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Scientific evidence of DTG in Clinical practice.

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Outlines:

- Background
- Dolutegravir
- Goals of ART
- Clinical trials
- Comparing profiles of new ARV drugs
- TLD transition in Namibia
- pDTG transition

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Background

In December 2018, the World Health Organization released the Interim Guidelines with updated recommendations on first line and second line ARV regimens, Post-exposure prophylaxis and recommendations for early infant diagnosis. The MOHSS has revised its 5th Guidelines to incorporate new recommendations from the global normative guidance. These guidelines as the previous ones address clinical, operational and programmatic aspects of using ARV medicines for HIV treatment as well as for prevention. The guidelines are intended for use by national HIV program managers, clinicians and other health service providers in both public and private sectors, managers of laboratory services, People Living with HIV and AIDS (PLHIV), community based organisations, national HIV treatment and prevention advisory bodies as well as international and bilateral agencies that provide financial and technical support. These guidelines make reference other policies, guidelines and standards, and must therefore be used in tandem. The country will continue to implement the 'Treat All' recommendations with promotion of same

day ART start.

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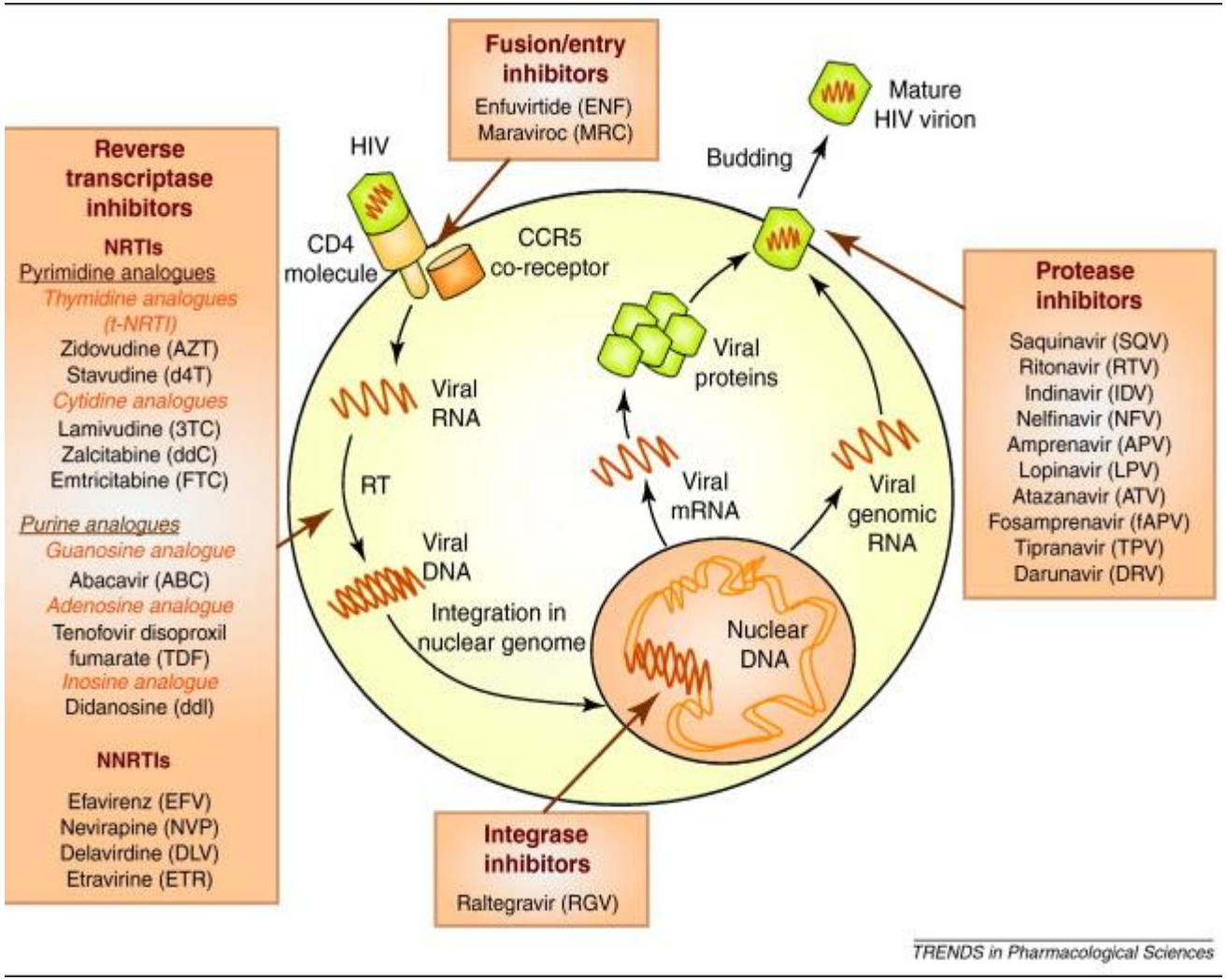
Dolutegravir (DTG)

