1.5)
Neonatal death (< 28 d)	11 (1.3)	60 (1.3)	1.0 (0.5-1.9)
Preterm birth (< 37 wks)	149 (17.8)	844 (18.5)	1.0 (0.8-1.1)
▪ Very preterm (< 32 wks)	35 (4.2)	160 (3.5)	1.2 (0.8-1.7)
SGA (< 10th percentile weight)	156 (18.7)	838 (18.5)	1.0 (0.9-1.2)
▪ Very SGA (< 3rd percentile weight)	51 (6.1)	302 (6.7)	0.9 (0.7-1.2)

*For DTG vs EFV; adjusted for maternal age, education, gravida.

Zash R, et al. IAS 2017. Abstract MOAX0202LB.

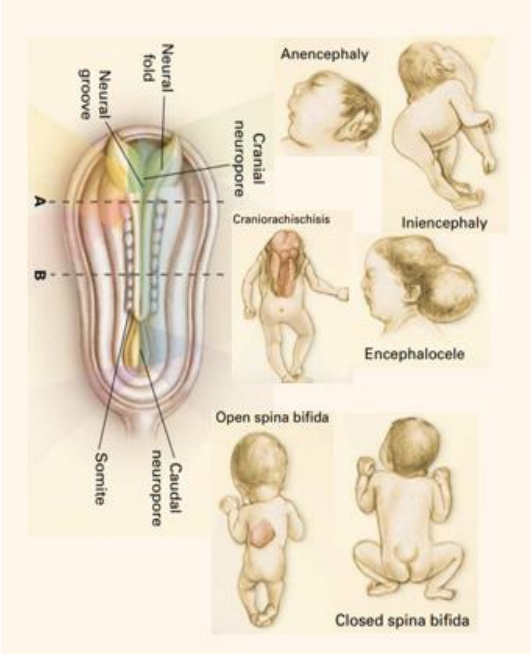
- Few first-trimester ART exposures (DTG, n = 116; EFV, n = 396)
- Only 1 major congenital abnormality observed (skeletal dysplasia in EFV-exposed group)
- Investigators concluded ABO risks comparable when initiating first-line DTG vs EFV in pregnancy



NTDs/Exposures	4/426	14/11,300	3/5,787	0/2.812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0.00% (0.00%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95% CI)	**ref**	**-0.82% (-0.24%, -2.3%)**	**-0.89% (-0.31%,-2.3%)**	**-0.94% (-0.35%, -2.4%)**	**-0.85% (-0.27%, -2.3%)**

Neural Tube Defects on DTG at conception

- The 4 defects identified were all pre-specified as NTDs, and included:
  - encephalocele (with photo)
  - anencephaly (no photo)
  - myelomeningocele (with photo)
  - iniencephaly (with photo)
- None of the women were reported to be on folate supplementation PRIOR to pregnancy
  - Botswana does not fortify grains with folate
- Review of maternal data found no other risk factor for NTD present

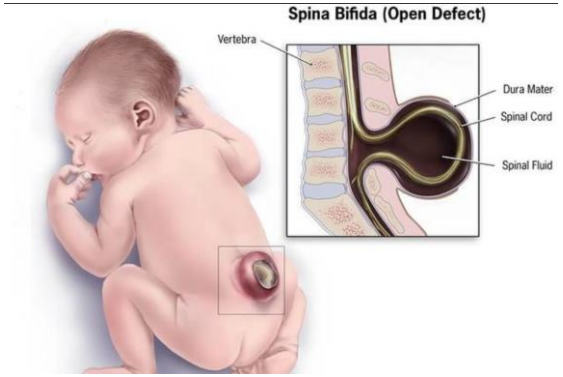


NEJM Botto 1999

c/o Rebecca Zash

TSEPAMO UPDATE

- Final study results available in ~1 year
- Risk higher in 1st trimester
- No neural tube defects if DTG began later in pregnancy



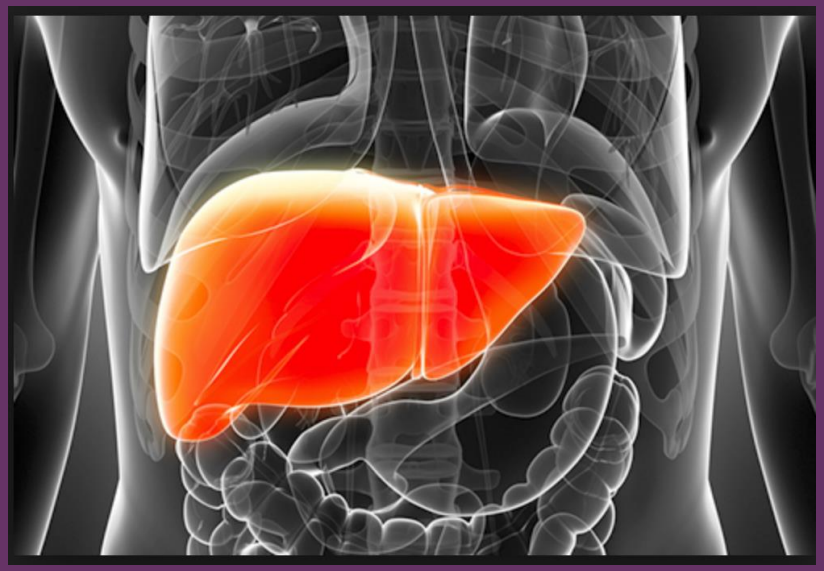
HIV/AIDS News

Recommendations Regarding the Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or of Child-Bearing Potential

Date: May 30, 2018
Source: AIDS*info*

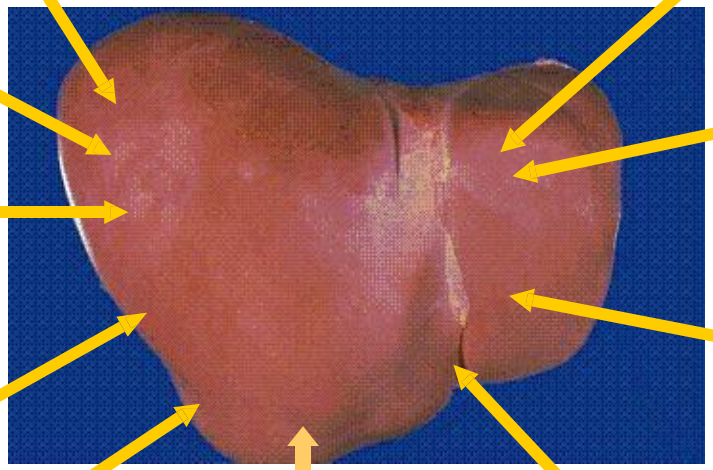
Clinical Bottom Line

Pending availability of additional data, it would be prudent to avoid the use of dolutegravir (either in ART or PEP) regimens for women who are planning pregnancy or may become pregnant (note that this applies to cis-gender women and also to trans men who may be planning pregnancy). For pregnant women who are taking dolutegravir, there is no need to stop dolutegravir.



Hepatic Injury in HIV-infected Patients

Causes of Hepatic Injury



Mechanisms of drug-related liver injury in HIV-infected patients

Mechanism	
Metabolic host mediated (intrinsic and idiosyncratic)	NNRTIs and PIs Usually 2-12 months after initiation Occurrence can vary by agent Dose-dependence for intrinsic damage
Hypersensitivity	NVP>ABC Early, usually within 8weeks Often associated with rash HLA-linked
Mitochondrial toxicity	NRTIs ddI>d4T>AZT>ABC=TDF=FTC/3TC
Immune reconstitiution	Chronic HepB Within 1st month More common if low CD4 count/large rise

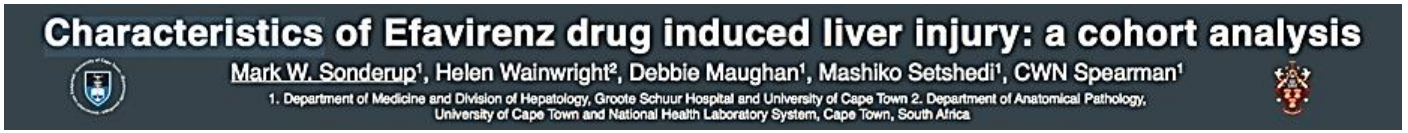
Soriano et al. AIDS 2008; 22: 1-13

Liver profiles of the histological patterns of EFV DILI

Pattern	Total Bilirubin (0-21 µmol/L)	Conjugated Bilirubin (0-6 µmol/L)	ALT (5 - 40 U/L)	AST (5 - 40 U/L)	ALP (40 - 120 U/L)	GGT (0 – 35 U/L)
Submassive necrosis	184 (91-104)	145 (61-285)	659 (412-1333)	985 (515-1905)	194 (143-367)	239 (150-336)
Mixed cholestatic-hepatitic	84 (31-217)	50 (16-156)	116 (60-182)	150 (102-444)	391 (182-1160)	646 (513-1254)
Non-specific hepatitis	8 (4-19)	5 (1-12)	114 (86-286)	98 (65-368)	240 (128-390)	322 (220-541)

Data expressed as medians and interquartile ranges

Abbreviations: ALT, alanine aminotransferase; **AST,** aspartate aminotransferase; **ALP**, alkaline phosphatase; **GGT**, gamma-glutamyl transferase



Multivariate analysis of factors associated with a specific histological patter of DILI

