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

Dolutegravir/TLD Roll Out in South Africa

Southern African HIV Clinicians Society

Steven Smith, Health Attaché U.S. Embassy

October 2018

15 YEARS OF SAVING LIVES THROUGH AMERICAN GENEROSITY AND PARTNERSHIPS

#PEPFAR15

HIV Medicines

National Institutes of Health

FDA Approval of HIV Medicines

'80-'84	1981 First AIDS cases reported in the United States				
'85-'89	1987 Zidovudine (NRTI)				
'90-'94	1991 Didanosine (NRTI)	1992 Zalcitabine (NRTI)	1994 Stavudine (NRTI)		
'95-'99	1995 Lamivudine (NRTI) Saquinavir (PI)	1996 Indinavir (PI) Nevirapine (NNRTI) Ritonavir (PI)	1997 Combivir (FDC) Delavirdine (NNRTI) Nelfinavir (PI)	1998 Abacavir (NRTI) Efavirenz (NNRTI)	1999 Amprenavir (PI)
'00-'04	2000 Didanosine EC (NRTI) Kaletra (FDC) Trizivir (FDC)	2001 Tenofovir DF (NRTI)	2003 Atazanavir (PI) Emtricitabine (NRTI) Enfuvirtide (FI) Fosamprenavir (PI)	2004 Epzicom (FDC) Truvada (FDC)	
'05-'09	2005 Tipranavir (PI)	2006 Atripla (FDC) Darunavir (PI)	2007 Maraviroc (CA) Raltegravir (INSTI)	2008 Etravirine (NNRTI)	
'10-'14	2011 Complera (FDC) Nevirapine XR (NNRTI) Rilpivirine (NNRTI)	2012 Stribild (FDC)	2013 Dolutegravir (INSTI)	2014 Cobicistat (PE) Elvitegravir (INSTI) Triumeq (FDC)	
'15-'18	2015 Evotaz (FDC) Genvoya (FDC) Prezcobix (FDC)	2016 Descovy (FDC) Odefsey (FDC)	2017 Juluca (FDC)	2018 Biktarvy (FDC) Cimduo (FDC) Delstrigo (FDC) Doravirine (NNRTI) Ibalizumab (PAI) Symfi (FDC) Symfi Lo (FDC) Symtuza (FDC)	

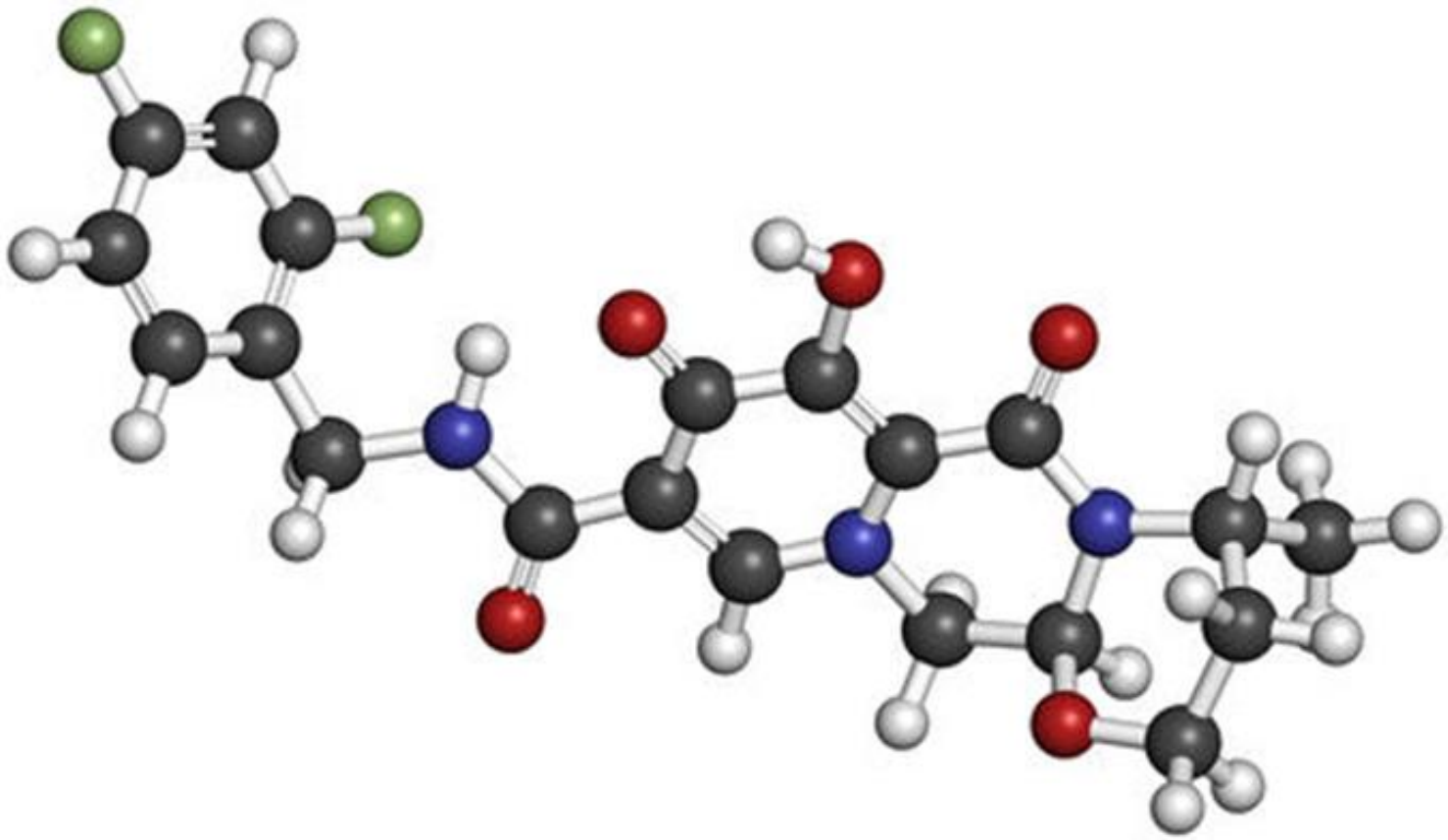
Drug Class Abbreviations:
CA: CCR5 Antagonist; **FDC:** Fixed-Dose Combination; **FI:** Fusion Inhibitor; **INSTI:** Integrase Inhibitor; **NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor; **NRTI:** Nucleoside Reverse Transcriptase Inhibitor; **PE:** Pharmacokinetic Enhancer; **PI:** Protease Inhibitor; **PAI:** Post-Attachment Inhibitor

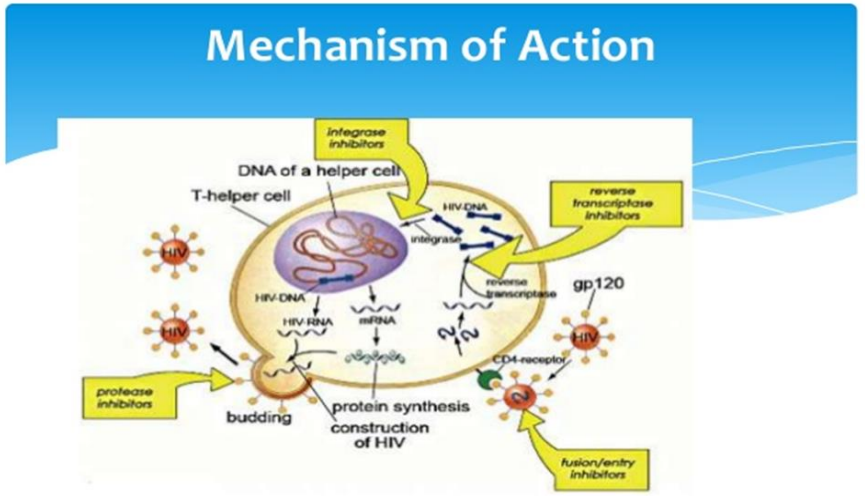
Note: Drugs in gray are not available in the United States and/or are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations.

AIDSinfo

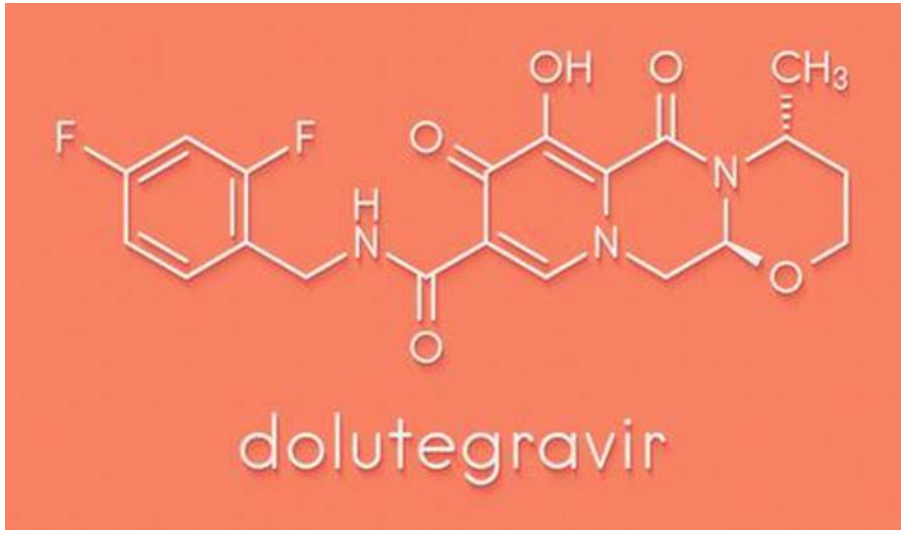
FDA has approved over 200 HIV Medicines

Dolutegravir





Inhibits catalytic activity of HIV-1 integrase, an HIV encoded enzyme required for viral replication



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MOLEKUUL.BE/ALAMY STOCK PHOTO

What is the Global Goal for HIV?

The HIV/AIDS SDG Goal:
Control the HIV Pandemic by 2030
90/90/90 by 2020 and 95/95/95 by 2030

The global strategy to achieve these objectives:
FAST TRACK STRATEGY

PEPFAR's role is to support the above in the most effective and efficient manner possible to ensure the above can be sustained