- High genetic barrier to developing drug resistance.
- Advantages compared to most ARVs:
  - lower potential for drug interactions,
  - shorter median time to viral suppression
  - a long half-life
- A potential safety issue related to neural tube defects among infants born to women who were taking DTG at the time of conception,
- Weight gain is another adverse effect that has been observed with the use of DTG in some studies.

Goals of ART



- HIV treatment involves the use of combined antiretroviral therapy (ART) to effectively suppress the viral load, preserve (or improve) immune function, reduce the risk of opportunistic infections. prevent HIV transmission, and improve the quality of life

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Clinical Trials

	efavirenz	raltegravir	darunavir	atazanavir
dolutegravir	SUPERIOR (naive) SINGLE	SUPERIOR (experienced) SAILING NON INFERIOR (naive) SPRING²	SUPERIOR (naive) FLAMINGO	SUPERIOR (women / naive) aria
elvitegravir / cobicistat	NON INFERIOR (naive)			SUPERIOR (women / naive)
raltegravir	NON INFERIOR (naive)			NON INFERIOR (naive)

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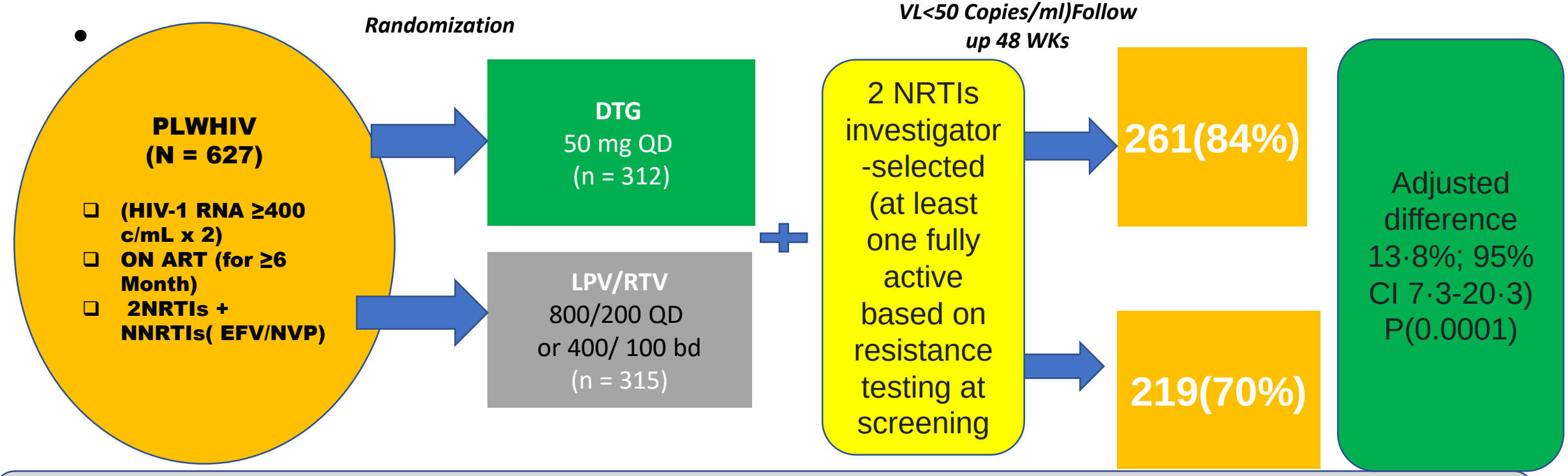
DAWNING STUDY: DTG vs LPV/RTV with dual NRTI for Second-line Therapy

