DTG Global Roll Out
Challenges & Opportunities

XXVII International Workshop on HIV-DR &
Treatment Strategies
October 2018

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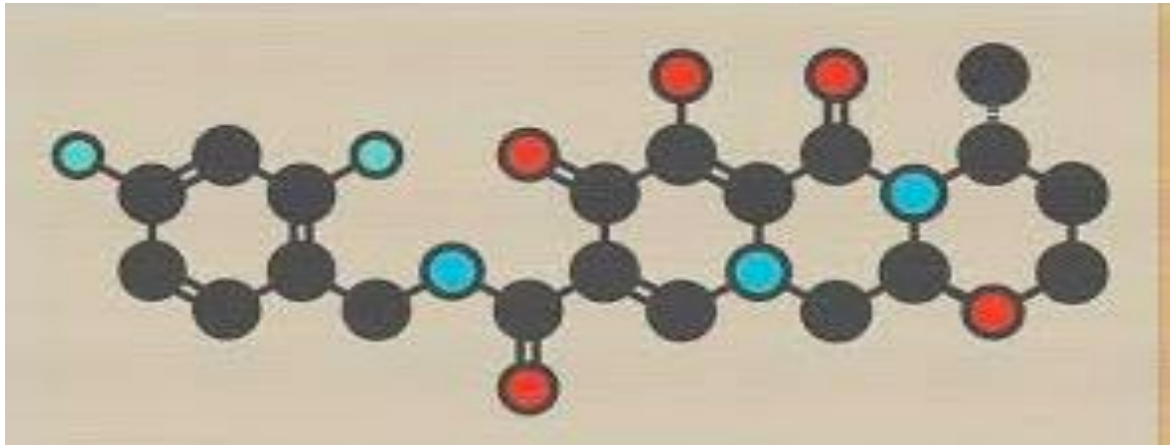
DTG



In the history of developing ART – there has never been drug that was been developed as quickly, had its patents released, been developed and distributed by generic companies and been made available across most LMICs within such a short time.

There are likely more than 1 million people receiving DTG world-wide.

And while this very encouraging news - it also comes with both challenges and opportunities

DTG ROLLOUT - ACTIVISM AT THE CENTER

- Even before DTG was made available in the private sector there were plans being put in place to grant involuntary licenses for the development of generic formulations in LMICs.
- Economic analysis and modelling allowed countries like Botswana to show how ART treatment optimization was highly likely to be cost effective, prevent most HIV infections, save most lives, reduce TB incidence and prevent HIV-Drug Resistance
- PEPFAR was also instrumental in negotiating with generic companies to provide DTG formulations as the lowest costs.

WOMEN RESPOND TO THE NTD SIGNAL

- After the NTD was made known globally, WOMEN ACTIVISTS ACROSS AFRICA came together to discuss the issues and make their voice heard.

- At the International AIDS Society (IAS) in Amsterdam this July these women made sure that global community clearly understood their position on the NTD signal and listened to their recommendations.

- It was because of these African Activists that WHO were able to make their most recommendations.