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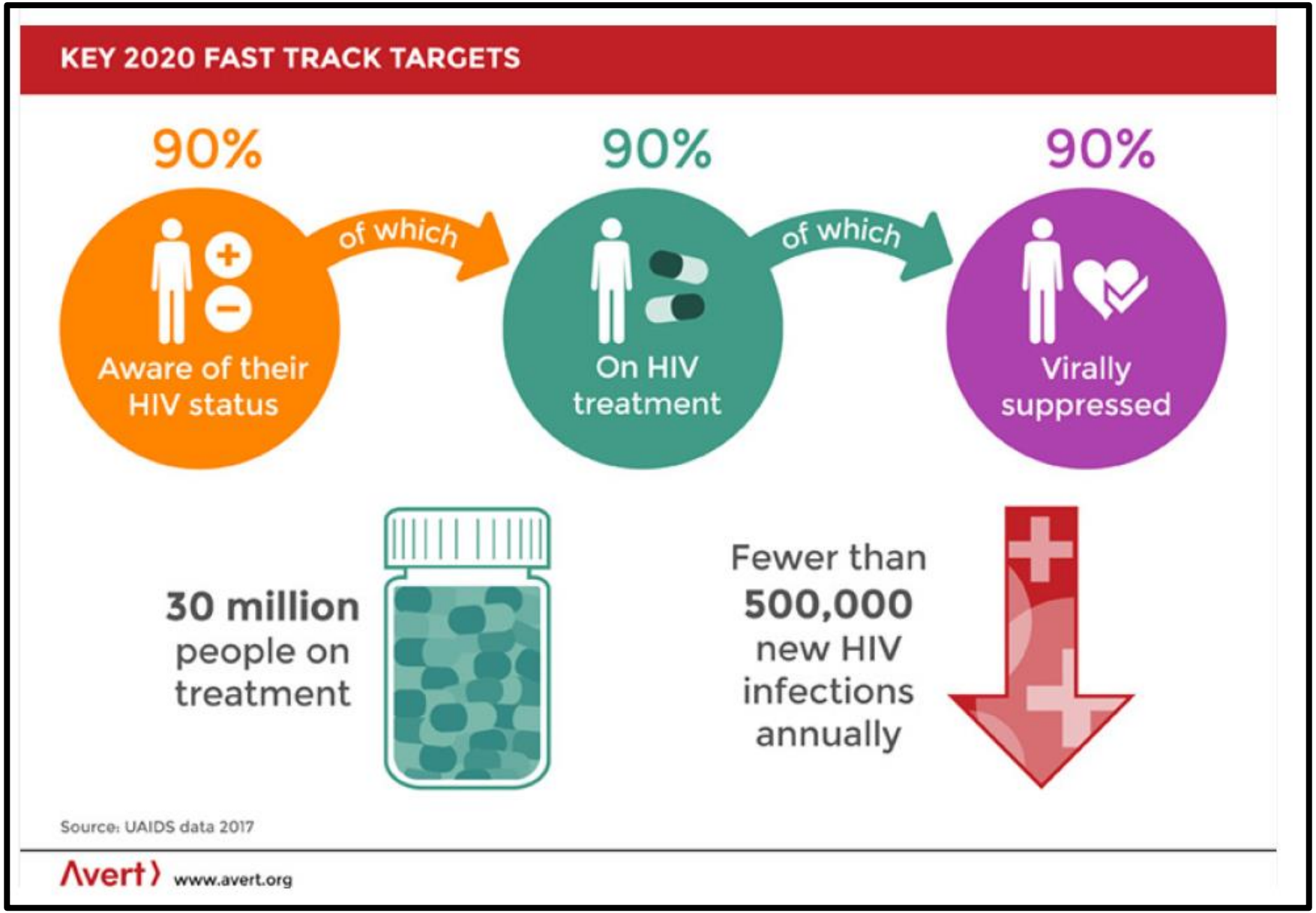
Fast Track Targets



PEPFAR Strategy for achieving epidemic control

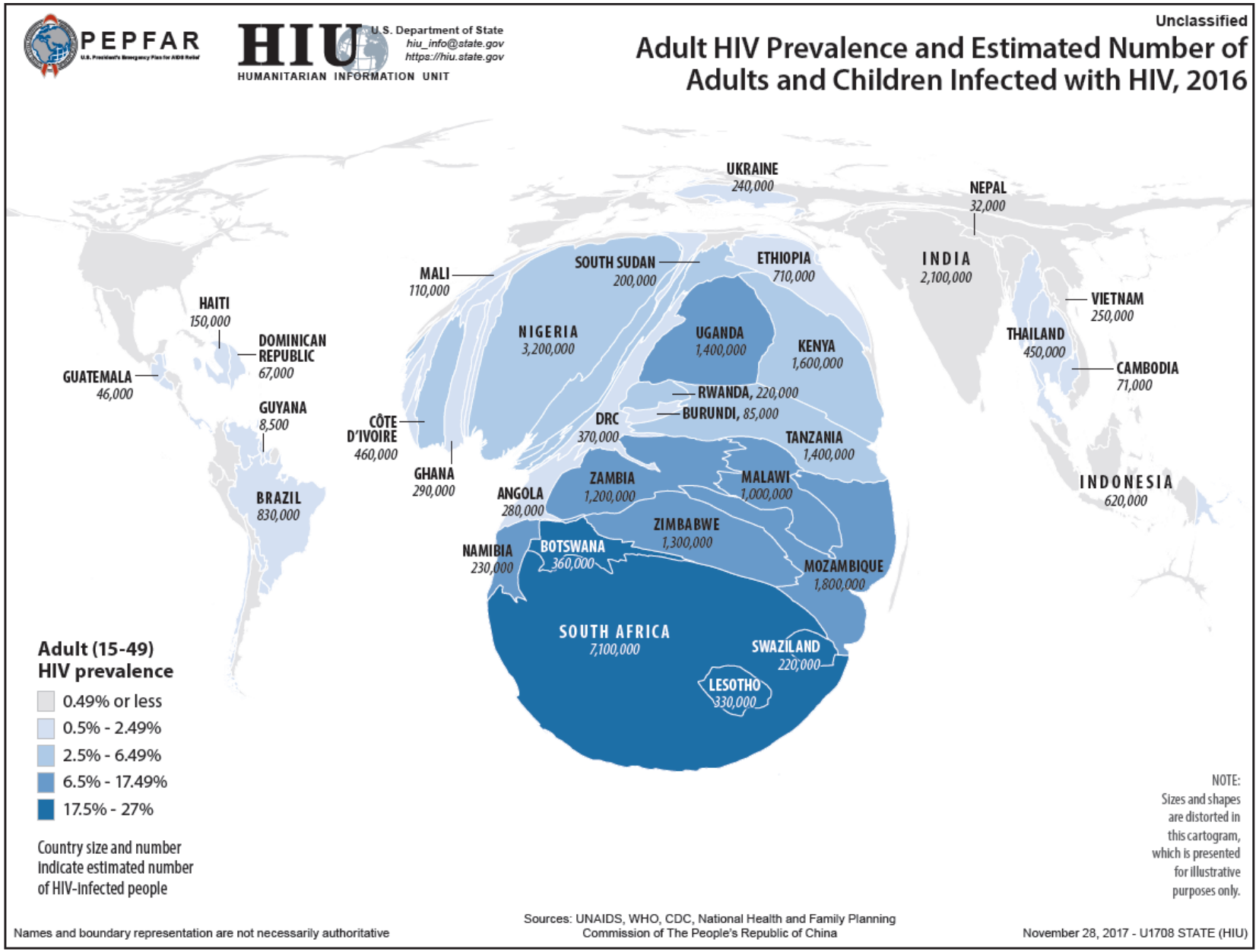
- 90-90-90 cascades targeted by sex and 5 year age bands
- Focus efforts on populations with greatest gaps:
  - Men
  - Younger women
  - <15 yo
- Maximize viral suppression among PLHIV successfully linked to ART initiation
  - ART optimization
  - Retention strategies
  - Increased access to routine viral load monitoring

Achieving the 3rd 90: ART optimization

- Aggressive transition to Dolutegravir-containing fixed dose combinations
- TLD for the following populations:
  - 1st-line ART initiators (and re-initiators)
  - ART continuations with viral suppression (or unknown VL)
  - First-line ART failures
  - 2nd-line ART continuations
  - 2nd-line ART failures

Near universal use of a fixed dose combination with greatest tolerability and high barrier to development of resistance will achieve maximum population levels of viral suppression

South Africa HIV Burden



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South Africa HIV Overview

- **South Africa has the largest HIV epidemic in the world**
- **4.3 million on ART in public sector (June)**
- **Goal to add TWO MILLION PLHIV on ART by December 2020**
- **High incidence (UNAIDS est. 270,000 new infections/yr.) especially in young women ages 20-24**

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"This year, we will take the next critical steps to eliminate HIV from our midst.

By scaling up our testing and treating campaign, we will initiate an **additional two million people on antiretroviral treatment by December 2020**."

President Cyril Ramaphosa, State of the Nation Address, February 16, 2018

South Africa ART Program Goals

Additional Two Million PLHIV on ART to reach UNAIDS 90-90-90 Targets

1) **1st 90: Knowledge of status among PLHIV**
   - Strategies: targeted HIV testing; index case finding; self-screening; community outreach; community healthcare workers; launch of National Wellness Campaign; reach men and AGYW
2) **2nd 90: ART**
   - Strategies: active and effective linkage to care; improve adherence and retention; strengthen facility services; same-day ART initiation; expansion of differentiated service delivery; and alternate drug delivery
3) **3rd 90: Viral load suppression**
   - Strategies: viral load testing dashboards and strengthened information reporting and use; **introduction of dolutegravir-based regimens**

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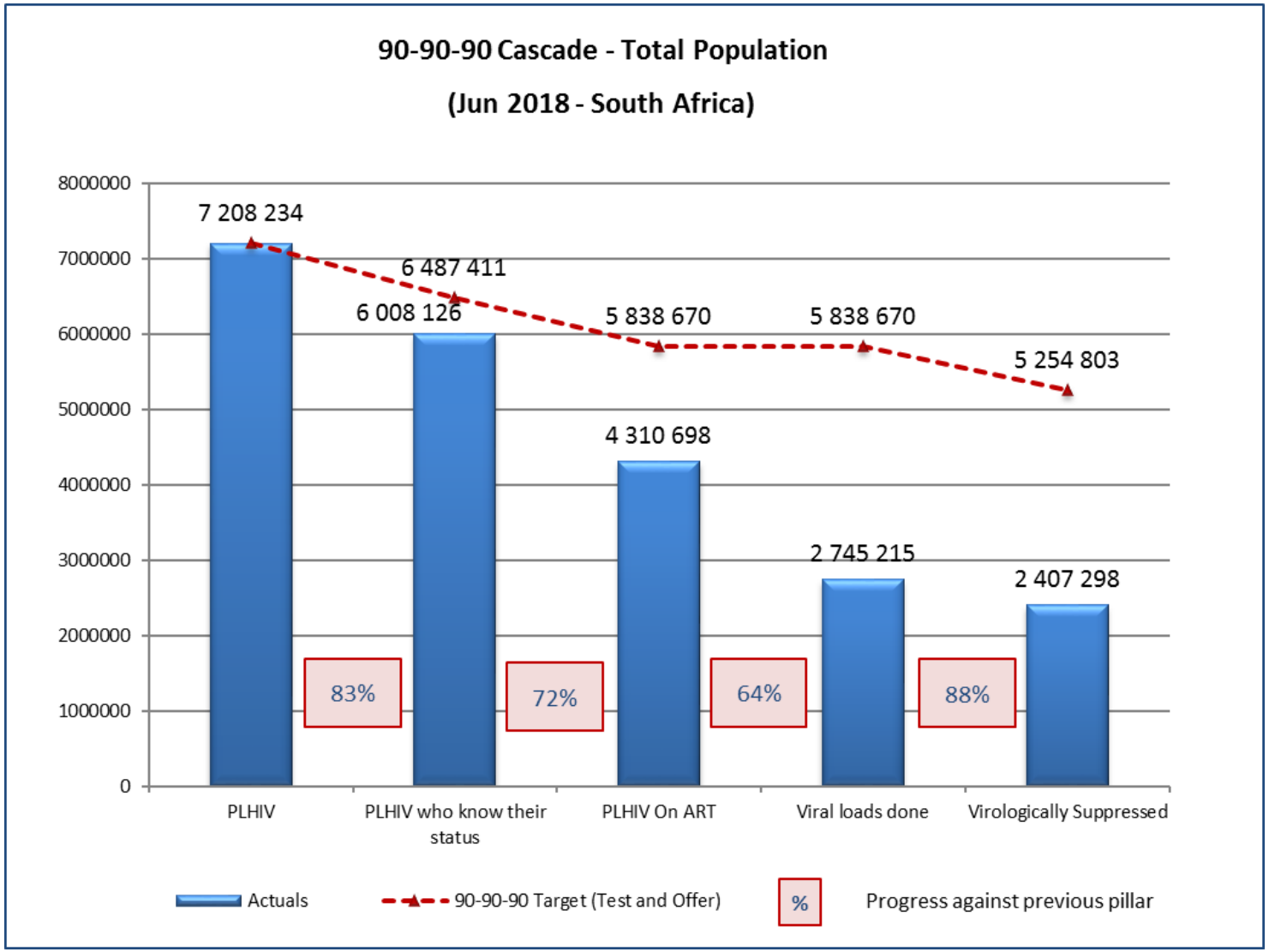
TLD

- **TLD is important for reaching the 3rd 90**
  - HE2RO: We found that introduction of DTG would greatly reduce new HIV infections, reduce AIDS deaths, and **would be by far the most effective intervention in increasing progress towards the third UNAIDS 90-90-90 target**