Randomized, open-label, noninferiority phase III B trial(58 sites 13 Countries) 2014-2016



- DTG arm better than LPV/R regardless of baseline NRTI resistance patterns and second-line background NRTI use.
- The safety profile favorable in the DTG group than LPV/R

Excluded: PLWHI without predicted active NRTIs and no frequent VL monitoring

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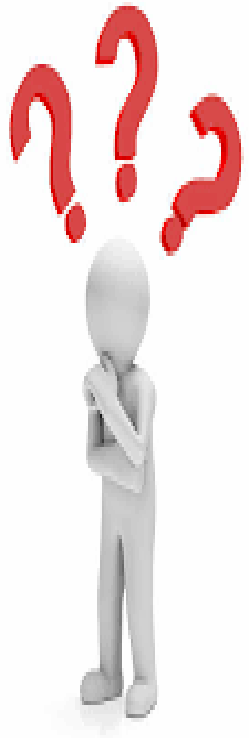
DAWNING : Implication and Gap

- DTG > LPV/R at 48 weeks and can be considered a suitable option for second-line treatment When administered with two NRTIs(1 fully active)
- WHO guidelines recommend DTG plus NRTIs for second-line HIV therapy, with NRTI switching from first-line tenofovir to zidovudine.



- PERFORMANCE OFDTG WITH NRTIS(With no or unknown predicted active value) !!!!!
- DTG Vs DRV/R

NADIA TRIAL

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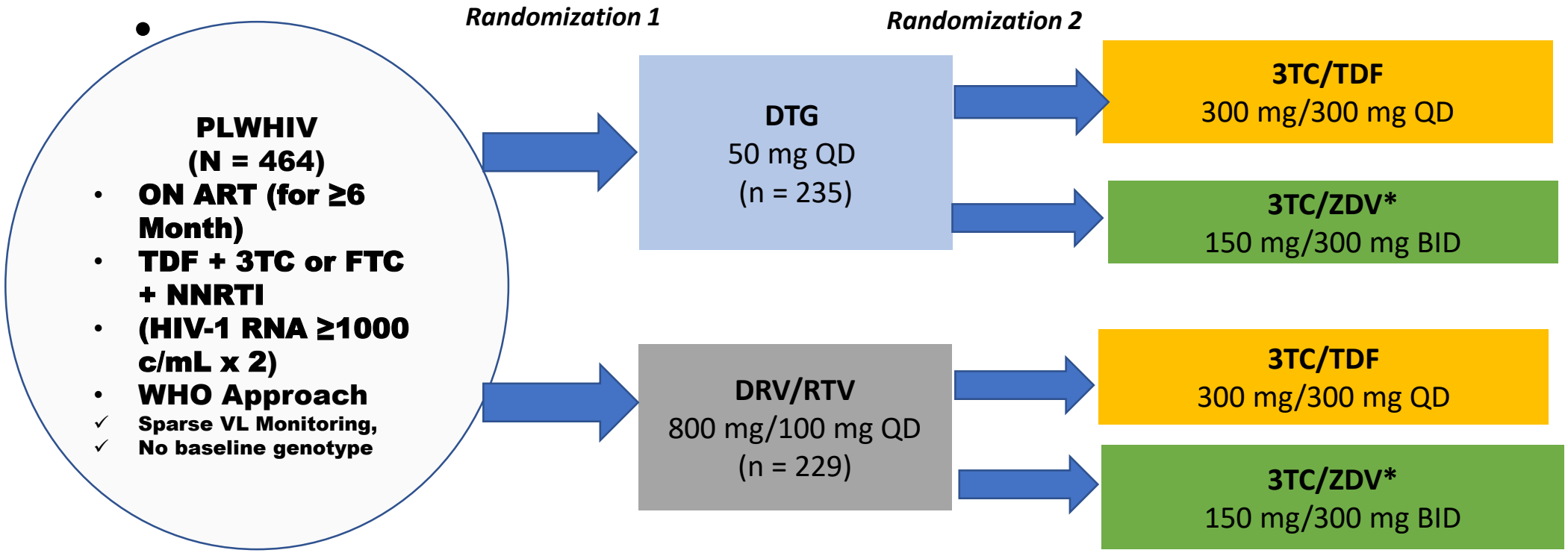
NADIA STUDY: DTG vs DRV/RTV and TDF vs ZDV for Second-line Therapy