Factor	Non-specific hepatitis		Mixed cholestatic/ hepatitic		Submassive necrosis	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Age	1.0 (0.91-1.11)	0.88	1.08 (0.98-1.19)	0.09	0.86 (0.76-0.97)	0.02
Female Gender	0.26 (0.06-1.03)	0.05	1.39 (0.34-5.66)	0.64	5.1 (0.7-33.5)	0.09
CD4>200	0.82 (0.22-3.09)	0.7	0.19 (0.04-0.76)	0.01	11.6 (2.1-37.2)	0.007
Alcohol use	0.20 (0.02-2.07)	0.18	0.8 (0.11-5.75)	0.82	6.25 (0.58-67.2)	0.12

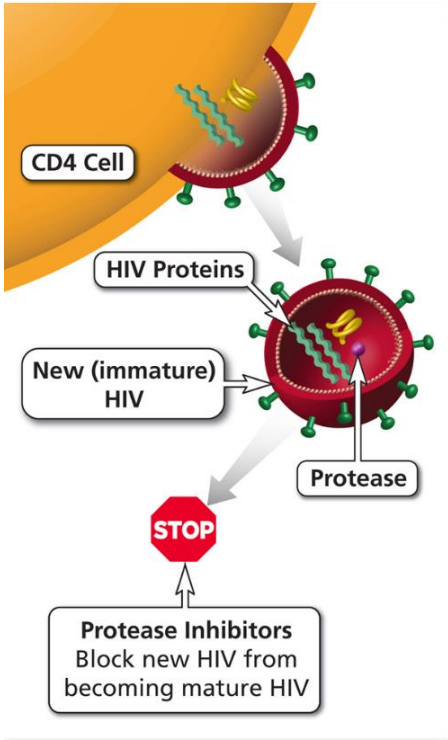
Characteristics of Efavirenz drug induced liver injury: a cohort analysis

Mark W. Sonderup[1], Helen Wainwright[2], Debbie Maughan[1], Mashiko Setshedi[1], CWN Spearman[1]

1. Department of Medicine and Division of Hepatology, Groote Schuur Hospital and University of Cape Town 2. Department of Anatomical Pathology, University of Cape Town and National Health Laboratory System, Cape Town, South Africa

Protease Inhibitors (PI)

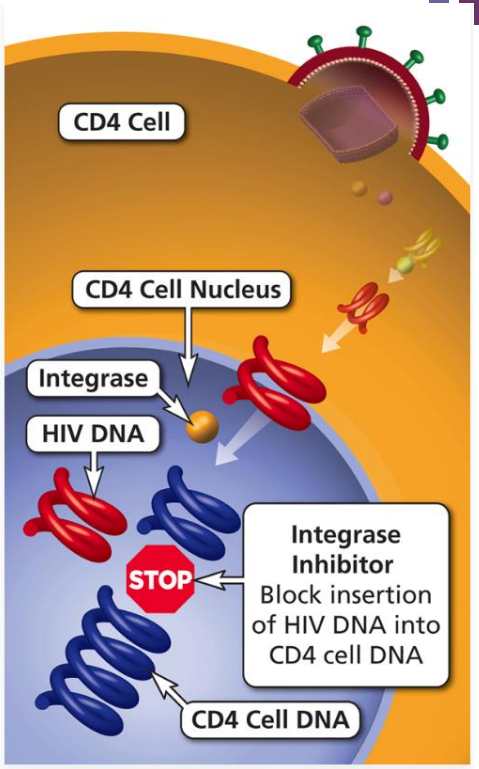
- Hyperbilirubinaemia
  - Atazanavir
  - "Gilberts'" like syndrome: benign
- Direct hepatotoxic effect
  - ? Level related; higher levels with co-infection
- Indirect metabolic effect
  - Insulin resistance; Hyperlipidaemia
  - Insulin resistance is the metabolic hallmark of predisposition to non-alcoholic fatty liver disease (NAFLD)
- Similar rates of raised ALT/AST with conventional PIs
  - LPV, ATV
  - Lower rates with DRV than LPV in Artemis



Cooper, Curr Opin HIV AIDS 2007; Mills et al, AIDS 2009

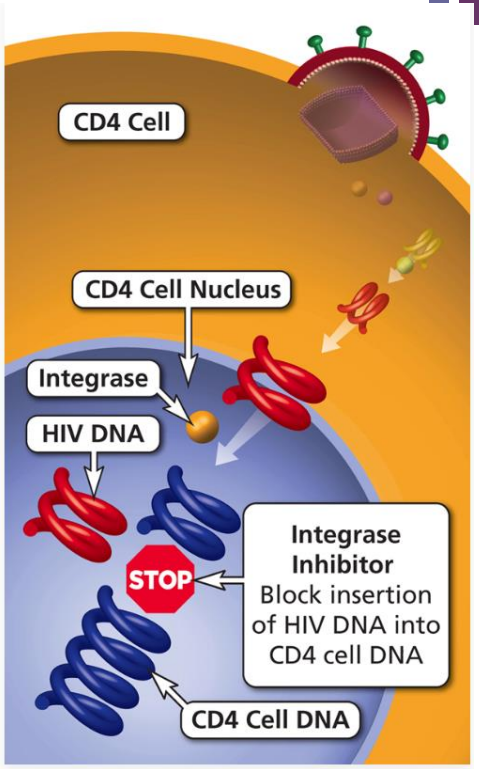
Raltegravir

- Naïve patients (STARTMRK)
  - Vs efavirenz
  - G3/4 LFTs 2% vs 2%
- Experienced patients (SWITCHMRK)
  - Vs stable regimen
  - G3/4 LFTs 4% vs 2%
- Experienced patients (BENCHMRK)
  - Vs OBR
  - G3/4 ALT 3 v 3.7%; AST 2.8 v 3.7%
- Well tolerated in HBV/HCV co-infected (1.3% G3/4)



Dolutegravir

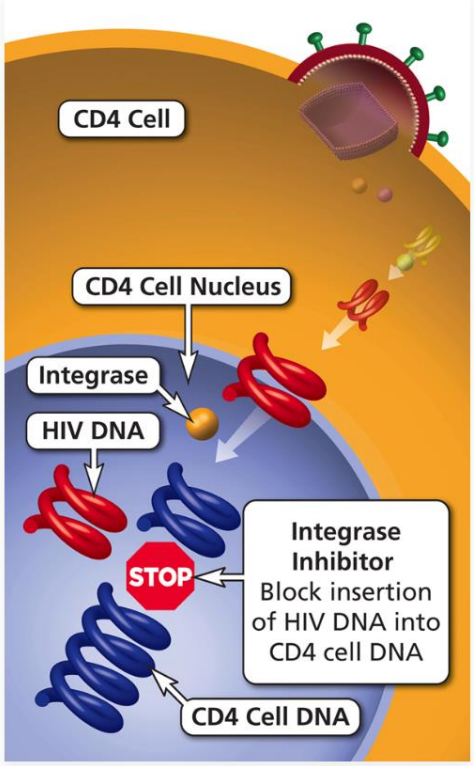
- Naïve patients (SPRING 1)
  - Dolutegravir vs efavirenz
  - 9% HCV coinfected
  - Liver AEs: G3/4 0.6% (DTG) and 2% (EFV)
- Naïve patients (SPRING 2)
  - Dolutegravir vs raltegravir
  - 2% HBV and 10% HCV co-infected
  - Liver AEs: G3 2% each arm; G4 1%
    - D/C with DTG: 2 acute HCV, 2HBV IRIS, 1 con-med, 1 drug-induced
- Naïve patients (SINGLE)
  - Dolutegravir vs efavirenz
  - 7% HCV at baseline; HBV and "impairment" excluded
  - No G3/4 LFT abnormalities; G2 1 vs 4%



Van Lunzen, Lancet 2011; Raffie et al, Lancet 2013; Walmsley et al, IAS 2012

Dolutegravir

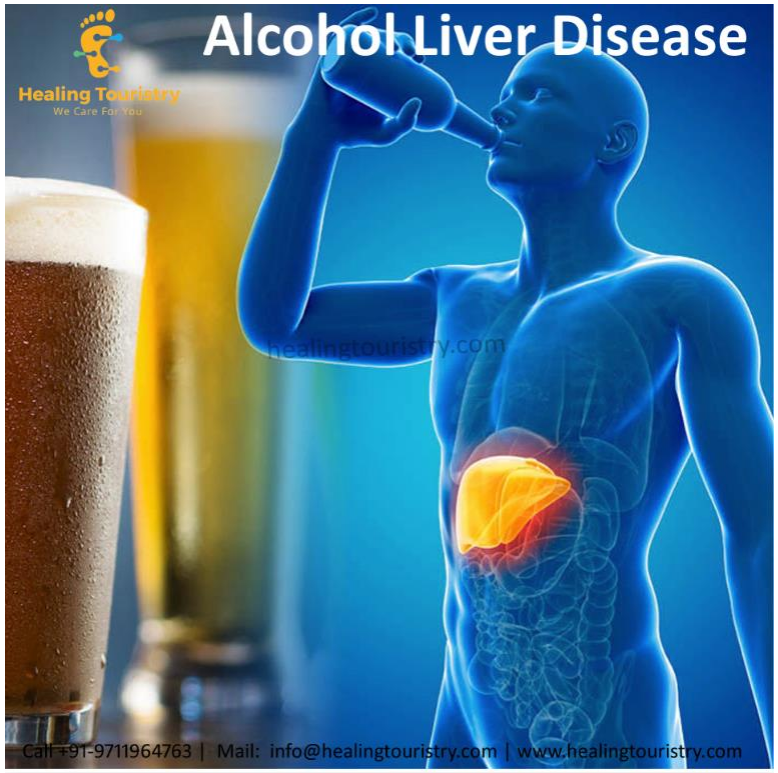
- Experienced patients (VIKING)
  - No comparator (od vs bd)
  - 4% HBV and 16% HCV co-infected
  - No G3/4 transaminase abnormalities
- Experienced patients (SAILING)
  - Dolutegravir vs raltegravir
  - HBV/HCV coinfected: 14% vs 18%
  - G3/4 ALT: 3% vs 2%
  - "high rate of IRIS with HBV/HCV; more with DTG"