South Africa 90-90-90 Cascade



Source: South Africa National Department of Health

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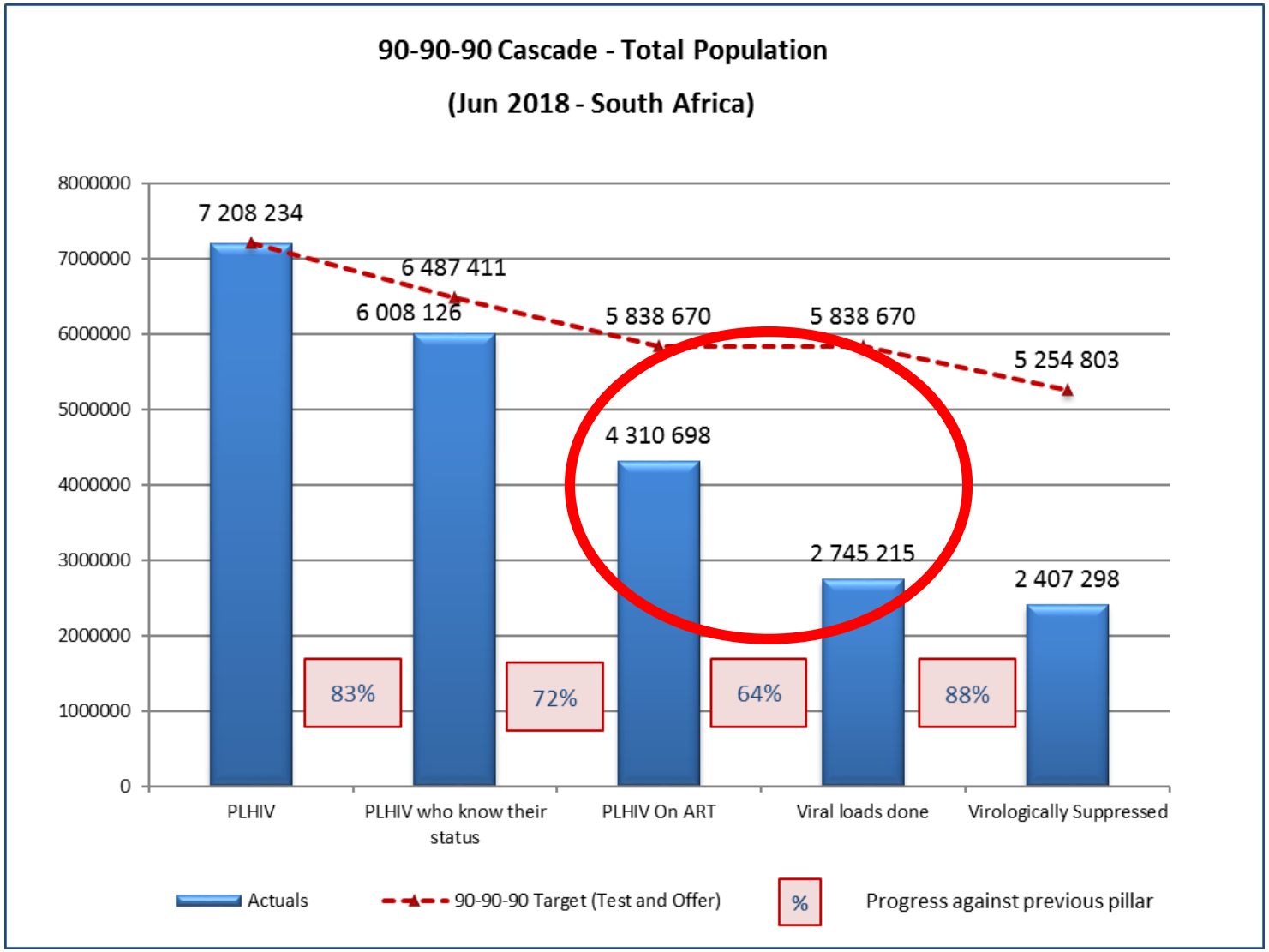

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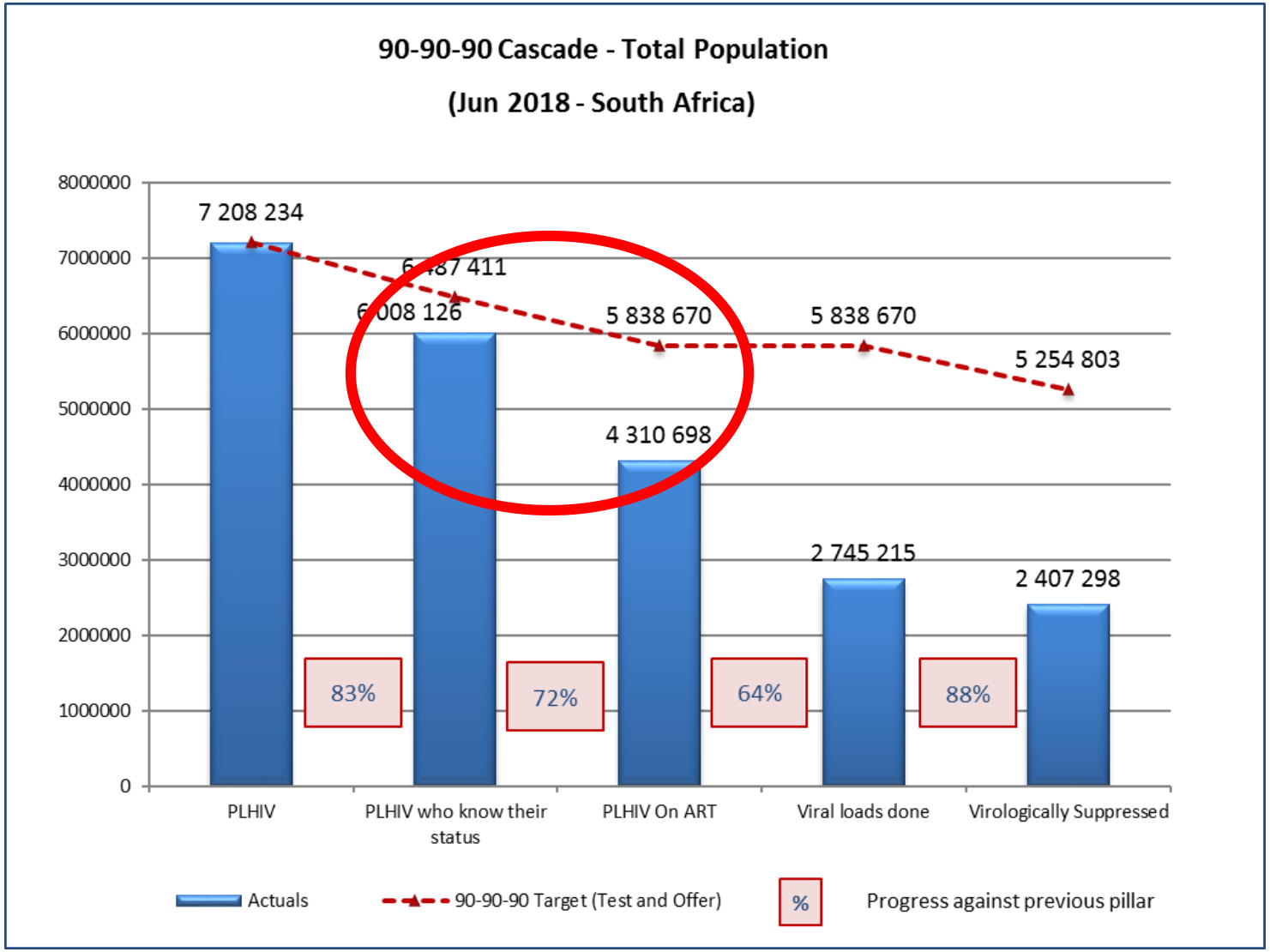

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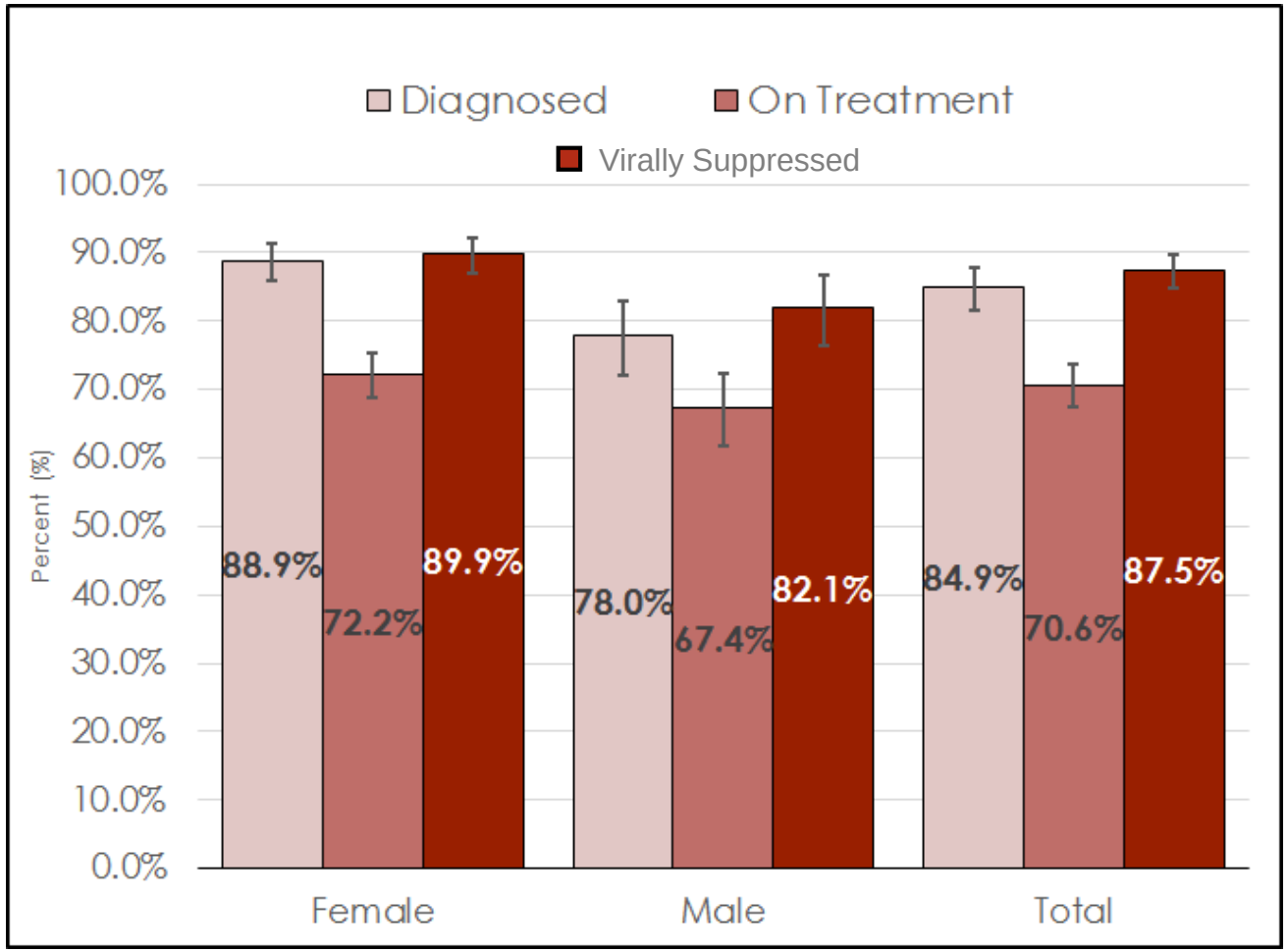
HSRC Survey (2017): 90-90-90 Progress by Sex, 15 to 64 Years of Age