Multicenter, 2 x 2 randomized, open-label, noninferiority phase III trial(Uganda, Kenya , Zimbabwe) 2019.



Follow up for 96 wk

AIM:

- Evaluate noninferiority of DTG to DRV/RTV and of 3TC/TDF to 3TC/ZDV in 2nd line
- TDF in second-line therapy is non-inferior to switching to zidovudine.
- Primary outcome: HIV-1 RNA <400 c/mL at Wk 96 by FDA snapshot

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Comparing profiles of new ARV drugs

Optimization criteria		DTG	EFV_{400}	TAF	$DRV/r_{400/50}$
Efficacy and safety	Virologic potency				
	Lower toxicity				
	High genetic barrier to resistance				
Simplification	Available as generic FDC				
	Low pill burden/pill size				(*)
Harmonization	Use in pregnant women				
	Use in childbearing age women				
	Use in children				
	Use in HIV-associated TB				
	Few drug interactions				
Cost	Low price				

yes no ongoing studies

Updated TLD News: Dolutegravir in pregnancy and neural tube defects (September 2019)

- Final results of the Tsepamo study, which included a larger number of dolutegravir exposures, an elevated risk remained but was substantially lower than previously reported.
- Overall incidence of neural tube defects was 0.3 percent with exposure to dolutegravir-based antiretroviral therapy (ART) at conception versus 0.1 percent with non-dolutegravir-based ART.
- World Health Organization concluded that the benefits of dolutegravir outweighed this risk and confirmed dolutegravir-based ART as the preferred first-line regimen for people with HIV, including pregnant women and those of child-bearing potential.

Understanding the Risk of NTDs with DTG Exposure

The recent updated data from the Tsepamo Study showed that:

- The risk of NTDs was 0.3% among DTG exposed compared to 0,1% for those non-exposed to DTG regimens. This implies that:

- The risk of NTD was 1 out of every thousand pregnancies exposed to other non-DTG based regimens and 999 had no NTD

- Out of a thousand pregnancies exposed to DTG-about 3 infants may develop NTDs and 997 born without NTD

This risk has to be considered against the advantages of DTG which include:

- Faster time to viral load suppression
- Reduced chances of developing HIVDR

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DTG Transition Guidance

- Implementation started October 2019
- Criteria:
  - New initiations:
    - Adults and adolescents
  - On treatment
    - Viral load < 40
    - Viral load less than 6/12 old
  - Second line
    - New failures of AZT based regimen
    - AZT/TDF/3TC/ATV+r (previously failed AZT) – Simplify to TLD

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Approach to TLD transition

- Two important steps to achieve full implementation;

STEP 1;

- Transition the minds of HCWs first

STEP 2;

- Then transition clients from old ART regimens to the preferred current regimens

Transitioning to TLD

- Know your product (DTG) and know it real well
- Describe your product to potential buyers (mentees)
- What is it that makes it stand out from the rest?
- If you cannot buy it yourself, you cannot sell it!