Eron et al; JID 2012; Pozniak et al, CROI 2013

Alcohol

- Alcohol – more rapid progression of HCV/HBV liver disease
- Little known about the combined effects of alcohol and ARVs on the liver
- Alcohol affects adherence and risk behaviour – main reasons to advise against alcohol use



Managing abnormal LFTs

- Repeat specimen to confirm
- Include ALP, GGT, albumin & INR
- Check for other co-infections: acute HCV, syphilis
- Check for other medications
  - including unprescribed
- Check for toxins
  - alcohol, herbs, traditional medication

Asboe et al, HIV Medicine 2011; Walker Curr Opin HIV AIDS 2007

Assess Pathogenic Mechanism

1. **Toxins**
   - Alcohol, Traditional medicines
2. **Medication**
   - TB drugs, cotrimoxazole, azoles
3. **Infections**
   - Viruses, Mycobacteria, Syphilis
4. **Metabolic factors**
   - Insulin resistance, lipodystrophy, ↑ triglicerides
5. **Liver diseases**
   - Alcohol-induced hepatitis

When to stop ARVs for hepatotoxicity?

- Symptomatic hepatitis
- Jaundice
- Lactic acidosis
- Hypersensitivity
- ALT or AST >5x ULN
- Liver decompensation
- Newly-marketed drugs

Severe liver toxicity (grades 3–4), even in the absence of symptoms warrants discontinuation of the ARV's

Guidelines for managing hepatotoxicity

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	< 2.5 x ULN	2.5 – 5 x ULN	> 5 x ULN	> 10 x ULN
ALT	Monitor	Repeat 1 week	Stop relevant drug(s)	Stop all drugs
GGT/ALP	Monitor	Repeat 2 weeks	Ultrasound ? Biopsy	Ultrasound ? biopsy
Bilirubin	Repeat 4 weeks	Stop relevant drug(s)	Stop relevant drug(s)	Stop all drugs

TB Treatment-related Hepatotoxicity

- More common than in HIV-uninfected patients
  - DILI complicates TB treatment in 5 - 33% of HIV+ patients
- First-line anti-TB drugs associated with hepatotoxicity:
  - INH, RIF and PZA
- SA study: in-hospital & 3-month mortality of TB Rx or ART-associated DILI
  - 27% and 35%
- In some studies HBV carrier status & alcohol associated with liver injury in patients on TB drugs

GUIDELINE

Consensus statement: Management of drug-induced liver injury in HIV-positive patients treated for TB

E Jong,[1] MD, PhD; **F Conradie**,[1] MB BCh, DTM&H, Dip HIV Man; **R Berhanu**,[2] MD, DTM&H, Dip HIV Man;
A Black,[3] BSc, MB BCh, FCP (SA), Cert Pulm (SA); **M-A John**,[4] MB ChB, FCPath (Micro), Dip HIV Man, DTM&H;
G Meintjes,[5] MB ChB, MRCP (UK), FCP (SA), Dip HIV Man, MPH, PhD; **C Menezes**,[6] MD, MMed, Dip HIV Man, DTM&H, FCP (SA)

Table 2. DILI definition advocated in the SA setting

- ALT level >120 IU/l **and** symptomatic (nausea, vomiting, abdominal pain, jaundice); **or**
- ALT level >200 IU/l **and** asymptomatic; **or**
- Total serum bilirubin concentration >40 µmol/l

Table 3. Overview of management of TB-DILI according to existing guidelines

Authority	Stopping TB drugs if clinical or symptomatic hepatitis	When to restart TB drugs	What TB drugs to start	Recommended LFT monitoring on rechallenge	If DILI recurs
ATS[10]	Yes	ALT <80 IU/l	• RIF +/- EMB full dose • After 3 - 7 days INH (full dose) • PZA only if mild DILI	• Check ALT 3 - 7 days after INH rechallenge	• Stop last drug added
BTS[29]	Yes	ALT within normal limits	• STR + EMB (if unwell or sputum is smear-positive within 2 weeks of commencing treatment) • INH (dose titration, every 2 - 3 days) • RIF (dose titration, every 2 - 3 days) • PZA (dose titration, every 2 - 3 days)	• Daily monitoring of LFT	• Stop offending drug, alternative regimen advised by fully trained physician
ERS, WHO, IUATLD[30]	Yes	LFT within normal limits	• Start all drugs at full dosage	• LFT monitoring (no recommendation on frequency)	• Stop all drugs, start STR + EMB and start other drugs one at a time
HKTBS[31]	Yes	-	-	-	-

TB = tuberculosis; DILI = drug-induced liver injury; LFT = liver function test; ALT = alanine transaminase; ATS = American Thoracic Society; BTS = British Thoracic Society; ERS = European Respiratory Society; WHO = World Health Organization; IUATLD = International Union Against Tuberculosis and Lung Disease; HKTBS = Hong Kong Tuberculosis Service; RIF = rifampicin; EMB= ethambutol; INH = isoniazid; PZA = pyrazinamide; STR = streptomycin.

Table 4. TB treatment regimen for patients with drug-susceptible TB when a first-line drug is omitted

Drug omitted	Intensive phase	Continuation phase
RIF	INH, MOX, EMB, STR × 2 months*	INH, MOX, EMB × 16 months
INH	RIF, MOX, EMB × 2 months*	RIF, MOX, EMB × 10 months
PZA	RIF, INH, EMB × 9 months	

TB = tuberculosis; RIF = rifampicin; INH = isoniazid; MOX = moxifloxacin; EMB = ethambutol; STR = streptomycin; PZA = pyrazinamide.

*May consider PZA rechallenge and use during the intensive phase, particularly if DILI occurred early during the intensive phase.

Co-trimoxazole

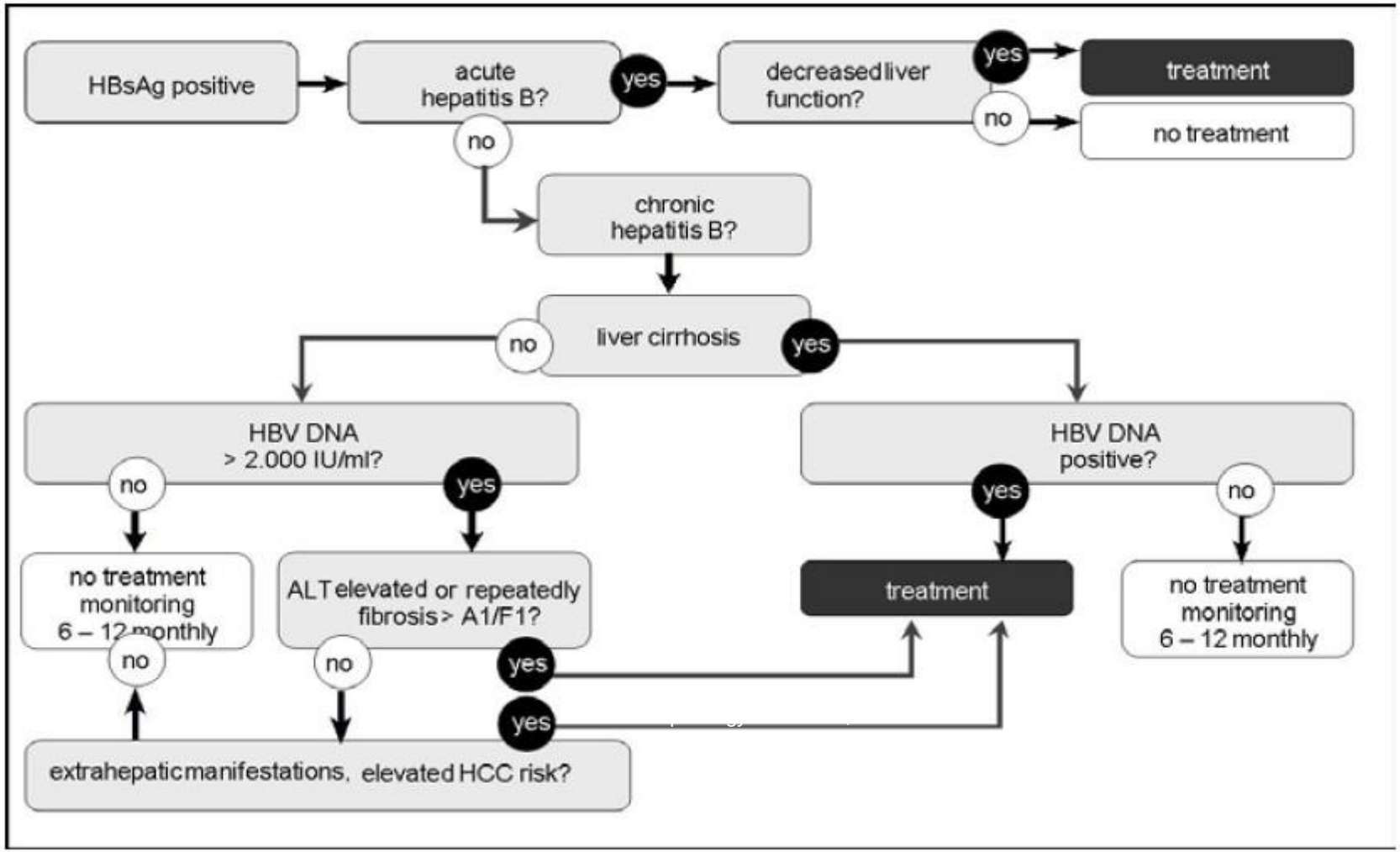
- Co-trimoxazole is associated with cholestatic jaundice & hepatic necrosis
- Can be part of a systemic drug hypersensitivity syndrome that occurs independent of plasma drug concentrations