HSRC Human Sciences Research Council

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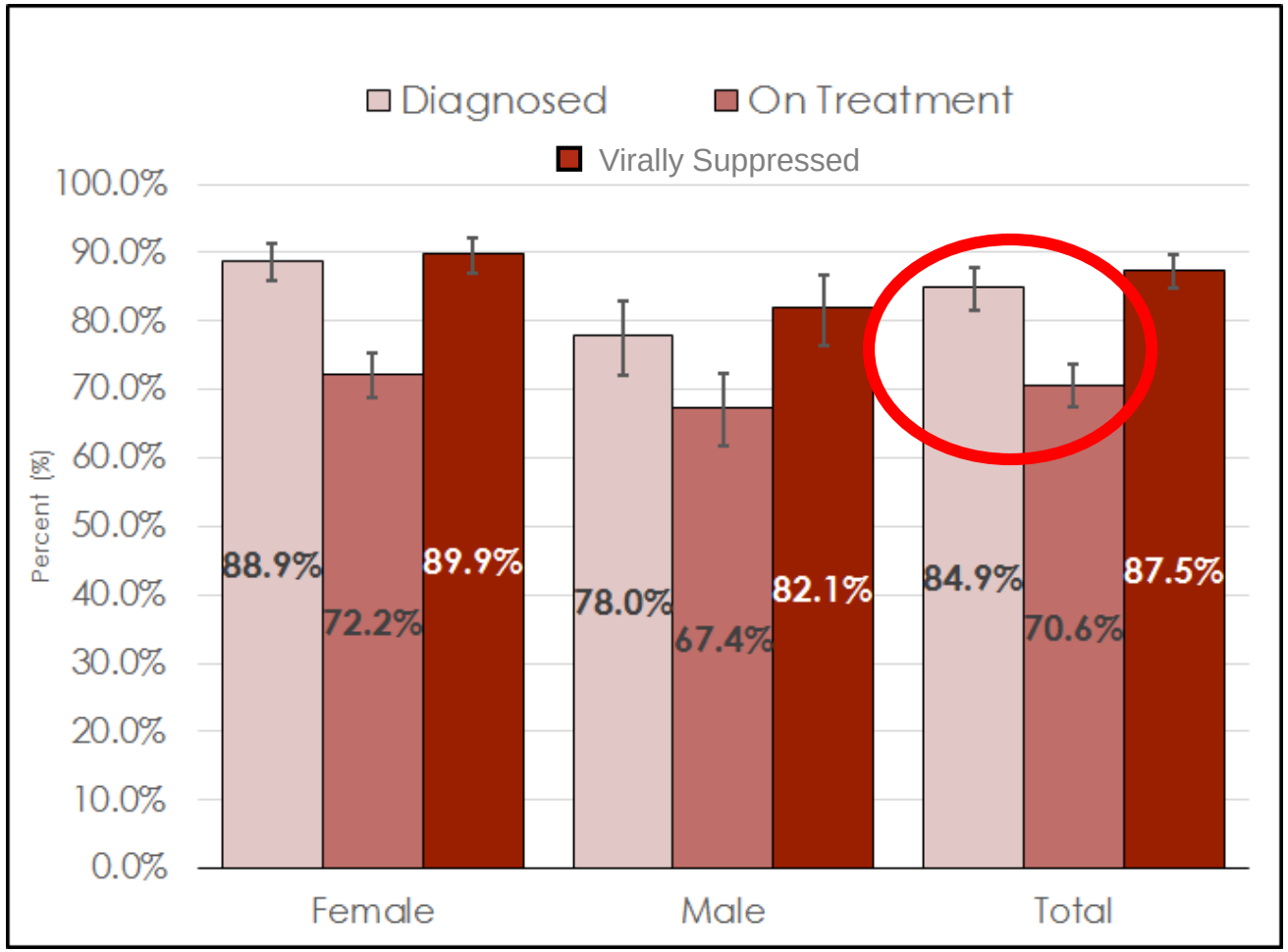

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HSRC Survey (2017)

District	PLHIV (2017)	Category	Dx %	Dx 95%CI	ART %	ART 95%CI	VS %	VS 95 CI
gp City of Johannesburg Metropolitan Municipality	663,657	ScaleUp Sat	81.3	[62.4,91.9]	67.2	[49.5,81.1]	88.8	[76.4,95.1]
kz eThekwini Metropolitan Municipality	639,135	ScaleUp Sat	96.7	[93.4,98.4]	76.6	[65.4,84.9]	77.4	[66.3,85.6]
gp Ekurhuleni Metropolitan Municipality	526,924	ScaleUp Sat	89	[83.7,92.7]	59.8	[51.0,68.0]	88.9	[78.8,94.5]
gp City of Tshwane Metropolitan Municipality	395,589	ScaleUp Agg	77.4	[47.8,92.8]	55.1	[36.2,72.6]	91.1	[74.2,97.3]
mp Ehlanzeni District Municipality	319,984	ScaleUp Agg	90.6	[85.7,93.9]	73.2	[66.4,79.1]	84.9	[78.5,89.6]
wc City of Cape Town Metropolitan Municipality	315,212	ScaleUp Agg	87.8	[79.5,93.1]	76.2	[68.6,82.5]	92.4	[78.4,97.6]
nw Bojanala Platinum District Municipality	226,122	ScaleUp Agg	87.7	[80.0,92.7]	69.5	[60.9,76.8]	86.2	[78.0,91.7]
mp Gert Sibande District Municipality	204,844	ScaleUp Agg	81.2	[74.2,86.7]	81.2	[73.5,87.1]	77	[66.9,84.7]
ec Oliver Tambo District Municipality	183,957	ScaleUp Agg	94.1	[89.8,96.7]	69	[60.0,76.8]	82.5	[71.3,89.9]
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Variation in 90 90 90 progress across districts. Data indicates general drop-off in 2nd 90.

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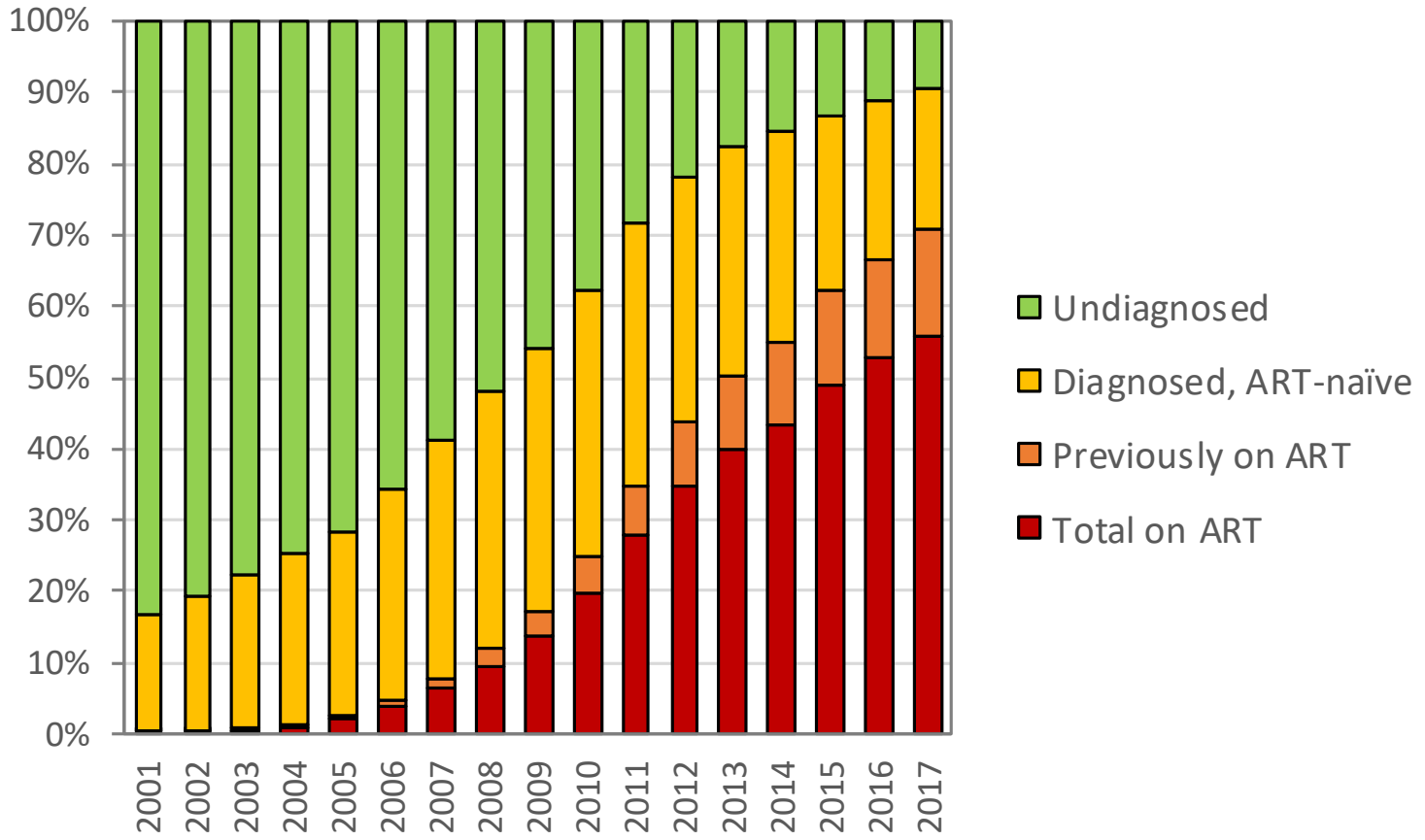
% of HIV+ adults at different levels of engagement in HIV care