Transitioning safely to preferred first line

TDF/3TC/EFV (TLE) (VL result < 12 months)	TDF {TAF}/3TC/DTG (TLD_1)
VL < 40	
VL 40 - 999	**Continue TDF/3TC/EFV**. Enhance adherence and repeat VL in 6 months or 3 months?
VL > 1000	**Continue TDF/3TC/EFV.** Enhance adherence, consider possible switch to 2nd line regimen if regimen failure confirmed

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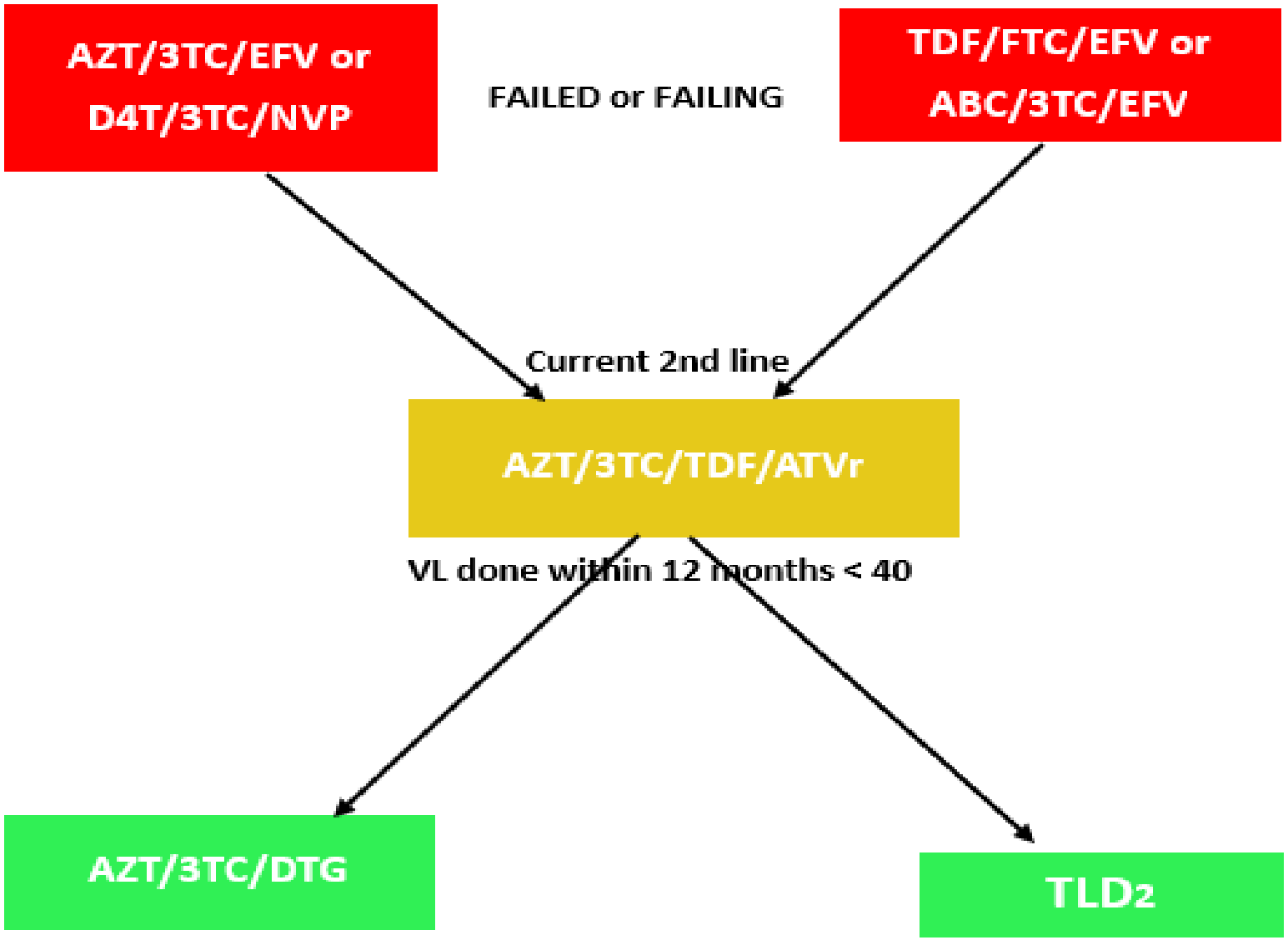
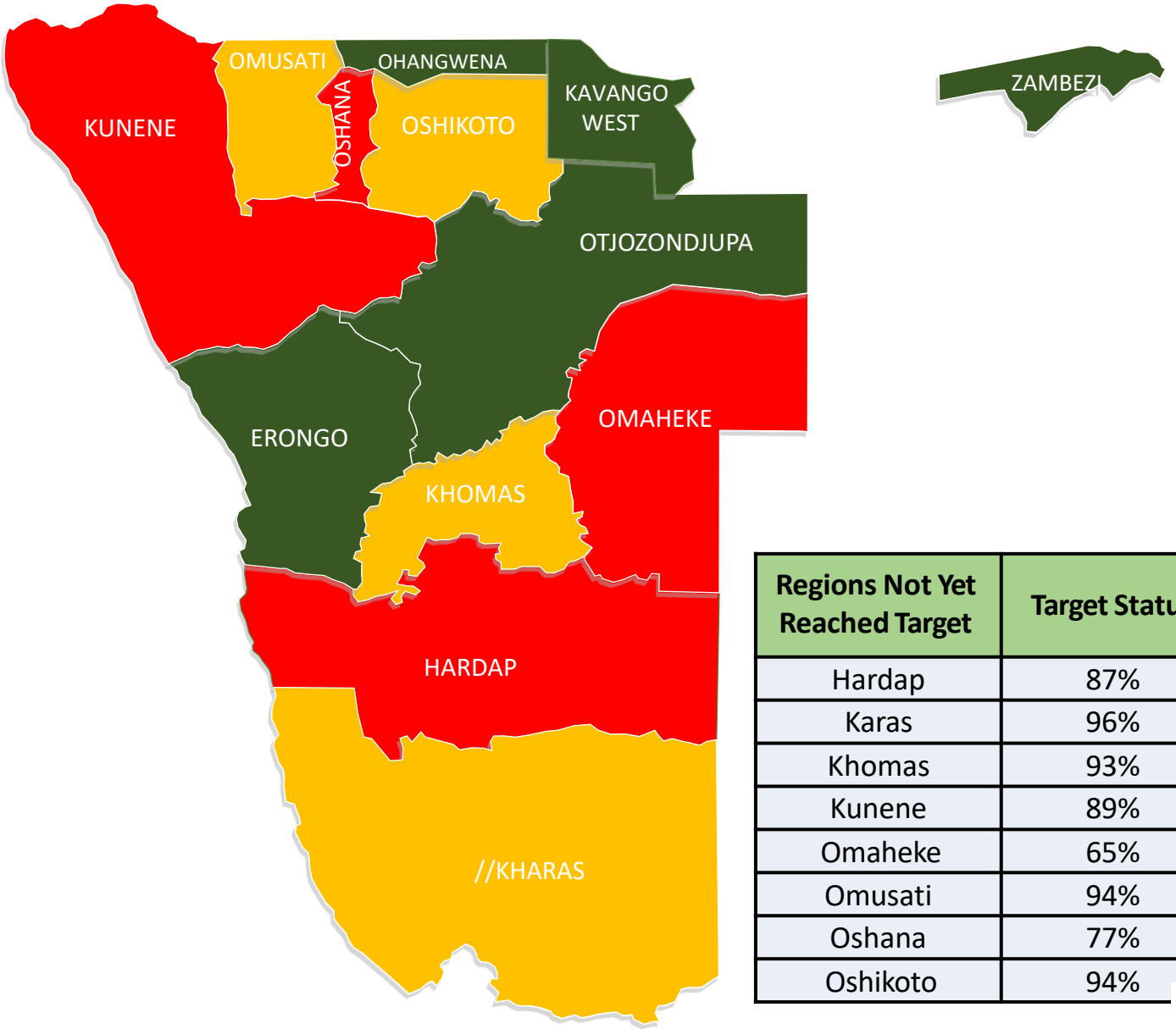
Transitioning to preferred second line