Negative impact of Hepatitis-HIV co-infections

Hepatitis B co-infections

- Commencement of HAART accelerates progression of liver disease
- Enhanced risk of hepatotoxicity
- Chronic carriers become highly infectious (increased MTCT of HBV)
- HBV vaccine failure in babies born to HBV/HIV mothers
- 3TC resistance after 12–24 months of ART
- **Hepatitis C co-infections**
- Enhanced chronic immune activation in HIV co-infected persons
- Increased all cause mortality & elevated risk of of complications e.g. renal insufficiency
- More rapid progression of liver fibrosis

Indications for HBV Treatment



HBV Treatment End Goals

- Chronic hepatitis B infection cannot be eradicated with currently available therapies
- In chronic hepatitis B, the goal of therapy is to prevent the progression to cirrhosis
- In HBV cirrhosis, the goal of therapy is to prevent decompensation and HCC
- In decompensated liver disease, the goal of therapy is to improve synthetic function through viral suppression
- The ideal endpoint of therapy for both chronic HBeAg-positive and chronic HBeAg-negative disease is HBsAg loss with or without seroconversion to anti-HBs, as this correlates with the loss of transcriptionally active cccDNA

HCC = hepatocellular carcinoma; HBeAg = hepatitis B 'e' antigen; HBsAg = hepatitis B surface antigen; cccDNA = covalently closed circular DNA.

Recommended drugs for treatment of Chronic HBV

Drug	Dose
Tenofovir	300 mg[a] once daily
Tenofovir plus emtricitabine	Tenofovir 245 mg; emtricitabine 200 mg
Entecavir (adult with compensated liver disease and lamivudine naive)	0.5 mg once daily
Entecavir (adult with decompensated liver disease)	1 mg once daily

[a] Tenofovir disoproxil fumarate (TDF) 300 mg is equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg.

Tenofovir alafenamide fumarate (TAF) is an orally bioavailable prodrug of tenofovir with reduced renal and bone toxicities compared to tenofovir.

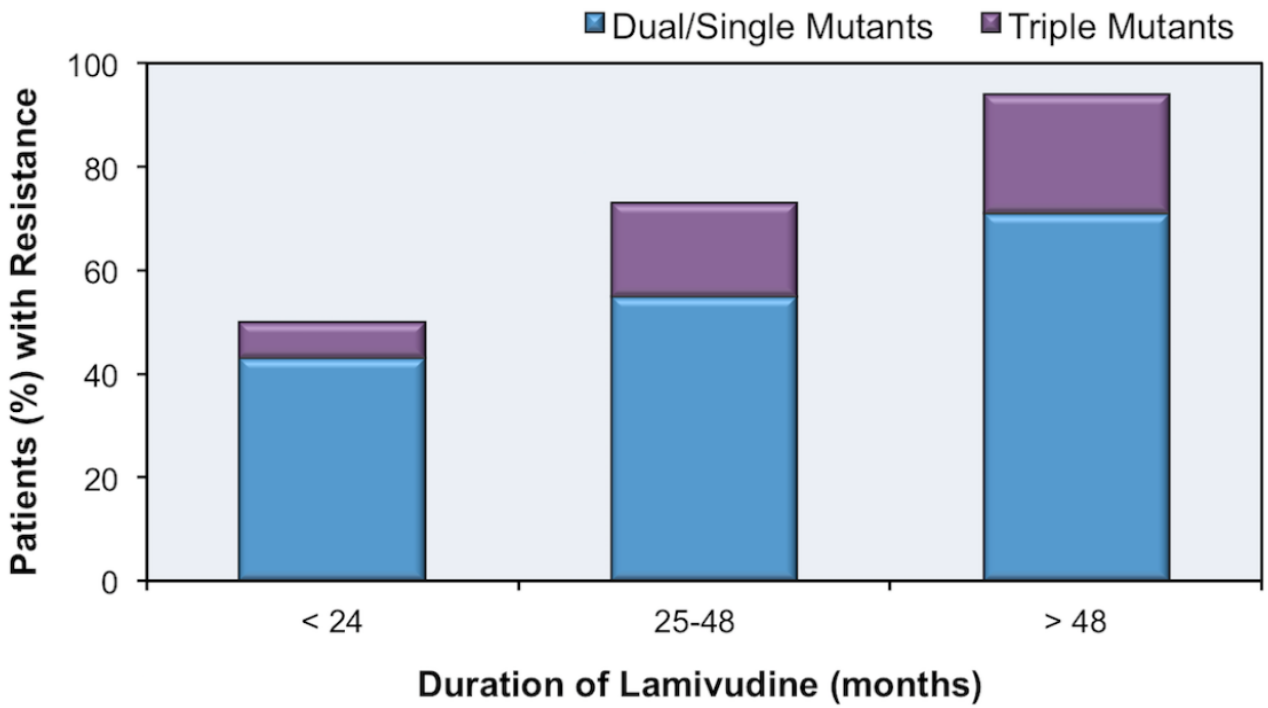
Drug	Dose
Telbivudine	600 mg once daily
Lamivudine	300 mg once daily
Adefovir	10 mg once daily
Pegylated interferon alpha-2a[b]	180 µg once per week[a]
Pegylated interferon alpha-2b[b]	0.5 or 1.0 µg per kg per week

[a] Reduced to 135 µg if creatinine clearance is less than 30 mL/min

[b] A number of relative and absolute contraindications to IFN also exist, which include the presence of decompensated cirrhosis and hypersplenism, thyroid disease, autoimmune diseases, severe coronary artery disease, renal transplant disease, pregnancy, seizures and psychiatric illness, concomitant use of some drugs, retinopathy, thrombocytopenia or leucopenia. IFN also cannot be used in infants less than 1 year.

http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guidelines/en/

Resistance to 3TC



https://www.hiv.uw.edu/go/co-occurring-conditions/hepb-coinfection/core-concept/all

Immunization against HBV in HIV Infection

- Screen everyone for HBsAb
  - Negative for HBsAg or occult HBV → vaccinate
- Vaccination
  - Transient HIV viremia after vaccination – not clinically relevant
- Less likely to develop protective HBsAb after vaccination
  - Response rate (18-71% Vs >90% HIV neg adults)
  - Associated with lower CD4 cell counts (<500), detectable HIV RNA
- Lower mean HBsAb titers & faster decline of sAb over time
  - Administration of a higher dose of HBV vaccine?
  - Revaccination?

Shire et al., 2006; Kim et al.,2009; Fonseca et al., 2005; Reyet al.,2000; Tayal et al.,1994