Thembisa version 4.1



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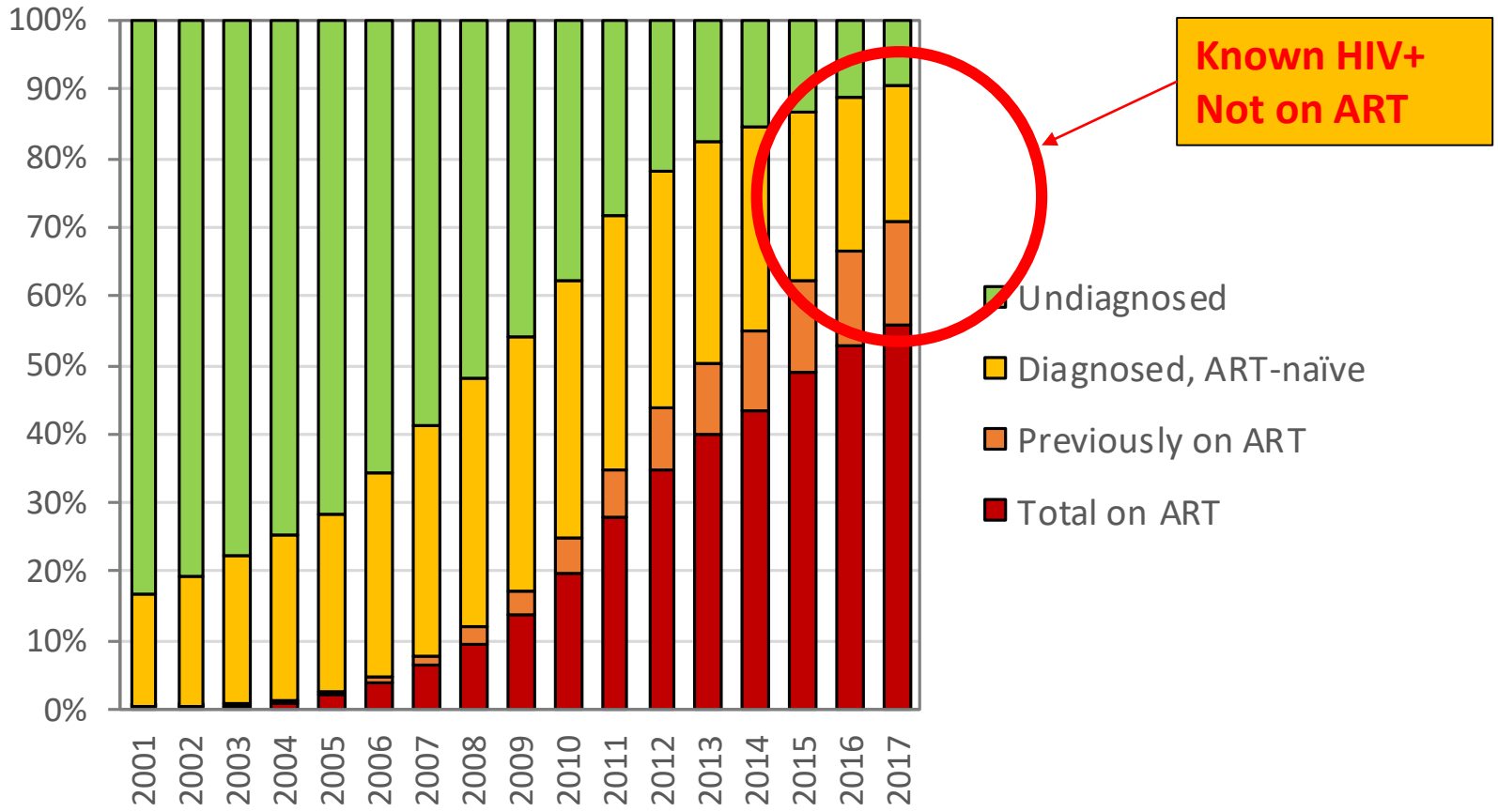
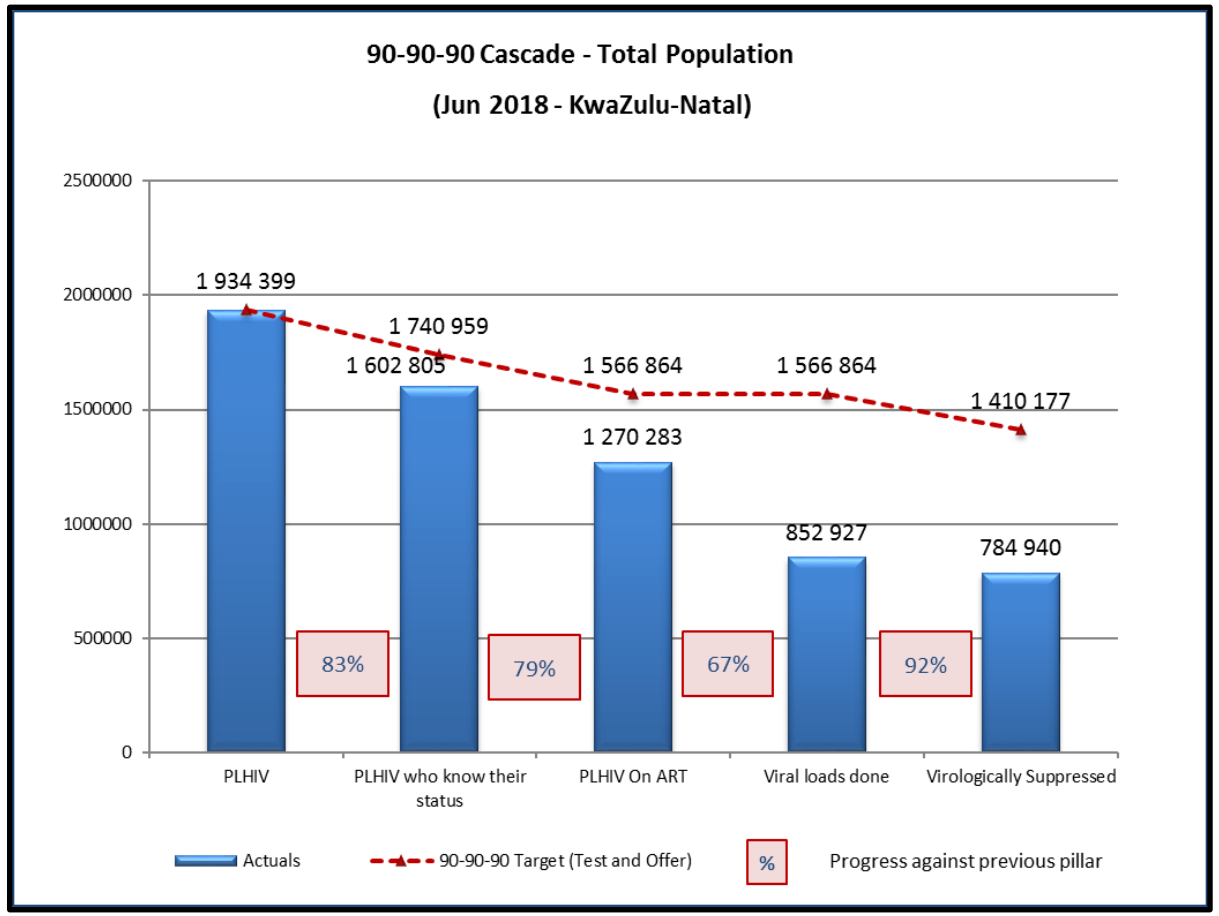
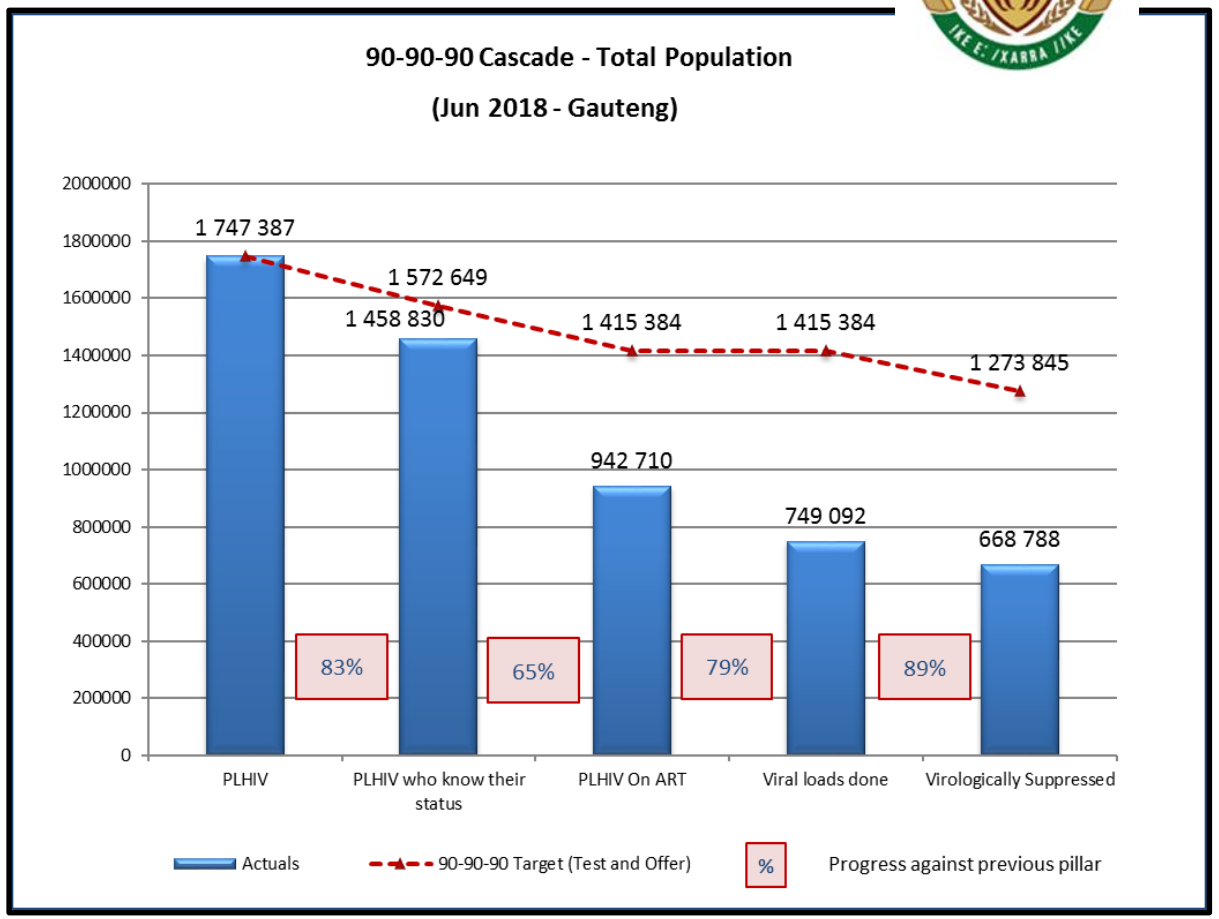


Cascades for Provinces





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Source: South Africa National Department of Health