AFRICAN WOMEN RESPOND

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

WOMEN'S MESSAGE

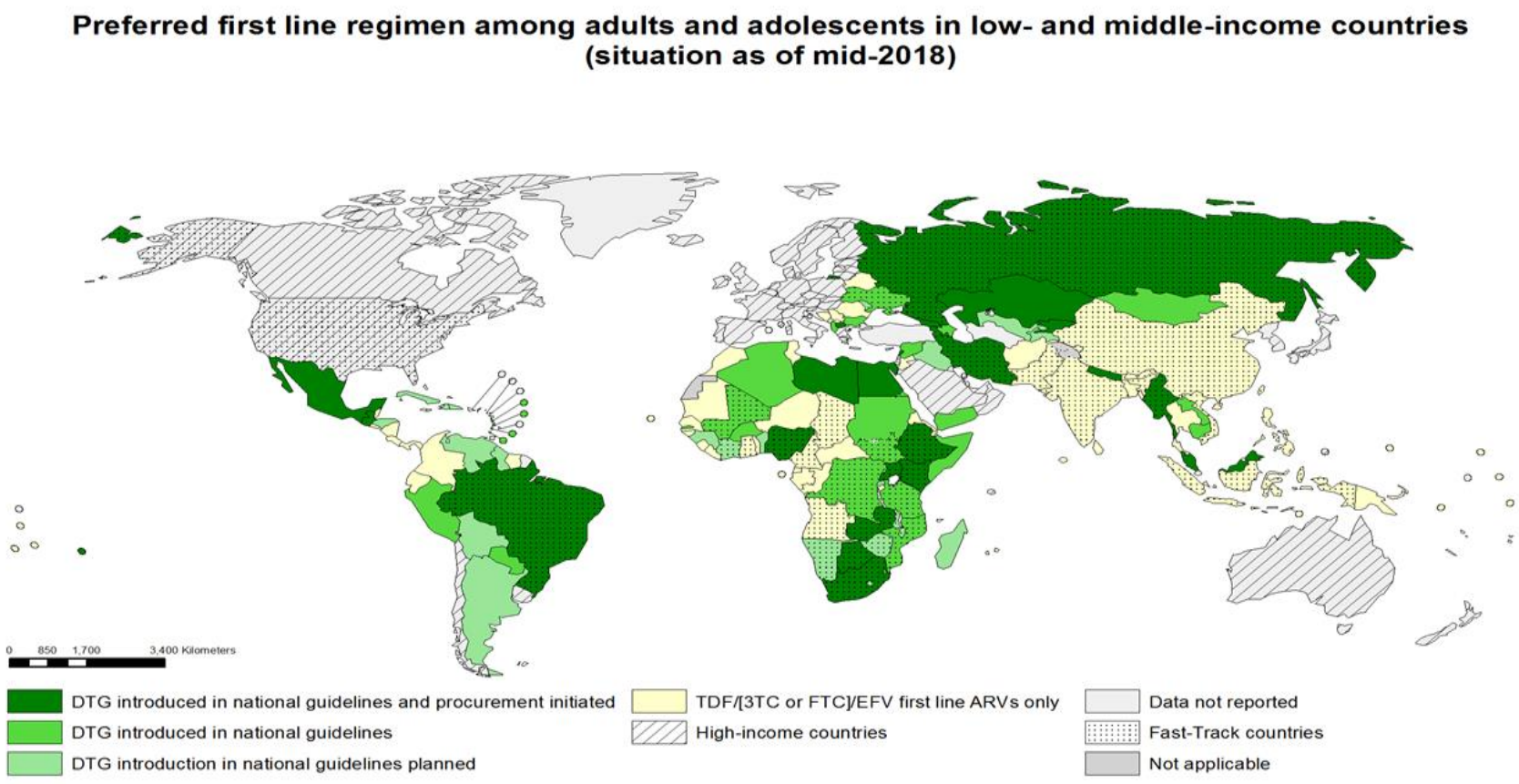
Unanimous decision based on the data currently available that **DTG's benefits** – reduced side effects, improved efficacy, and a high barrier to resistance – **outweigh its potential risks.**

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

Recommendations from African Women to 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.**