IRIS

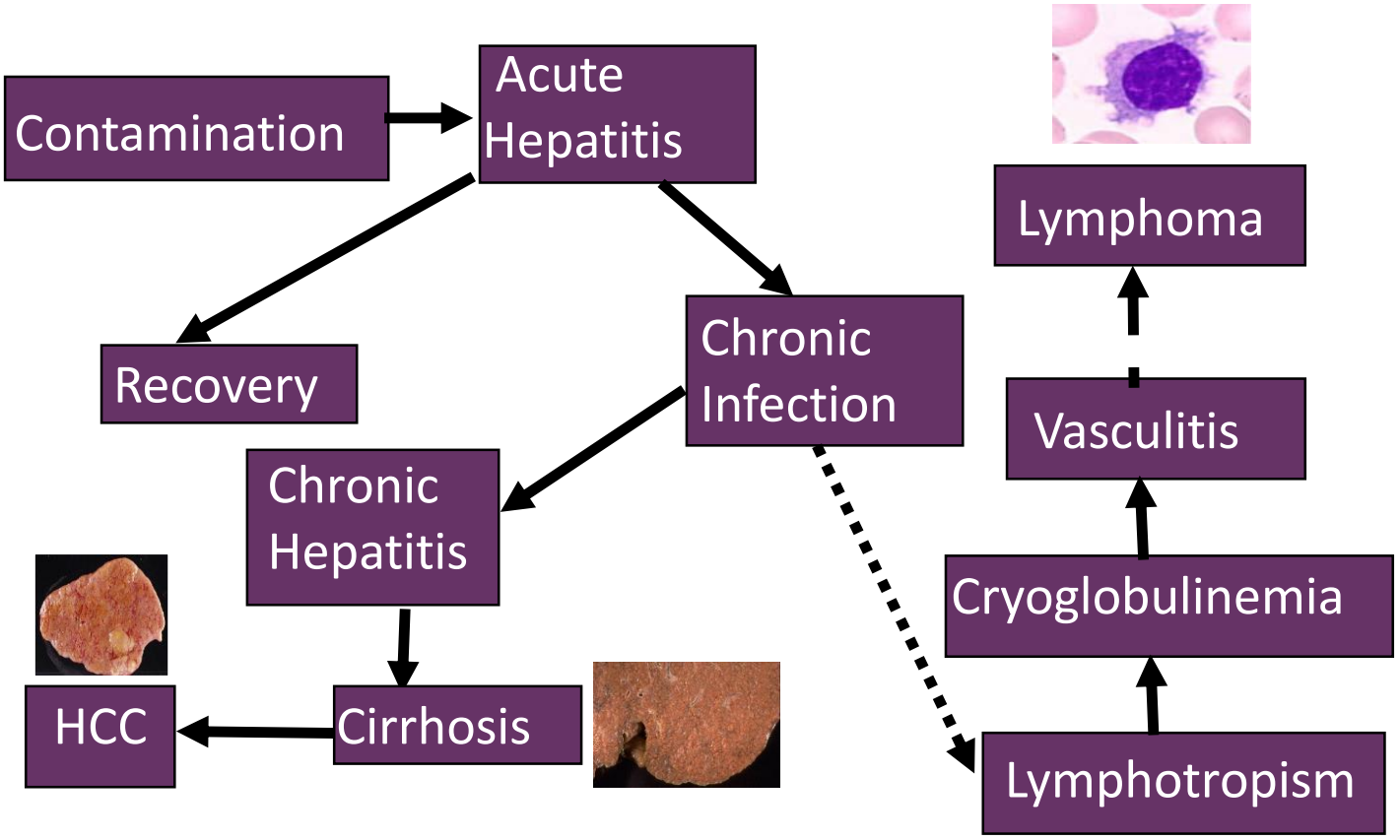
- Result of immune restoration and development of acute liver injury 2° to enhanced immune response to TB or HBV
- **HBV**-IRIS presents as acute hepatocellular injury
- **TB**-IRIS presents with an obstructive picture
  - Approximately 56% of patients with TB-IRIS have clinical hepatomegaly - frequently tender with symptoms of right-upper quadrant pain, nausea and vomiting
  - Typical pattern of liver enzyme abnormality is mixed with moderate elevation of transaminases, but a far more significant rise in the canalicular enzymes
  - Bilirubin may increase, but clinical jaundice is uncommon

HIV and HCV co-infection

- Prevalence of chronic HCV in PLWH varies substantially by **region** and **within sub-populations**
- 2% of PLWH have **chronic HCV** in African region as a whole (but in some countries, this reaches 10-15%), whilst in US 20% have HCV co-infection
- Among **people who inject drugs** who are HIV-infected, up to 90% may be **HCV** seropositive depending on setting

Singh et al 2017, Azevedo et al 2016, US Department of Health and Human Services 2016

HCV chronic infection is a systemic disease

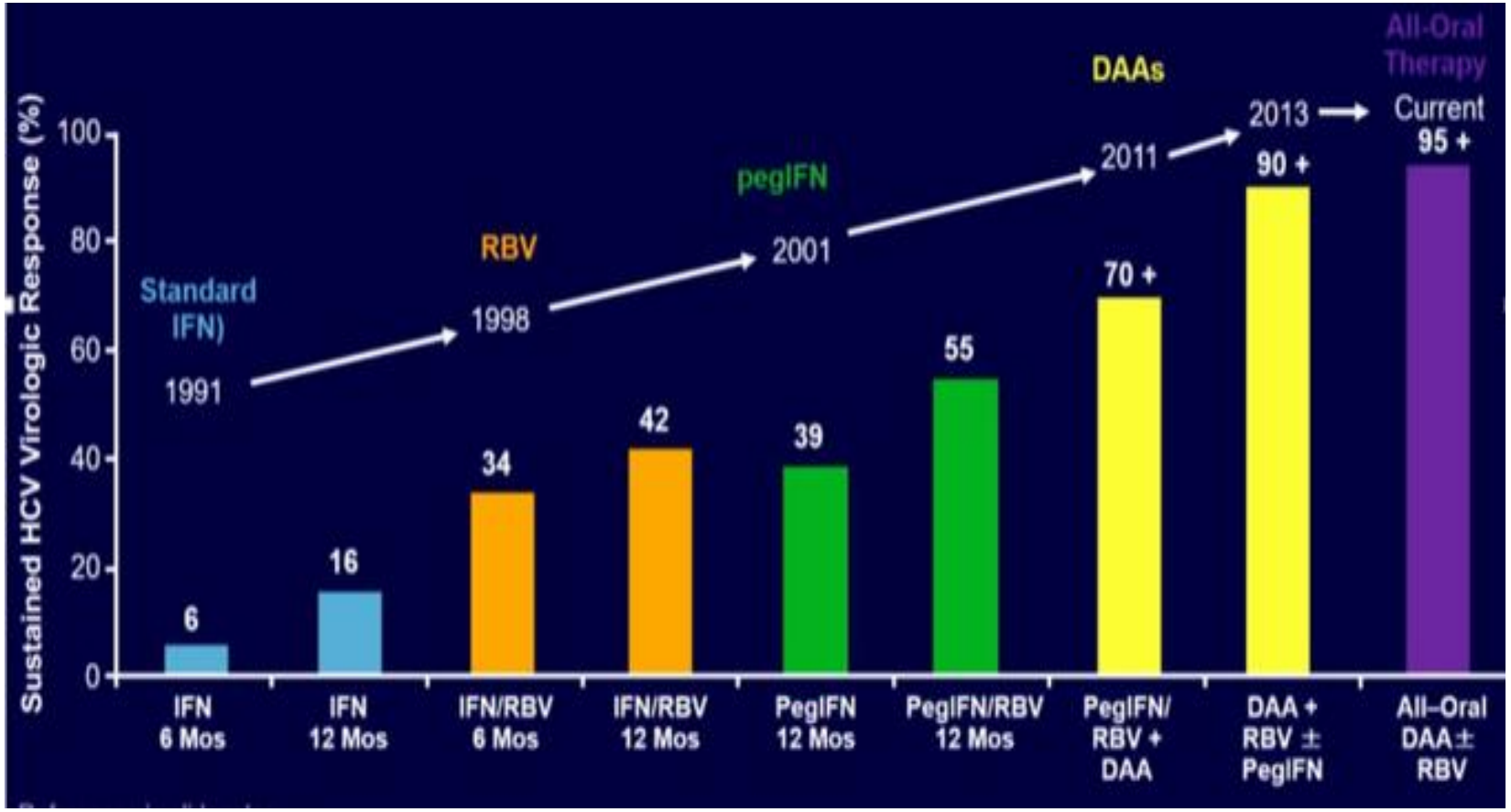


Liver disease

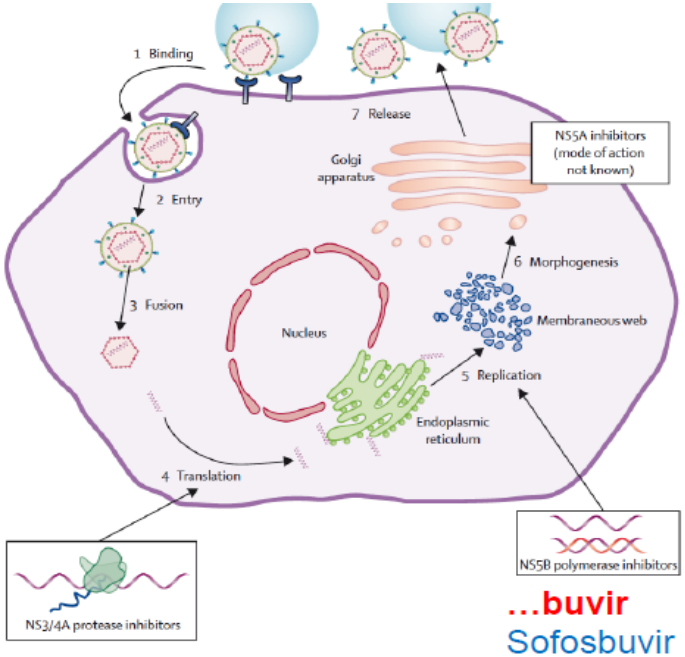
« Chronic inflammation »

Vasculitis

All anti HCV treatments are now efficient and well tolerated



Anti HCV medication: Mechanisms of action



…previr
Paritaprevir
Grazoprevir

…buvir
Sofosbuvir
Dasabuvir

…asvir
Daclatasvir
Ledipasvir
Ombitasvir
Elbasvir

Inhibitor Class	Reminder	Examples
Targeting HCV Protein Processing		
NS3/4A protease	PREVIR	▪ Grazoprevir, paritaprevir, simeprevir
Targeting HCV Replication		
NS5B polymerase	BUVIR	▪ Nucleos(t)ide: sofosbuvir ▪ Non-nucleos(t)ide: dasabuvir
NS5A	ASVIR	▪ Daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir