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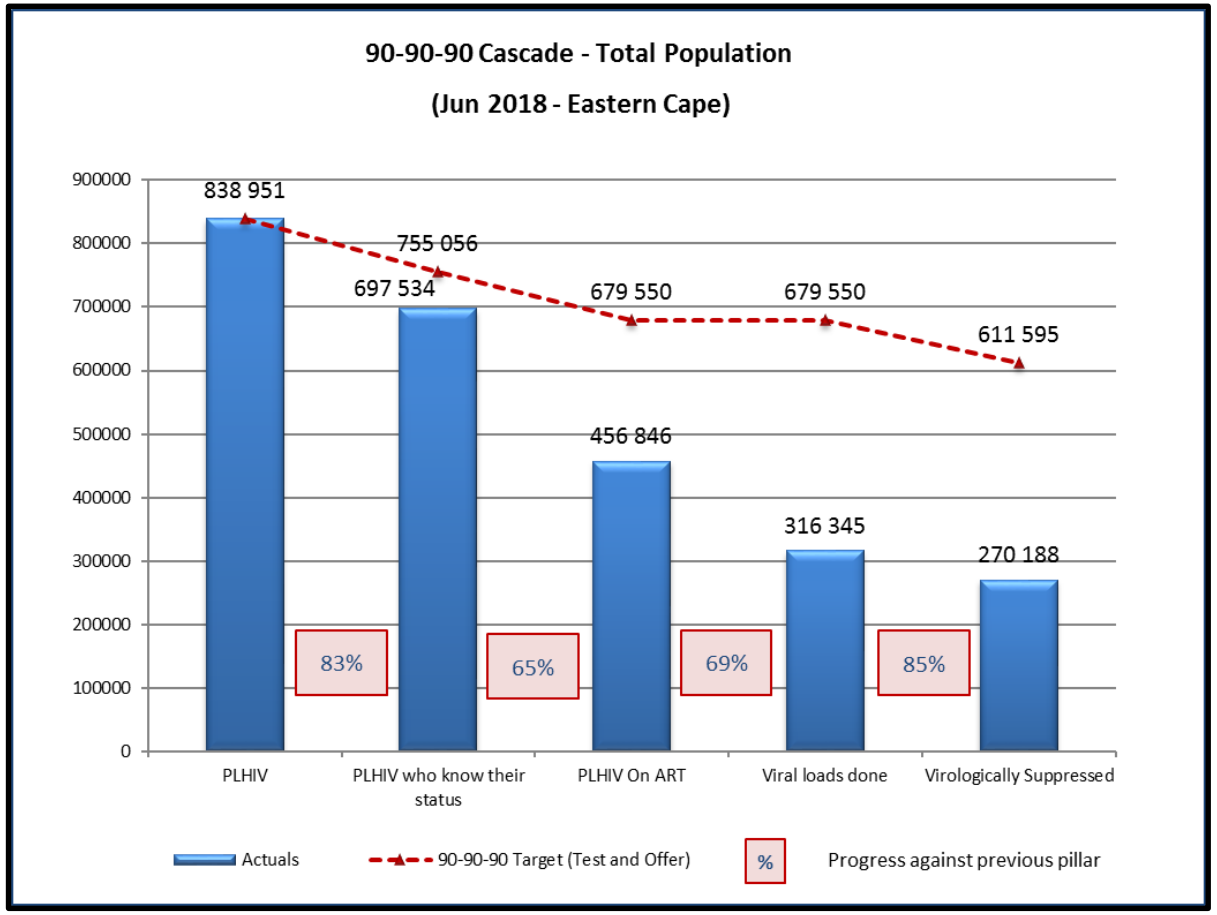
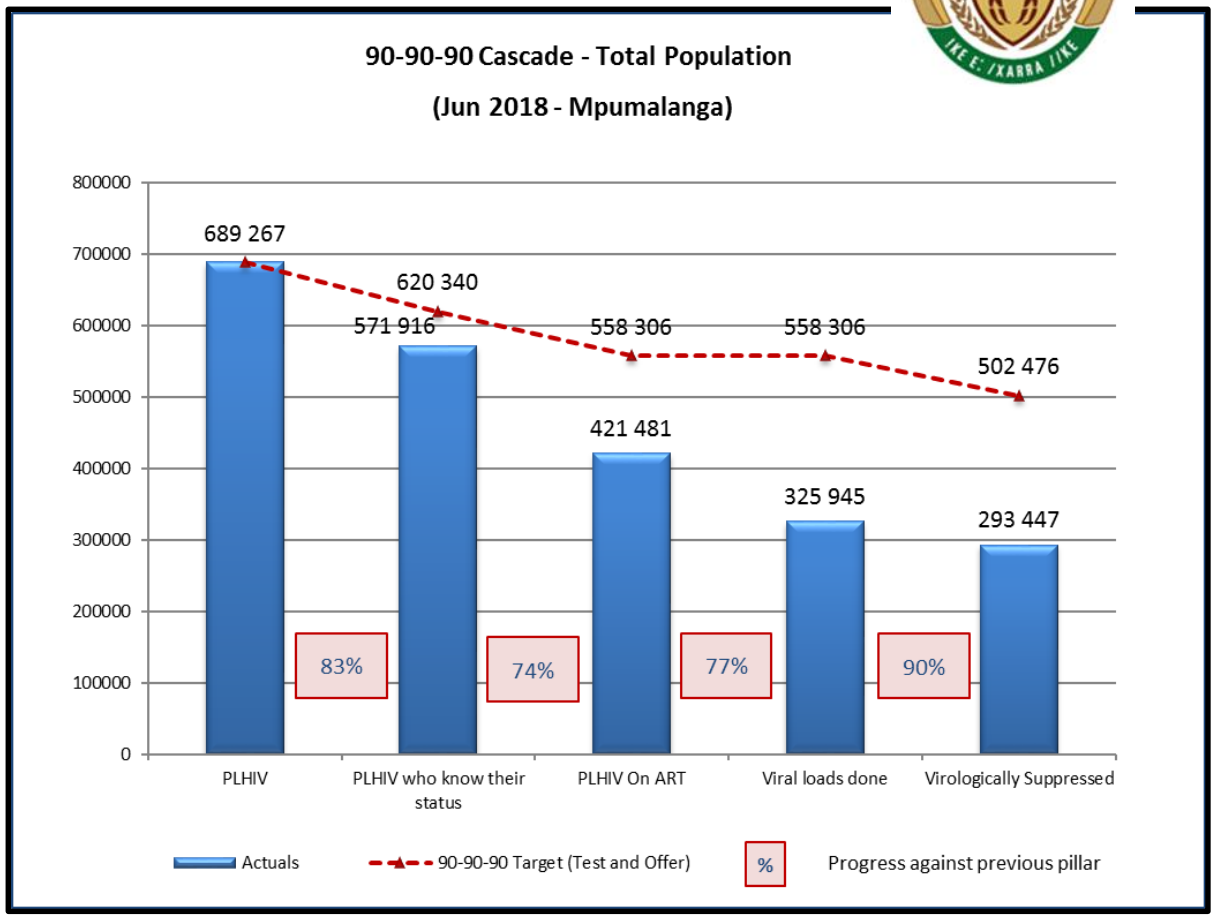
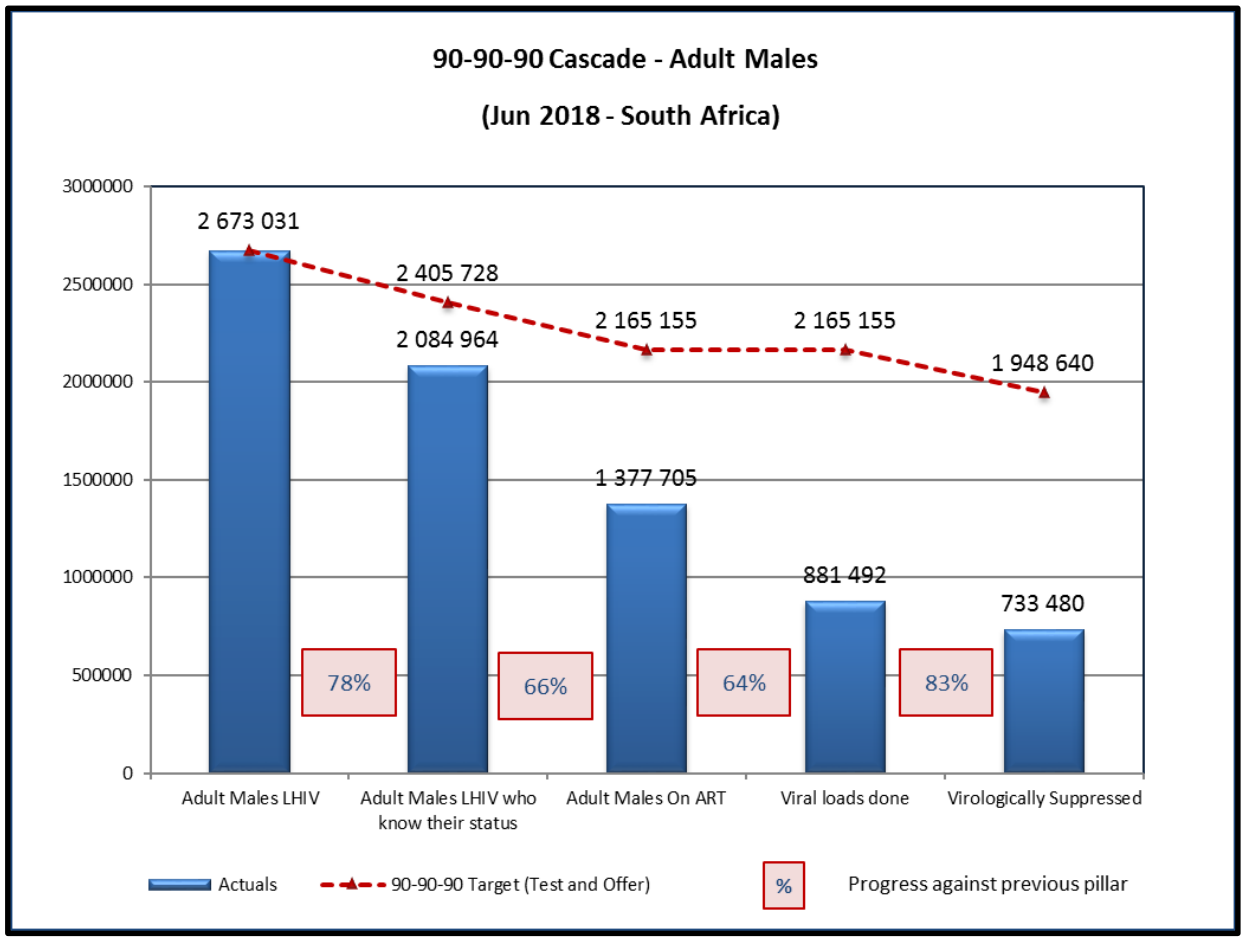
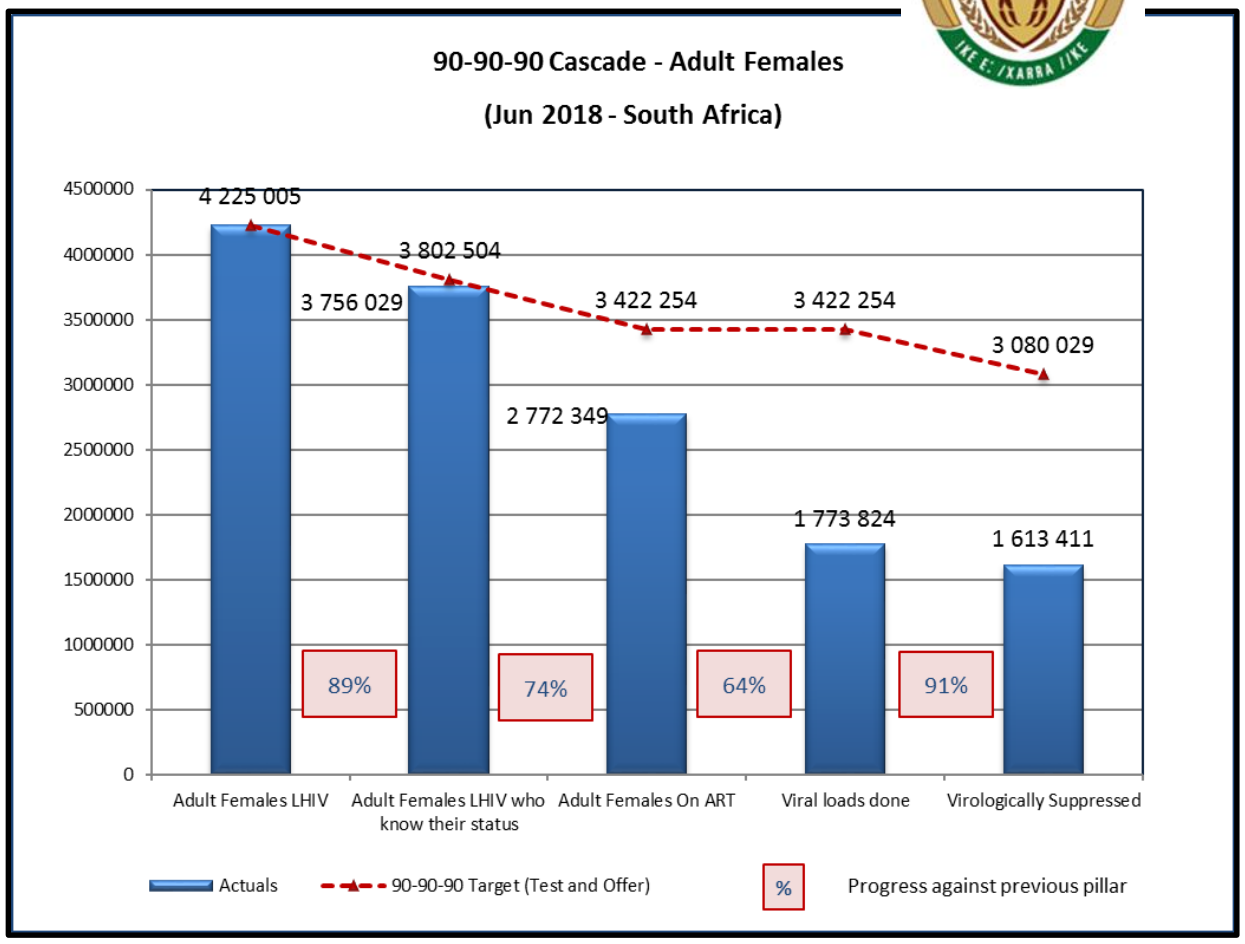




Source: South Africa National Department of Health

Cascades for Men, Women





Source: South Africa National Department of Health

South Africa HIV Treatment Program Priorities

- Improve targeted HIV testing
  - **ALWAYS** link to care
  - Same day ART initiation
- Strengthen adherence and retention
- Differentiated care
- Linkage with communities and community organizations
- Improve data for decision-making; Unique IDs
- Focus on target populations (e.g., men 25-34; AGYW 15-24)

SOUTH AFRICAN NATIONAL AIDS COUNCIL
OUR ACTIONS COUNT

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Focus on the HIV+ Client

- Client-friendly services
- Alternate drug delivery
- Adherence clubs / support groups
- Patient education
- Demand creation
- Integrate HIV services with other health services
- Recognize mental health issues
- Provide the **Best Available Medicines**