Dolutegravir Uptake by Countries
Preferred 1st Line Regimen in LMICs



Safety and Efficacy of DTG and EFV600 in 1st line ART

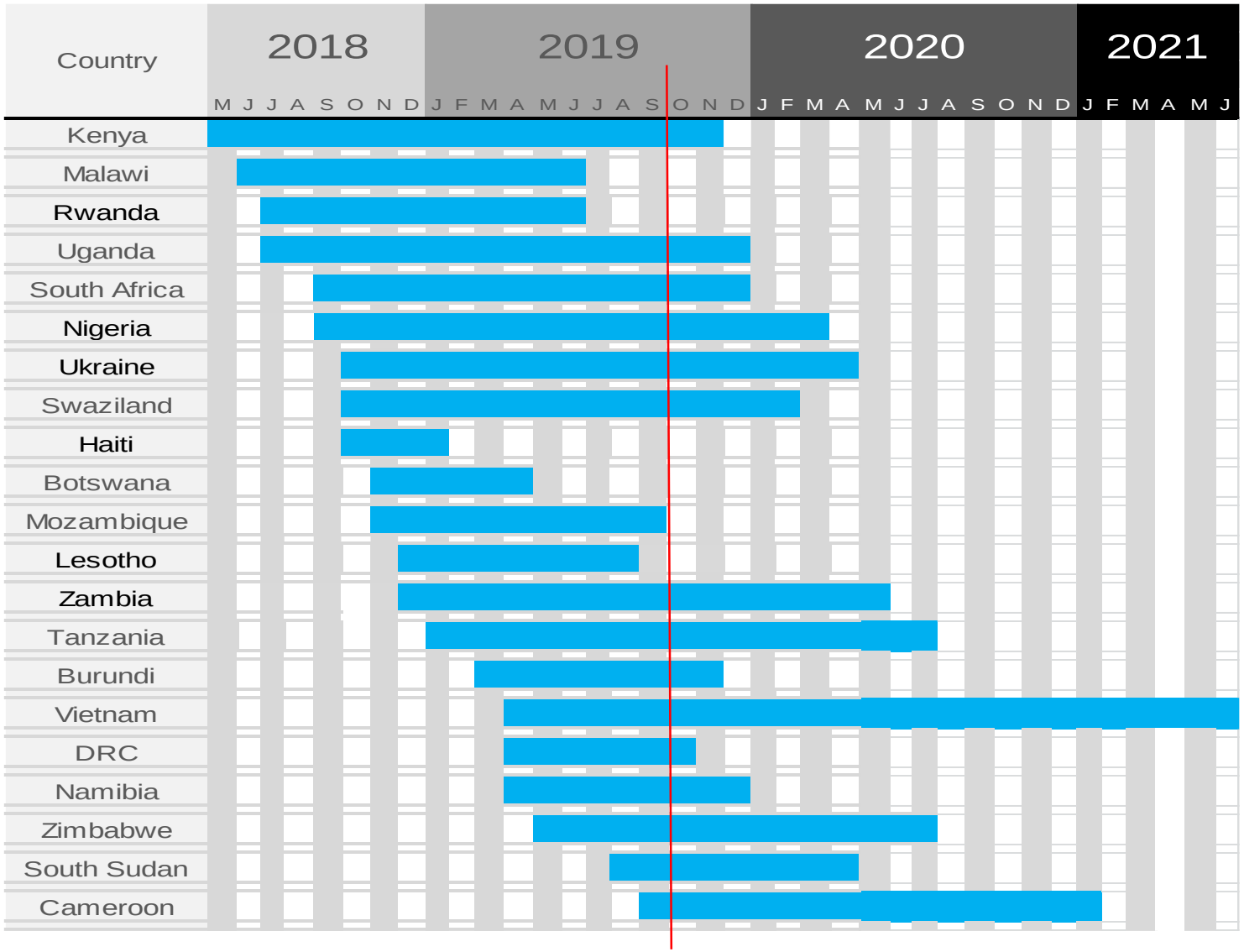
(Summary 2018 WHO Systematic Review & NMA)