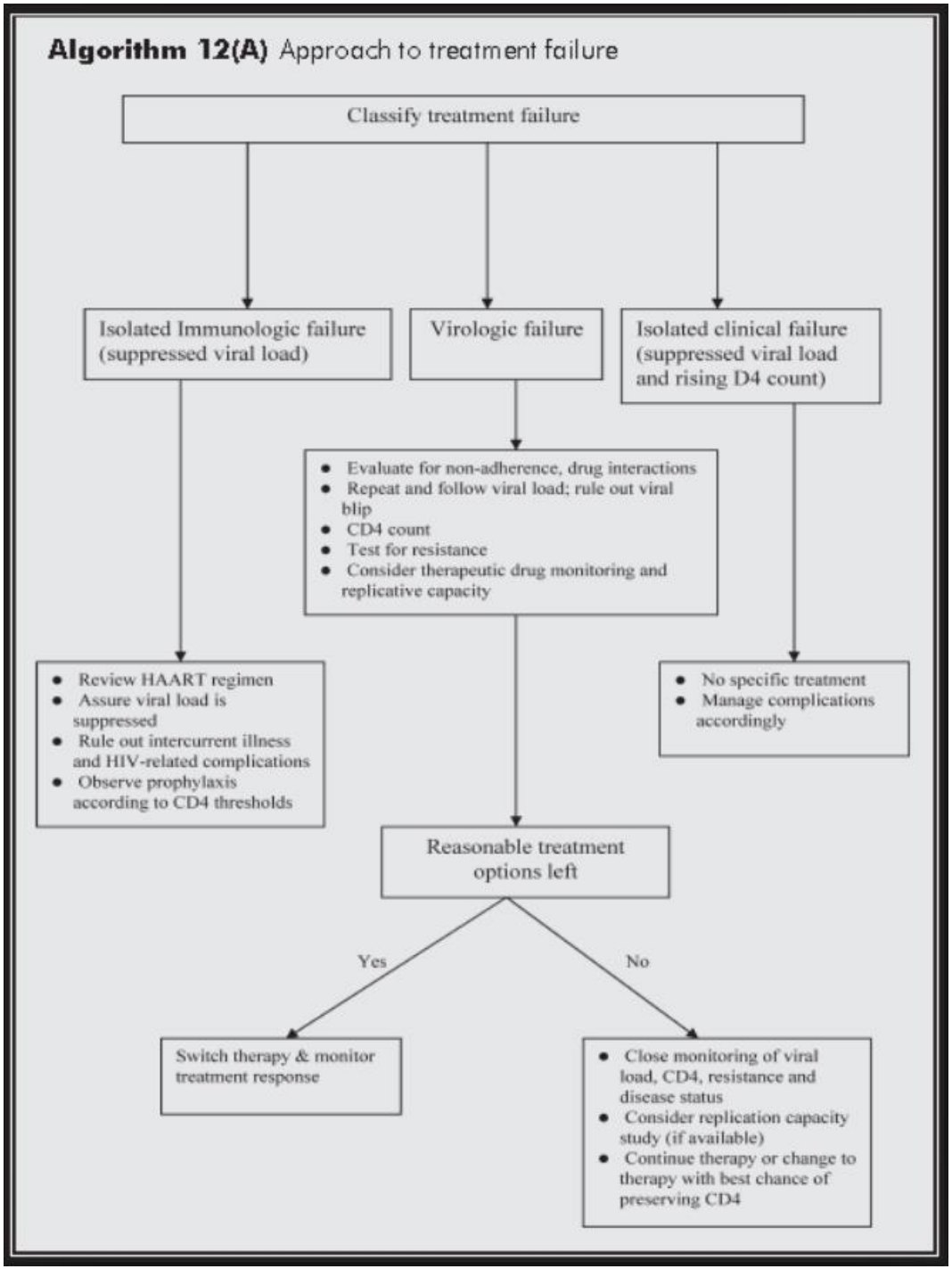
modif. after Manns, Cornberg, Lancet Inf Dis, 2013

	Sofosbuvir and ledipasvir*	Sofosbuvir and daclatasvir†	Sofosbuvir and velpatasvir‡	Sofosbuvir and ribavirin§
Genotype 1a/1b¶				
Treatment naive	12 weeks	12 weeks	12 weeks	No
Treatment experienced or cirrhosis	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks	No
Genotype 2				
Treatment naive	No	12 weeks	12 weeks	12 weeks
Treatment experienced or cirrhosis	No	12 weeks	12 weeks	16–24 weeks
Genotype 3				
Treatment naive	No	12 weeks	12 weeks	No
Treatment experienced or cirrhosis	No	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	No
Genotype 4				
Treatment naive	12 weeks	12 weeks	12 weeks	No
Treatment experienced or cirrhosis	12 weeks plus a bodyweight-based dose of ribavirin , or 24 weeks without ribavirin	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks	No
Genotype 5				
Treatment naive	12 weeks	12 weeks	12 weeks	No
Treatment experienced or cirrhosis	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks plus a bodyweight-based dose of ribavirin, or 24 weeks without ribavirin	12 weeks	No

When a patient is co-infected with HCV and HIV, careful consideration must be given to drug–drug interactions with existing antiretroviral therapy. If the HCV genotype is unknown, treatment using sofosbuvir and daclatasvir is recommended. *Sofosbuvir (400 mg) with ledipasvir (90 mg). †Sofosbuvir (400 mg) with daclatasvir (60 mg); daclatasvir doses might need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. ‡Sofosbuvir (400 mg) with velpatasvir (100 mg). §Sofosbuvir (400 mg) with a bodyweight-based dose of ribavirin. ¶If the subgenotype is known, bodyweight-based ribavirin is not required for patients who have genotype 1b infection and are treatment experienced or have compensated cirrhosis. The default treatment in the absence of subgenotype is to add ribavirin for 12 weeks or extend treatment to 24 weeks without ribavirin.

Table 2: **Treatment schedule for hepatitis C by genotype, treatment history, and presence of compensated cirrhosis**

Treatment Failure

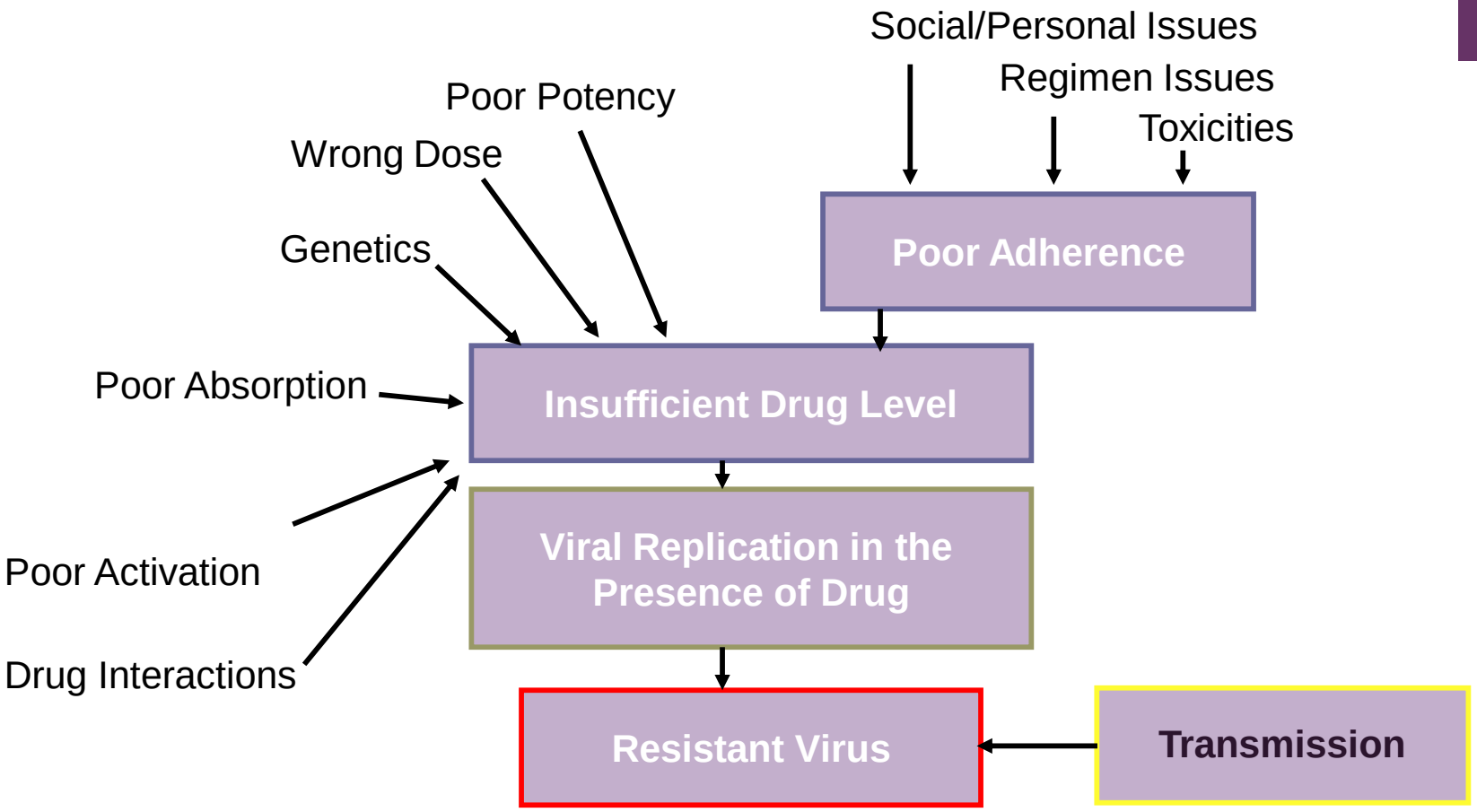

Algorithm 12(A) Approach to treatment failure
Classify treatment failure
Isolated Immunologic failure (suppressed viral load)
Virologic failure
Isolated clinical failure (suppressed viral load and rising D4 count)
Evaluate for non-adherence, drug interactions
Repeat and follow viral load; rule out viral blip
CD4 count
Test for resistance
Consider therapeutic drug monitoring and replicative capacity
Review HAART regimen
Assure viral load is suppressed
Rule out intercurrent illness and HIV-related complications
Observe prophylaxis according to CD4 thresholds
No specific treatment
Manage complications accordingly
Reasonable treatment options left
Yes
No
Switch therapy & monitor treatment response
Close monitoring of viral load, CD4, resistance and disease status
Consider replication capacity study (if available)
Continue therapy or change to therapy with best chance of preserving CD4