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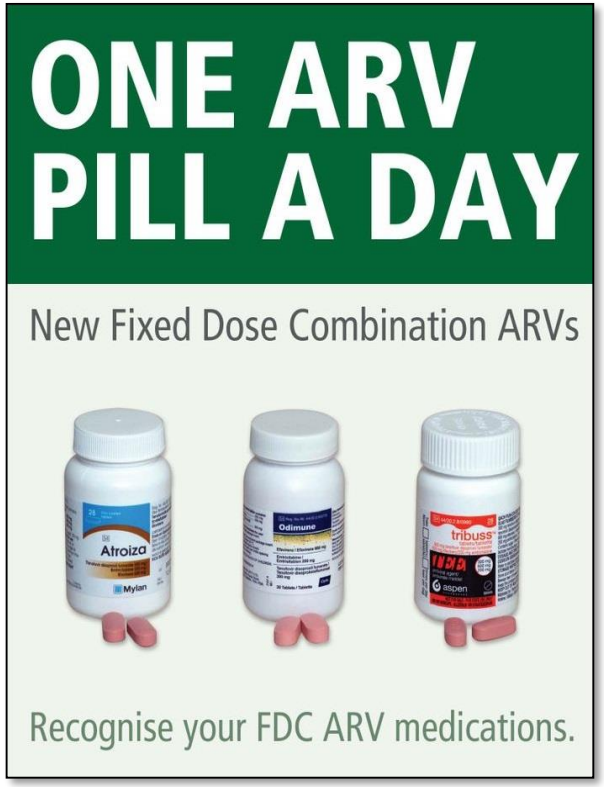
ARV Program in South Africa

- CCMDD expansion and other models of drug delivery
- Introduce dolutegravir as 1st line regimen
  - Next steps:
  - ➢ SA gov't tender awarded (expected December)
  - ➢ Dolutegravir/TLD guidelines
  - ➢ Dolutegravir roll-out support: health worker training, patient information



Global Dolutegravir Use

- Dolutegravir-based regimens widely used as first-line ART in U.S., U.K., Europe
- Dolutegravir-based regimens introduced in Botswana (2016), Brazil and Kenya (2017), and many countries currently transitioning

BOX 1. RECOMMENDATIONS: FIRST-LINE ARV DRUG REGIMENS

1. NEW A DTG based regimen may be recommended as a preferred first-line regimen for people living with HIV initiating ART *(conditional recommendation)*

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Dolutegravir: Safe and Effective (pending NTD signal)

- Superior efficacy, tolerability, durability
  - ❖ Faster viral suppression
  - ❖ Fewer side effects
  - ❖ Substantial resistance barrier ➡ Less use of 2d Line regimens
- Smaller tablet size
- *TLD important for patients who are early in their progression of HIV disease and still feeling well*

Lancet June 5, 2018

Viewpoint

Dolutegravir for first-line antiretroviral therapy in low-income and middle-income countries: uncertainties and opportunities for implementation and research

WHO Review

Safety and Efficacy of DTG and EFV600 in 1st line ART
(summary 2018 WHO Sys Review & NMA)

major outcomes	DTG vs EFV_{600}	QUALITY OF EVIDENCE
Viral suppression (96 weeks)	DTG better	moderate
Treatment discontinuation	DTG better	high
CD4 recovery (96 weeks)	DTG better	moderate
Mortality	comparable	low
AIDS progression	comparable	low
SAE	comparable	low

Reference: Steve Kanters, For WHO ARV GDG, 16-18 May 2018

WHO, 2018

80-90 (per 1000) excess cases of non-viral suppression at 96 weeks predicted with EFV600

TLD: Cost Saving and Better Health Outcomes

Conclusions

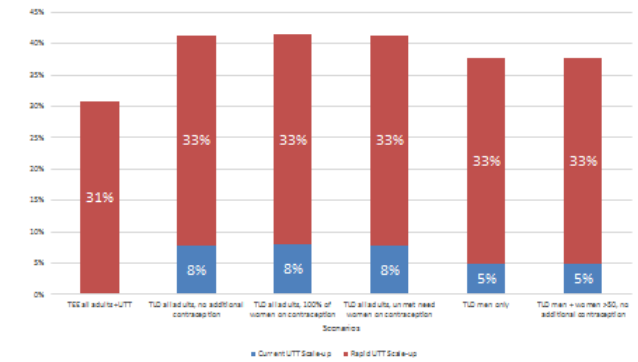
Switching adults from **TEE** to **TLD** and fully implementing **UTT** results in the following:

- A reduction of at least 5% in new HIV infections, and 1-2% in AIDS deaths
- A reduction in the cost of South Africa's HIV programme of between 3-9% due to *three factors*:
  - Lower drug cost per patient year
  - Less need for second line
  - Less new infections

Health Economics and Epidemiology Research Office

HE²RO

Key findings: New infections averted



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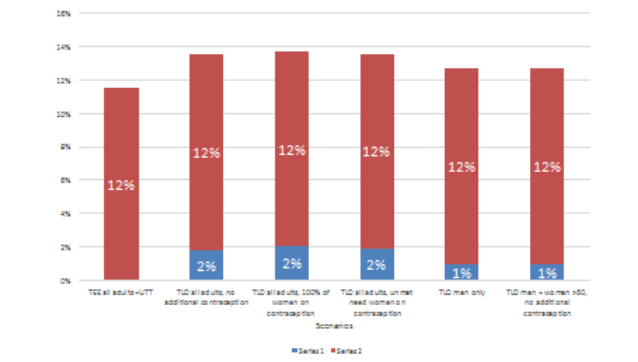
Key findings: AIDS deaths averted



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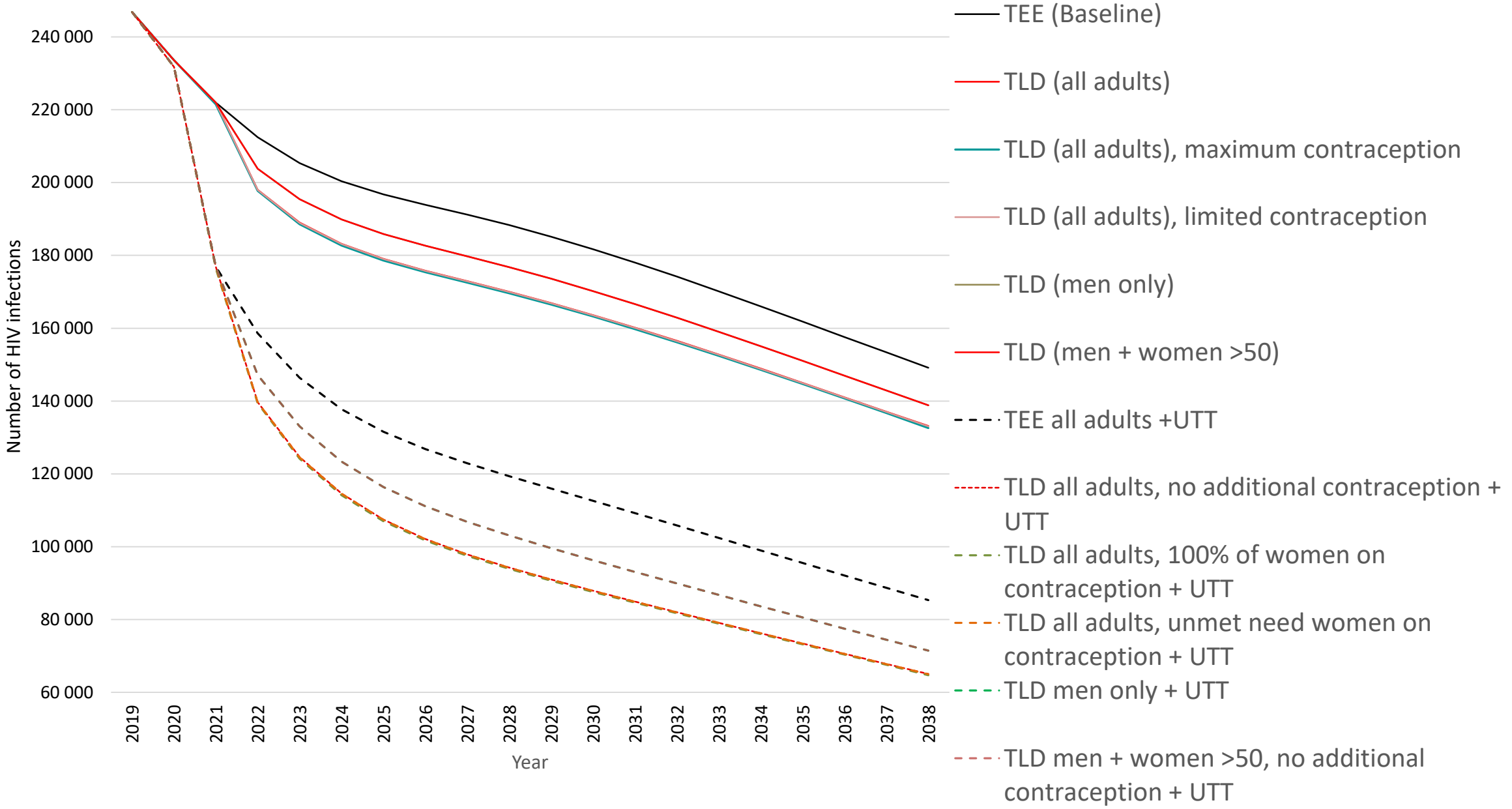
Impact on new HIV infections (2019-38)



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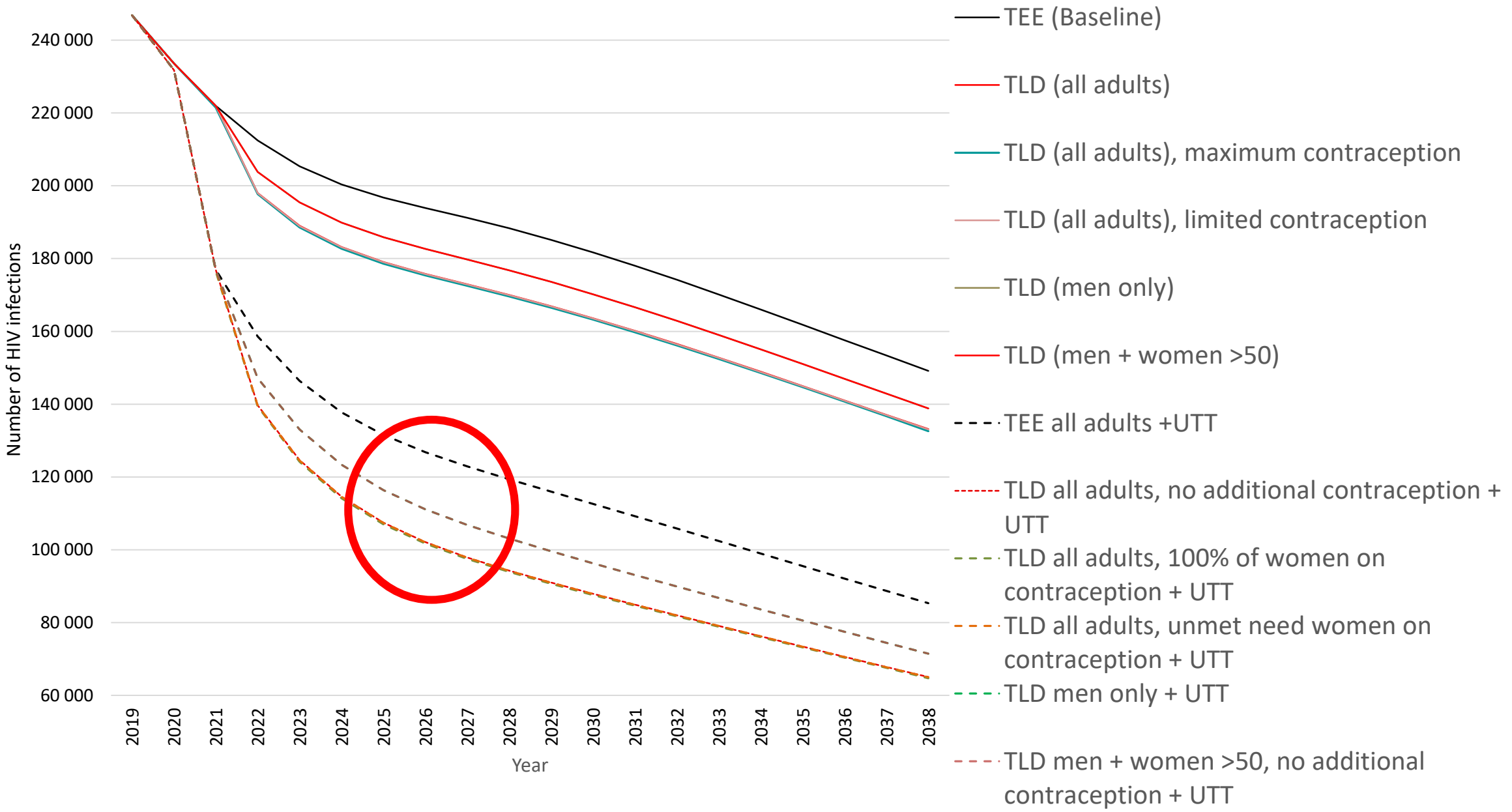


Conception and DTG

- Potential increased risk of neural tube defects in infants born to women who were taking DTG at time of conception.