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

Timeline for TLD Transition per Country TLD Plans, April, 2018



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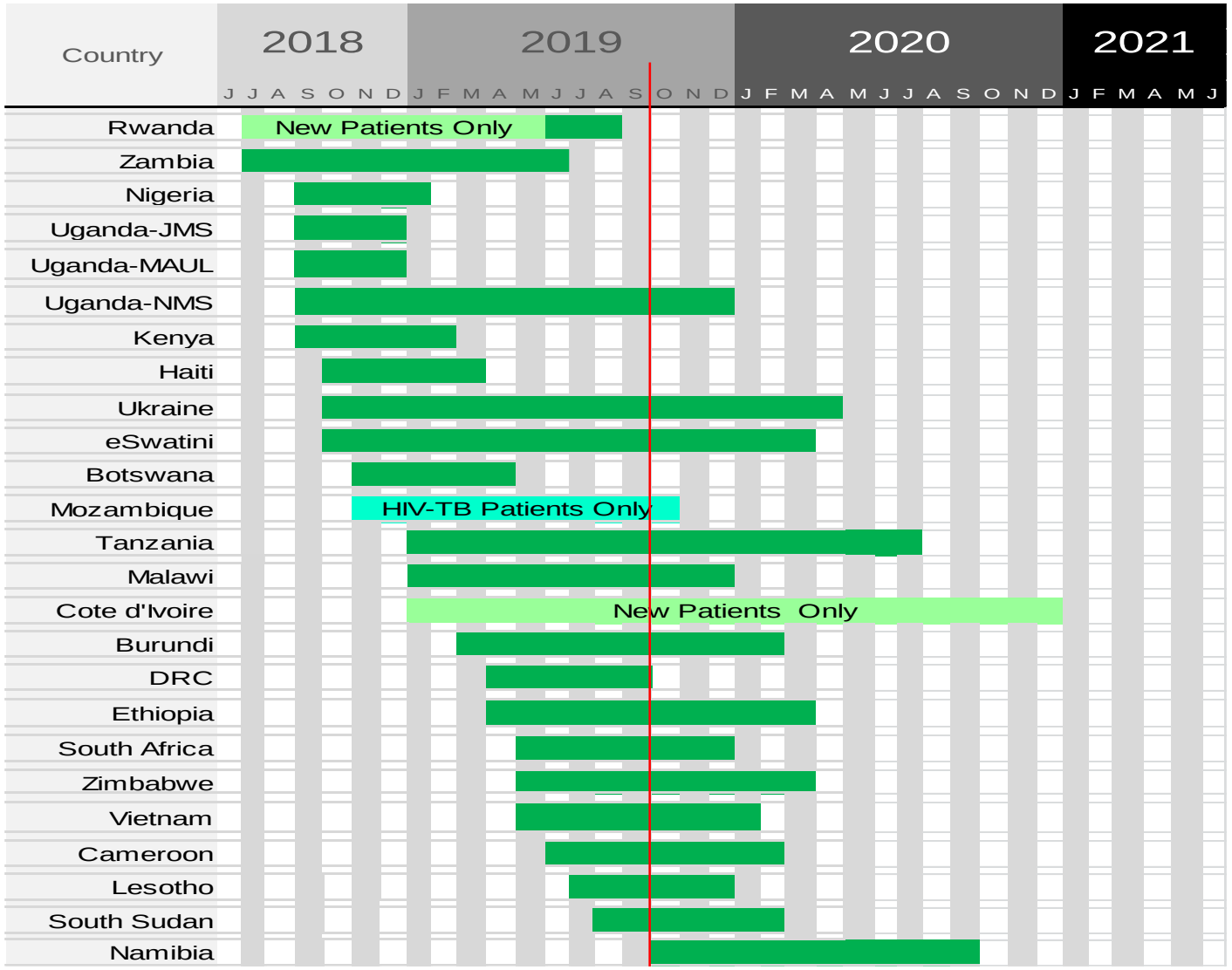
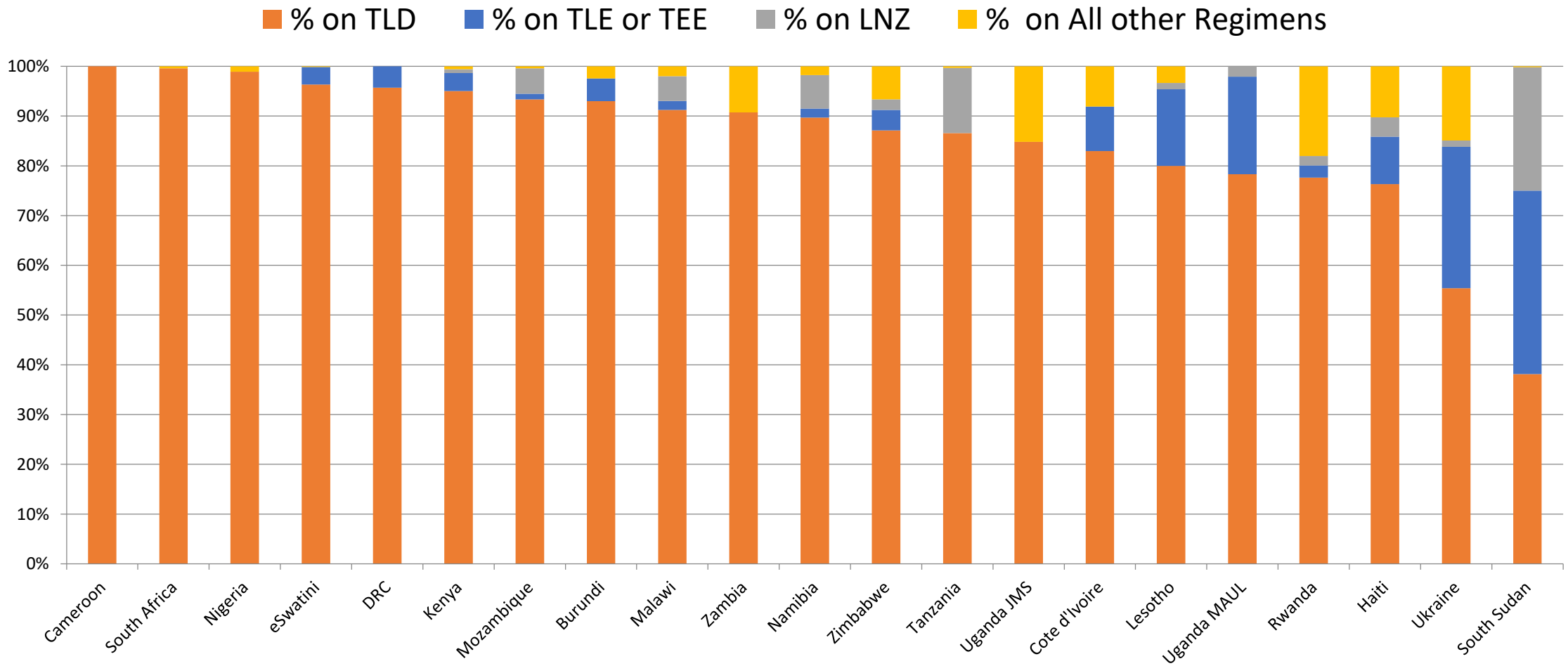
Current Timeline for TLD Transition