Resistance

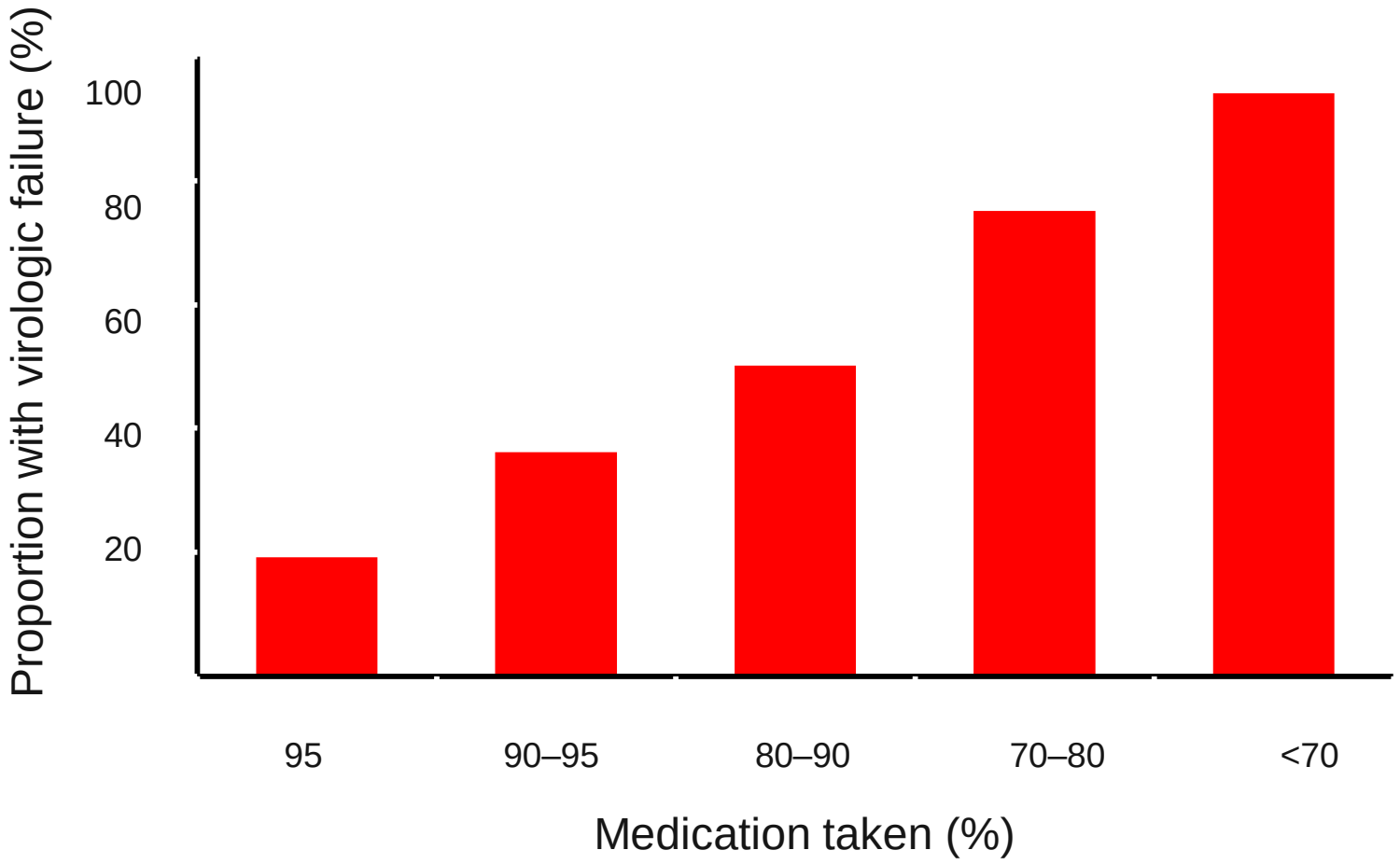
Definition of antiviral drug resistance

- Changes in the viral genetic sequence (mutations) that decrease drug activity
- Mediated by:
  - Changes in the molecular target of therapy
  - Changes in other viral proteins that indirectly interfere with a drug's activity

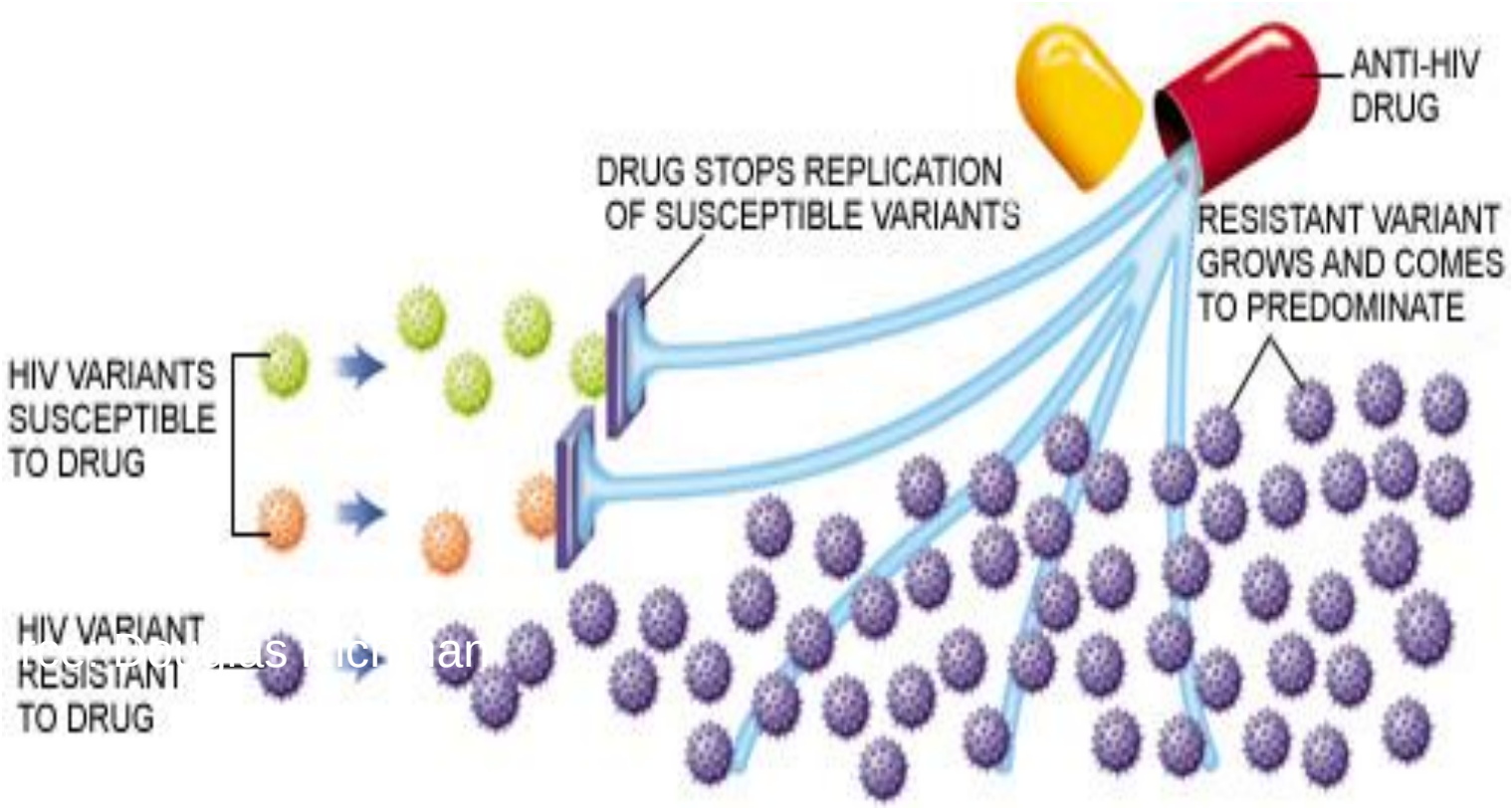
How does resistance develop?



Adherence


Proportion with virologic failure (%)
100
80
60
40
20
95
90–95
80–90
70–80
<70
Medication taken (%)

How does resistance emerge?