- WHO: DTG has been found to be effective for pregnant women and has also been shown to be found in breast milk, resulting in significant plasma concentration in infants and thus a potential important drug to reduce the mother-to-child transmission of HIV infection.
  - However, an ongoing observational study in Botswana recently identified a signal of potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception.

Expected Additional Data for DTG-Exposed Pregnancies

Attempting to ascertain outcomes for cohorts of women conceiving on DTG; full ascertainment key for unbiased results.

- Brazil: 490 DTG-exposed pregnancies; results expected at R4P meeting.
- Kenya: 800-1200 DTG-exposed pregnancies; CDC supporting birth surveillance at selected sites to capture outcomes.
- USA: CDC domestic HIV and BD groups working to link HIV surveillance and BD surveillance to identify ART exposure at conception and in early pregnancy and assess outcomes. Working in 15 states; expect results late in 2018 or early 2019.
- Limited number of pregnancies on UNITAID-supported trials in Cameroon, RSA, Uganda, Nigeria, and others.
- Ongoing BD surveillance in Uganda, Malawi.

Modeling Projections

- Two academic groups have modelled outcomes in women and children with implementation of DTG vs EFV-based ART in women of childbearing potential (Dugdale 2018; Phillips 2018).

- Both models indicate that providing DTG-based ART for all HIV-positive women, including those of childbearing potential, resulted in lower mortality than providing them with EFV-based ART, and that the reduction in mortality significantly exceeded the potential increase in neonatal mortality should the increased risk of an NTD be confirmed.

IAS Forum Statement

Forum on the risks of preconception dolutegravir exposure

- ART discontinuation is the least desirable outcome.
- "Women should be counseled about potential risks of NTDs with DTG use at conception and provided with contraceptives as desired. However, after appropriate risk/benefit counseling, use of contraception should not be a requirement for women to have access to DTG-based regimens."

http://www.iasociety.org/Portals/0/Files/DTG_FAQ.pdf

Civil Society Requests Dolutegravir: Afrocab Community Meeting

AfroCAB organized a meeting of **39 women living with HIV** representing **18 countries** in Kigali, Rwanda on July 13 and 14 to **discuss** the potential NTD safety signal and **develop a joint position on behalf of women** for access to optimal HIV treatment and prevention.


Botswana


Democratic Republic of Congo


Malawi


Rwanda


Swaziland


Uganda


Burundi


Ivory Coast


Mozambique


Senegal


Tanzania


Zambia


Cameroon


Kenya


Nigeria


South Africa


Togo


Zimbabwe

Topline Message

Unanimous decision based on the data currently available that DTG's benefits – reduced side effects, improved efficacy, and a high barrier to resistance – outweigh its potential risks.

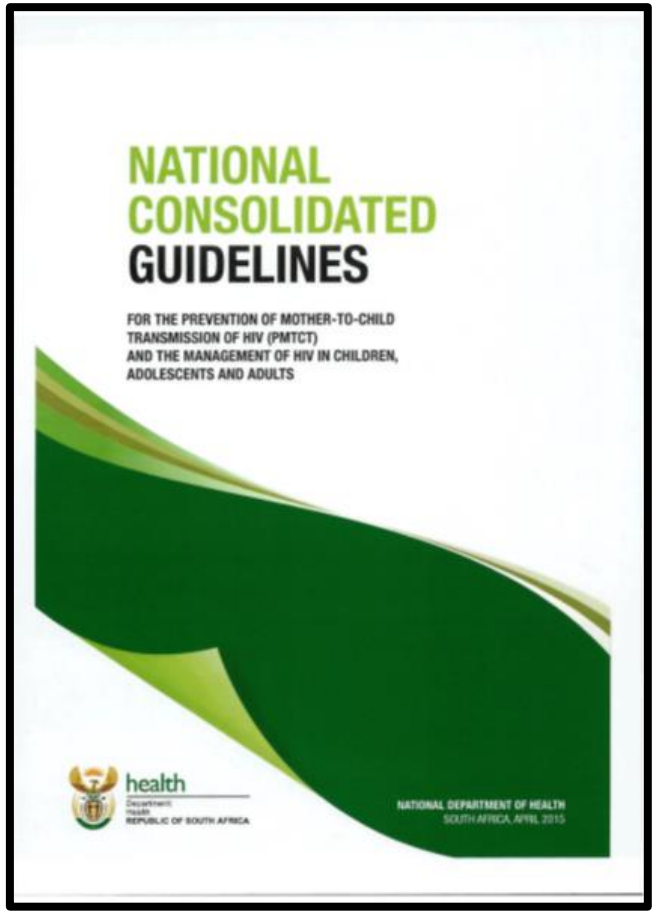
Concluded that blanket exclusions that deny women equitable access to this optimal HIV treatment are not warranted or justified.

Recommendations – Policymakers, Stakeholders & Governments

1. Do not deny us, WLHIV, access to DTG regardless of our childbearing potential.
2. Strengthen HIV and SRH services to ensure access to DTG together with acceptable, available, affordable and accessible contraception.
3. Do not force WLHIV to take a particular medication.
4. Involve us, the WLHIV, in local, national, and global discussions and decisions regarding HIV treatment options.
5. Include us in research studies and clinical trials.
6. Better integrate HIV, sexual and reproductive health (SRH), and other treatment support services.
7. Clearly communicate the short and long-term side effects of ARVs to enable us to make informed decisions.
8. Strengthen surveillance systems in order to detect any and all potential risk and harm due to use of ARVs.

South Africa Clinical Guidelines in Development

- South Africa to update clinical guidelines, including addressing TLD for women of childbearing potential
- Expected in December



TLD Roll-Out Next Steps

- TLD registrations with SAHPRA
  - Post-marketing pharmacovigilance for TLD
- ARV tender
  - Includes options for full or partial transition to TLD
- Transition planning for introduction of new regimen
- Health worker training (potential refresher for NIMART nurses)
- Patient information (pamphlets, posters)
  - Ensure patients are informed about risks and benefits

Additional TLD Roll-Out Issues

- TB patients; pediatrics; switch patients; use of dolutegravir in 2d line
- Potential for increased reliance on viral load results to identify adherence issues
- Link TLD roll-out with TB preventive therapy; contraceptive guidelines
- Harmonize ART regimens with private sector; neighboring countries

Conclusions / Dr. Francois Venter

- South Africa is a mature programme – reaping large prevention and morbidity/mortality benefits
- Close to 90-90-90 but key people left behind
- CD4 at initiation rising – but getting complex to interpret
- **DTG introduction is important but complex**
- System failures huge risk – poor linkage, drug stockouts, poor attention to clinical monitoring, M&E dependent on lab
- Attention to drug supply security and adherence vital for epidemic control
- Social context needs loud voices

WITS RHI

PEPFAR

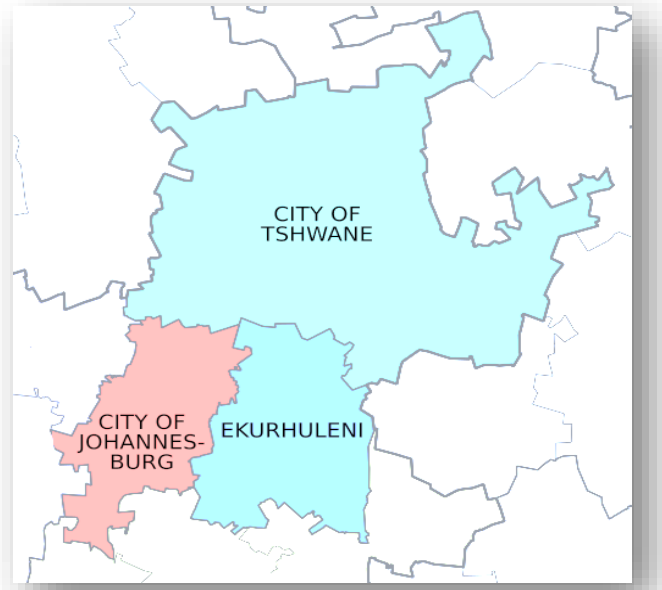
U.S. President's Emergency Plan for AIDS Relief

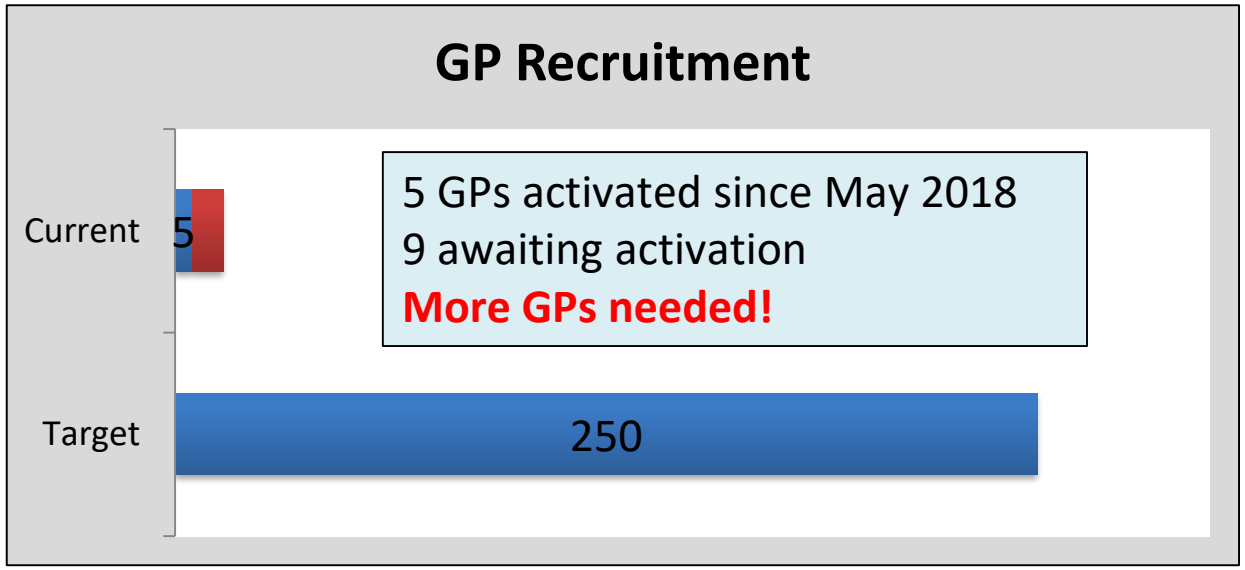
Thank You!

South Africa National Department of Health
Ambassador Deborah Birx/SGAC
Gesine Meyer-Rath/HE2RO
Leigh Johnson/Thembisa
Elliot Raizes
Afrocab
Francois Venter

Invitation to GPs to participate in GP Contracting

- **GP Contracting for Scale-up of ART**
  - **Services:** HIV testing; ART initiation and monitoring until stable and decanted
  - **Locations:** Gauteng (City of Tshwane, Ekurhuleni, City of Johannesburg) KwaZulu-Natal (eThekwini) (pending)
  - **Network managed:** Logistics admin support provided by network provider
  - **Commodities:** Commodities and laboratory services provided by Gov't





Contact Foundation for Professional Development for additional details: SuzanneM@foundation.co.za

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