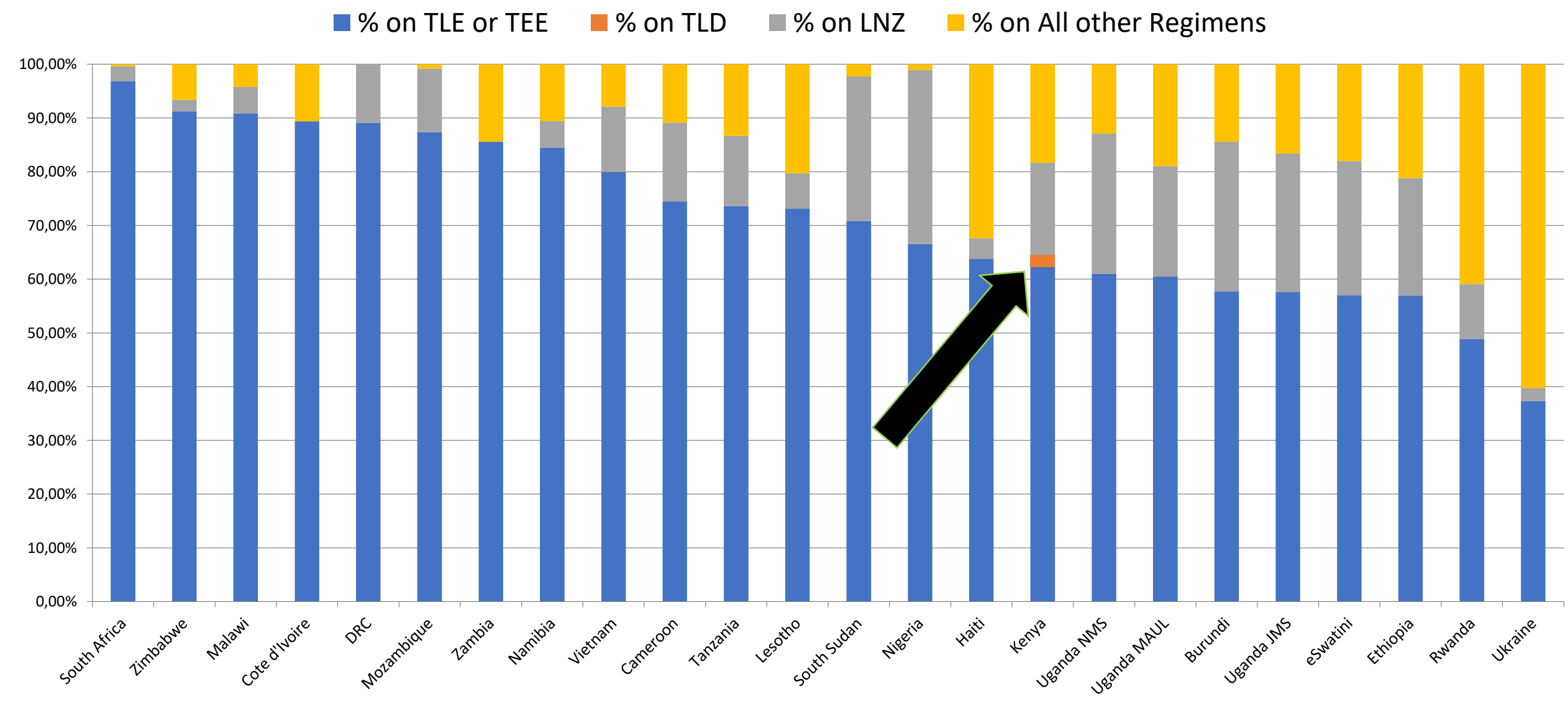


% of Adult ART Patients per Country on ARV Regimens, at the end of the COP18 TLD Transition (pre June, 2018 WHO/PEPFAR Revised Guidance)



- Based on submission of original TLD supply plans for PEPFAR work planning in February, 2018. Table does not include Ethiopia, Vietnam, or