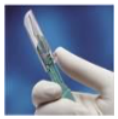


Prevention

ARV prophylaxis

HIV PREVENTION

Male circumcision



Auvert B, PloS Med 2005
Gray R, Lancet 2007
Bailey R, Lancet 2007

Treatment of STIs

Grosskurth H, Lancet 2000

Female Condoms

Male Condoms

HIV Counselling and Testing

Coates T, Lancet 2000
Sweat M, Lancet 2011

Behavioural Intervention

- Abstinence
- Be Faithful

Treatment for prevention

Cohen M, NEJM, 2011
Donnell D, Lancet 2010
Tanser, Science 2013

Post Exposure prophylaxis (PEP)

Scheckter M, 2002

Oral pre-exposure prophylaxis

Grant R, NEJM 2010 (MSM)
Baeten J , NEJM 2012 (Couples)
Thigpen M, NEJM 2012 (Heterosexuals)
Choopanya K, Lancet 2013 (IDU)

Microbicides for women

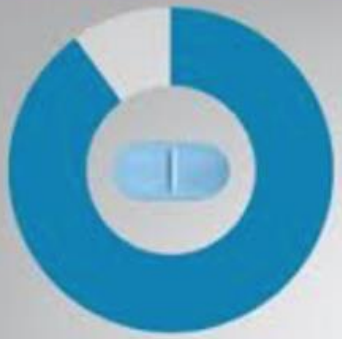
Abdool Karim Q, Science 2010

Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is on sexual transmission

CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

Not enough health care providers know about PrEP.

Pre-exposure prophylaxis (PrEP) is a medicine taken daily that can be used to prevent HIV infection. PrEP is for people without HIV who are at very high risk for acquiring it from sex or injection drug use.



90%

Daily PrEP can reduce the risk of sexually acquired HIV by more than 90%.

70%

Daily PrEP can reduce the risk of HIV infection among people who inject drugs by more than 70%.

1 in 3

1 in 3 primary care doctors and nurses haven't heard about PrEP.

SOURCE: CDC Vital Signs, Dec. 2015.

CDC Vitalsigns™

www.cdc.gov/vitalsigns/HIVPrEP

CDC

Summary of Guidance for PrEP Use

	Men Who Have Sex With Men	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection:	• Sexual partner with HIV • Recent bacterial STD • High number of sex partners • History of inconsistent or no condom use • Commercial sex work	• Sexual partner with HIV • Recent bacterial STD • High number of sex partners • History of inconsistent or no condom use • Commercial sex work • Lives in high-prevalence area or network	• HIV-positive injecting partner • Sharing injection equipment • Recent drug treatment (but currently injecting)
Clinically eligible:	• Documented negative HIV test before prescribing PrEP • No signs/symptoms of acute HIV infection • Normal renal function, no contraindicated medications • Documented hepatitis B virus infection and vaccination status		
Prescription	Daily, continuing, oral doeses of TDF/FTC (Truvada), ≤90 day supply		
Other services:	• Follow-up visits at least every 3 months to provide: • HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STD symptom assessment • At 3 months and every 6 months after, assess renal function • Every 6 months test for bacterial STDs		
	• Do oral/rectal STD testing	• Assess pregnancy intent • Pregnancy test every 3 months	• Access to clean needles/ syringes and drug treatment services

Source: US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States —2014: a clinical practice guideline.

PrEP Pitfalls

- Non-adherence
- Infrequent monitoring
- New HIV infection
- Transmitted/ acquired drug resistance
- No/ less condom use
- STIs

LONG-ACTING **FORMS OF HIV PREVENTION**

For some people, long-acting forms of HIV prevention may be more desirable than a daily pill.

Antiretroviral-based HIV prevention today — and in the future.

Taking an oral dose of the medication Truvada **once a day, every day** can prevent HIV infection.

NIAID-funded researchers are developing and testing **alternative HIV prevention products** that could be inserted, injected or implanted from

ONCE A MONTH...

...TO ONCE A YEAR

in people who commit to use the products on an ongoing basis.

Monthly

Yearly

NIAID is funding research on 3 types of long-acting HIV prevention.

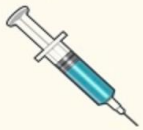
INTRAVAGINAL RING (IVR)

A polymer ring inserted into the vagina releases antiretroviral drug over time.

IMPLANT

Device implanted in the body releases antiretroviral drug over time.

INJECTABLE



Long-acting antiretroviral drug is injected into the body.

How many products are under investigation?

dapivirine IVR
(MTN 025/HOPE and MTN 034/REACH clinical trials)
Truvada IVR (Oak Crest Institute of Science)

cabotegravir (SLAP-HIV project)
dolutegravir (University of North Carolina)
tenofovir alafenamide (Oak Crest Institute of Science)
tenofovir alafenamide (SLAP-HIV project)
tenofovir alafenamide & emtricitabine
(Houston Methodist Research Institute)

cabotegravir (HPTN 077, 083 and 084 clinical trials)

At what stage is this research?

For more on the latest advances in HIV prevention research, visit:

NIH National Institute of Allergy and Infectious Diseases

www.niaid.nih.gov

facebook.com/niaid.nih

@NIAIDNews

Neglect of Attention to Reproductive Health in Women With HIV Infection

Contraceptive Use and Unintended Pregnancies in the Swiss HIV Cohort Study

K Aebi-Popp; V Mercanti; C Voide; J Nemeth; A Cusini; B Jakopp; D Nicca; M Rasi; A Bruno; A Calmy; B Martinez de Tejada

HIV Medicine. 2018;19(5):339-346.

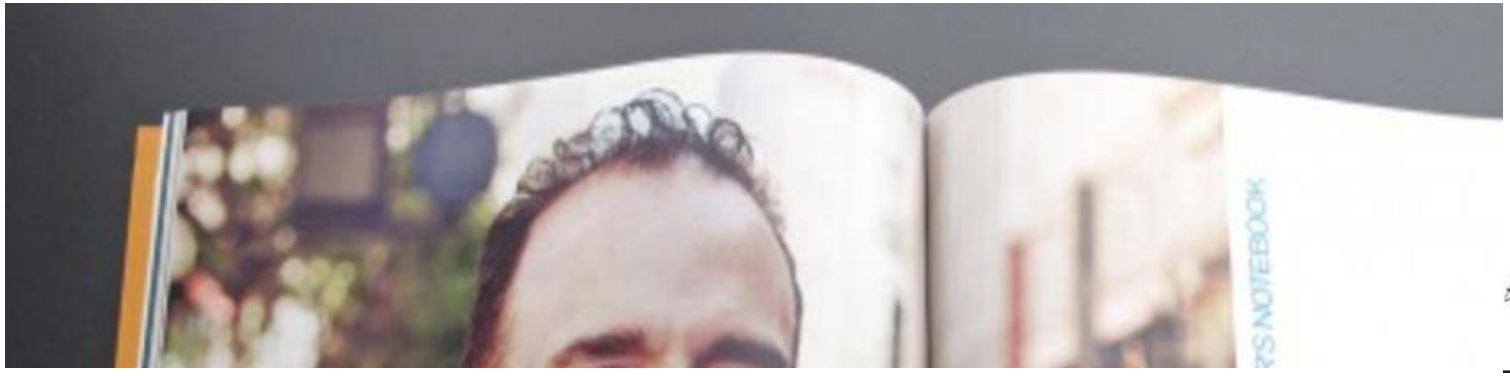
- Of 462 women, 164 (35.5%) not using any contraception
  - 65 (39.6%) sexually active
  - 29 (44.6%) not planning a pregnancy
- Of 298 women using contraception
  - 219 (73.5%) condoms; 32 (10.7%) OC; 28 (9.4%) IUCD
  - 48 (16%) unintended pregnancy while on contraception
  - 43.7% continued using the same contraception after event

! WARNING !

At least half of pregnancies in women with HIV are likely to be unplanned

Difficulties in HIV vaccine development

- Classical vaccination approaches failed
  - Epitopes on viral envelope are too variable
  - Epitopes of the gp120 protein are masked
- HIV is highly mutable (rapid rate)
- High genetic diversity
- Protective immune responses and relevant viral antigens not well characterised
- Target site is immune system
- No simple animal model exists



UKD Universitätsklinikum Düsseldorf

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Treatment of HIV and acute myeloid leukemia by allogeneic CCR5-d32 blood stem cell transplantation

Guido Kobbe[1], Rolf Kaiser[2], Elena Knops[2], Nadine Lübke[3], Gabor Dunay[4], Johannes Fischer[5], Falk Hüttig[6], Rainer Haas[1], Dieter Häussinger[6], Björn Jensen[6]

1 Department of Hematology, Oncology and Clinical Immunology, University of Düsseldorf, Germany; 2 Institute of Virology, University of Cologne, Germany; 3 Institute for Virology, University of Düsseldorf, Germany; 4 Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany; 5 Institute of Transplantation Diagnostics and Cell Therapeutics, University of Düsseldorf, Germany; 6 Department of Gastroenterology, Hepatology and Infectious Deseases, University of Düsseldorf, Germany

THE NEW YORKER

THE LONDON PATIENT AND A PLAN TO END THE H.I.V. EPIDEMIC IN THE UNITED STATES

By Jerome Groopman March 9, 2019

Conclusions

- Large numbers of people still newly infected
- Many prevention strategies
- Social determinants of infection have to be addressed
- Good treatment is available, but good life-long adherence is needed

Thank You