Uganda NMS, as supply plans for these programs were not submitted. Botswana was also excluded, given that their supply plan only includes current and future patients on DTG-based regimens.

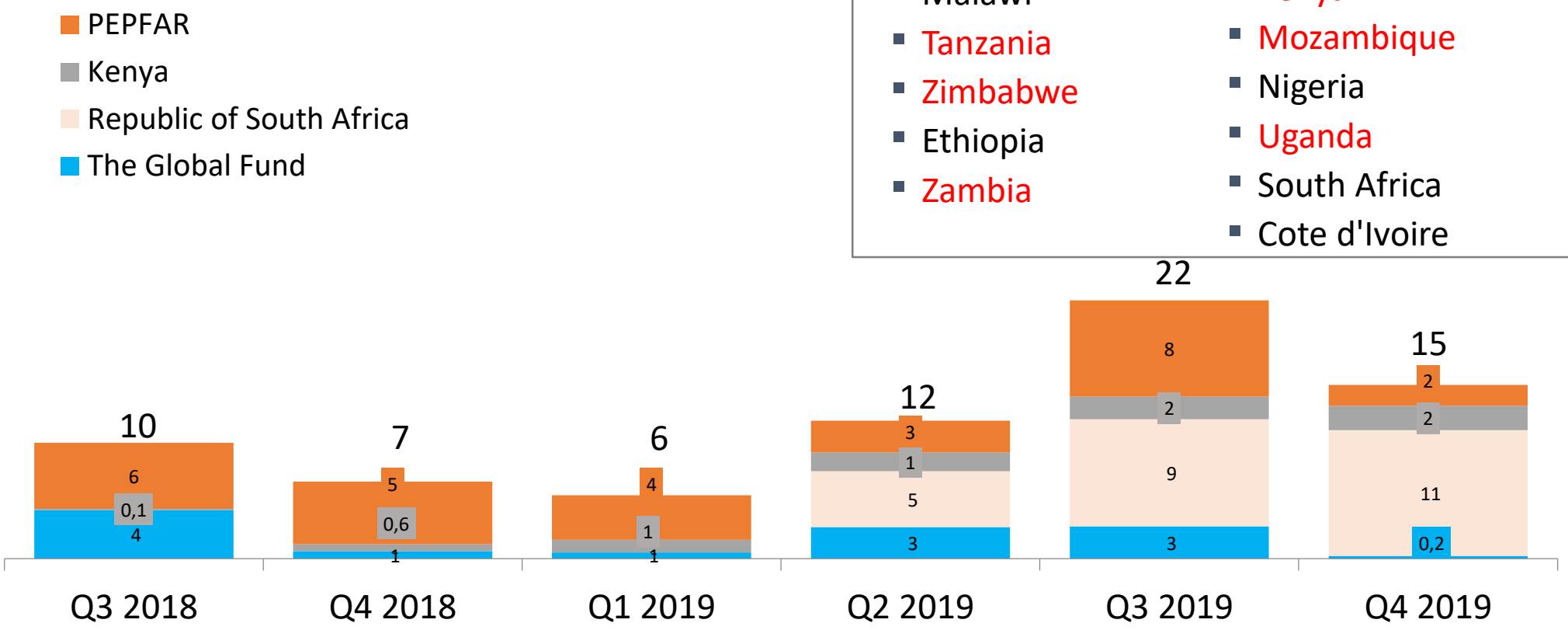
% of Adult ART Patients per Country on ARV Regimens, as of August, 2018



TLD – Consolidated Global Demand Forecast

Overall ARV Demand Outlook

July, 2018- Dec, 2019, Number of packs, millions



Countries Included Account for over 90% of Demand

- Malawi
- Tanzania
- Zimbabwe
- Ethiopia
- Zambia
- Kenya
- Mozambique
- Nigeria
- Uganda
- South Africa
- Cote d'Ivoire

DISCLAIMER: This is an initial version of the forecast, and may contain inaccuracies. These slides contain a conservative estimate for demand management between the three programs. As such, there may be future volumes not yet financially committed or confirmed.

SOURCE: PEPFAR (USAID and CDC), Kenya, Government of South Africa, The Global Fund

Modelling - Three-way pair-wise comparisons between strategies

Outcome*	Δ *DTG-EFV*	Δ *WHO-EFV*	Δ *DTG-WHO*
Outcomes among women			
Number of deaths among women	-31,600	-11,200	-20,400
Sexual transmissions	-60,300	-21,300	-39,000
Outcomes among children			
Non-neural tube defect-related pediatric deaths	-1,700	-100	-1,600
Neural tube defects	+7,600	+500	+7,100
Pediatric HIV infections	-5,300	-400	-4,900
Children alive and HIV-free	-2,600	-200	-2,400
Cumulative pediatric deaths**	+5,900	+400	+5,500
Combined outcomes among women and children			
Cumulative deaths among women and children	-25,700	-10,800	-14,900

*Out of projected 3.7 million women ever on first-line ART and 1.2 million HIV-exposed children.
**Cumulative pediatric deaths = non-neural tube defect-related + neural tube defect-related deaths

CEPAC Modelling for SA Conclusions:

- Dolutegravir-based ART would avert >30,000 deaths among women of childbearing age and >5,000 pediatric HIV infections compared to efavirenz-based ART, but result in ~6,000 excess pediatric deaths over a five-year period in South Africa

- A WHO guideline-concordant approach could mitigate adverse pediatric outcomes, but would result in many more deaths among women than dolutegravir for all

- Compared with a WHO contraception-based approach or an efavirenz for all strategy, using dolutegravir for all women of childbearing potential would avert greater than 5-fold more deaths among women with HIV than pediatric deaths added over 5 years in South Africa

MOVING FORWARD

Expanded Surveillance in Botswana

- Tsepamo: additional funding from NICHD to expand sites performing examinations of all births.
  - Will cover 70% of births in country
  - Full data set expected to be finalized 3/31/2019
  - Date review by monitoring committee after each 200 births, will release an update only if significant safety issue
- CDC funding to expand to additional sites using same protocol
- Together, these efforts will cover 94% of births in Botswana.
- Expect additional 900-1200 deliveries after DTG exposure at conception and in early pregnancy

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Moving Forward

Additional Countries with DTG-exposed Pregnancies

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

- Brazil: 490 DTG-exposed pregnancies; results expected at R4P mtg.
- Kenya: 800-1200 DTG-exposed pregnancies; CDC supporting birth surveillance at selected sites to capture outcomes, expected to start early October
- 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 PEPFAR-supported BD surveillance in Uganda, Malawi

Basic Science

ViiV-supported studies:

- **Rat whole embryo-culture model:** Investigating the utility of the rat whole embryo-culture model as this system is able to detect NTDs and therefore, if a signal was detected, could provide a model system for further evaluations. Early results are expected by October.
- **Folate receptor:** Investigating the potential of integrase inhibitors (DTG, CAB and marketed integrase inhibitors) to disrupt folate transport. Developing assays to determine if integrase inhibitors inhibit human transporters RFC (reduced folate carrier) and PCFT (proton coupled folate transporter) and folate receptor alpha mediated endocytosis. Results expected late 2018.

IMPAACT Study 2010 Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and their Infants

- Evaluating changes in folate levels with initiation of EFV versus DTG regimens in late pregnancy

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Timeline for WHO normative work

September 2018

1st meeting of WHO sub-committee on safety of dolutegravir:

- Review all safety reports on DTG from all sources incl. periodic safety updates by MAHs to FDA and EMA, trials and studies in countries
- Safety Assessment
- Recommendations for follow up and investigation

April 2019

WHO ACSoMP Annual Meeting:

- First report by the sub-committee
- Safety assessment
- Recommendations to WHO to guide and advice the WHO Member States, policy makers and health professionals
- Recommendations for follow up and investigation

WHO HIV & SRH activities

Short term (next 6 months)

- **Scoping/mapping of key existing documents** relevant to contraception access in the context of HIV programmes
- **Policy brief (target length 5-10 pages)** to support country efforts to increase access to a range of reliable and effective contraception in the context of DTG scale up; including a framework for decision making
- Review of **DTG & contraceptives**
- **Plan** for country support to promote integration of targeted HIV & SRH activities

PEPFAR Conclusions

PEPFAR remains committed to broad implementation of DTG-based regimens as first and second line treatment.

PEPFAR will continue to work closely with their country teams to advocate for broader availability of DTG for women and to provide resources for implementation.

PEPFAR supports integration of reproductive health services into HIV care and are working with countries to increase contraceptive options.

PEPFAR are supports multiple efforts to obtain additional data on BD risk rapidly and ongoing birth defect surveillance in Uganda and Malawi.

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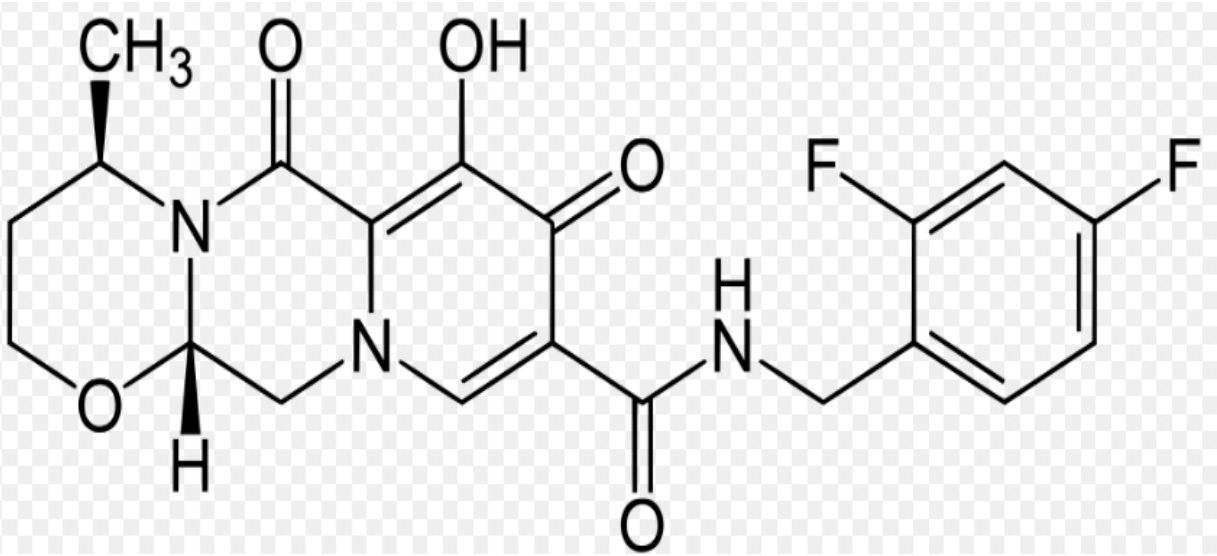
make medicines affordable

END UNFAIR MONOPOLIES

Countries where the use of DTG is patented:

Algeria
Belarus
Brazil
Colombia
Macedonia
Russia
Trinidad & Tobago
Turkey
Azerbaijan
Bosnia & Herzegovina
China
Kazakhstan
Mexico
Serbia

MANY THANKS



HIV ACTIVISTS & PATIENTS ALL OVER THE WORLD

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Diana Dickinson
Richard Lessells
Tulio de Oliveria
Bob Shafer