TLD TRANSITION UPDATE

149,083 *Total on TLD*

149,021 *Target*



Regions Not Yet Reached Target	Target Status
Hardap	87%
Karas	96%
Khomas	93%
Kunene	89%
Omaheke	65%
Omusati	94%
Oshana	77%
Oshikoto	94%

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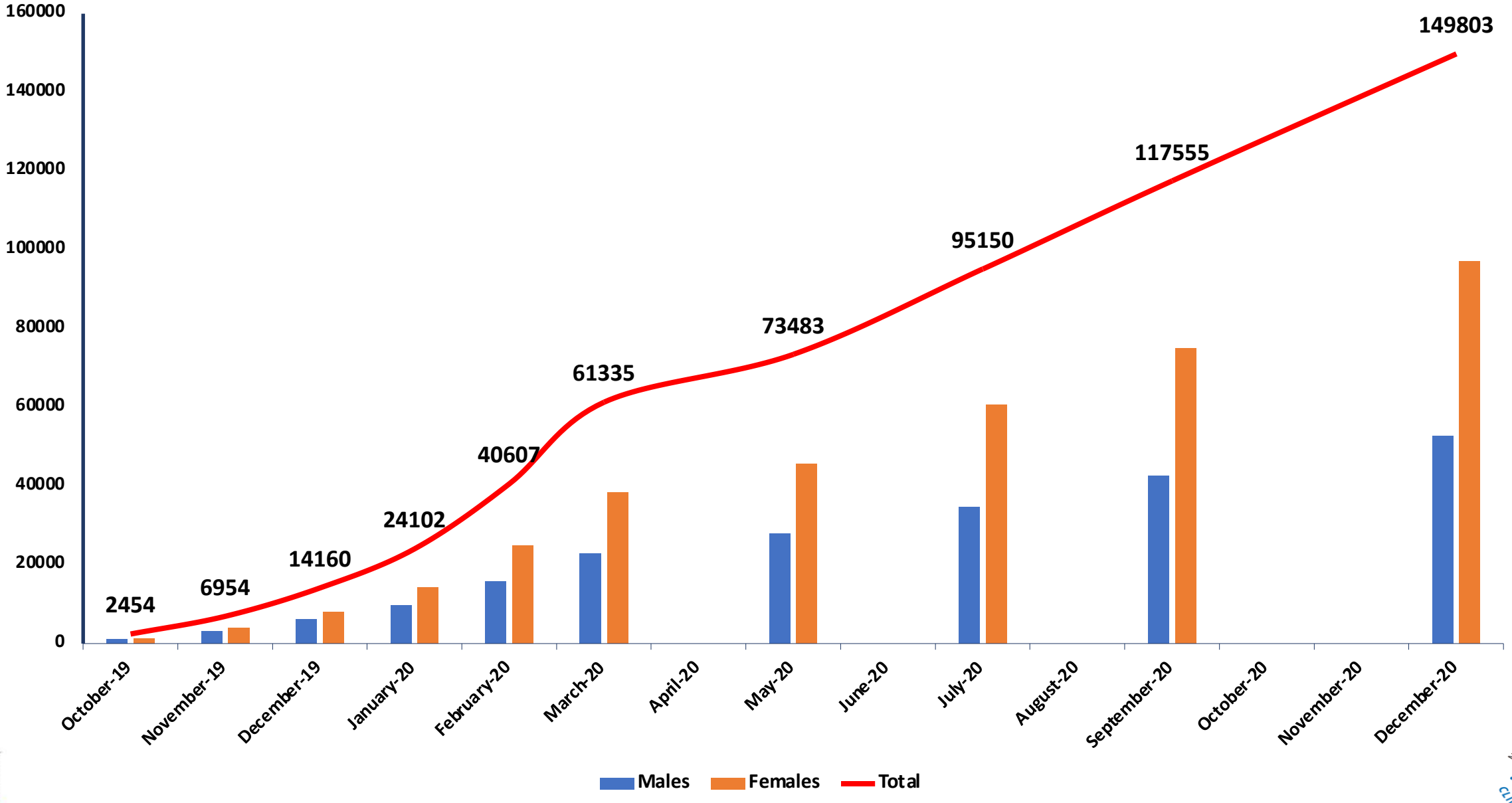
TLD Transition Trend



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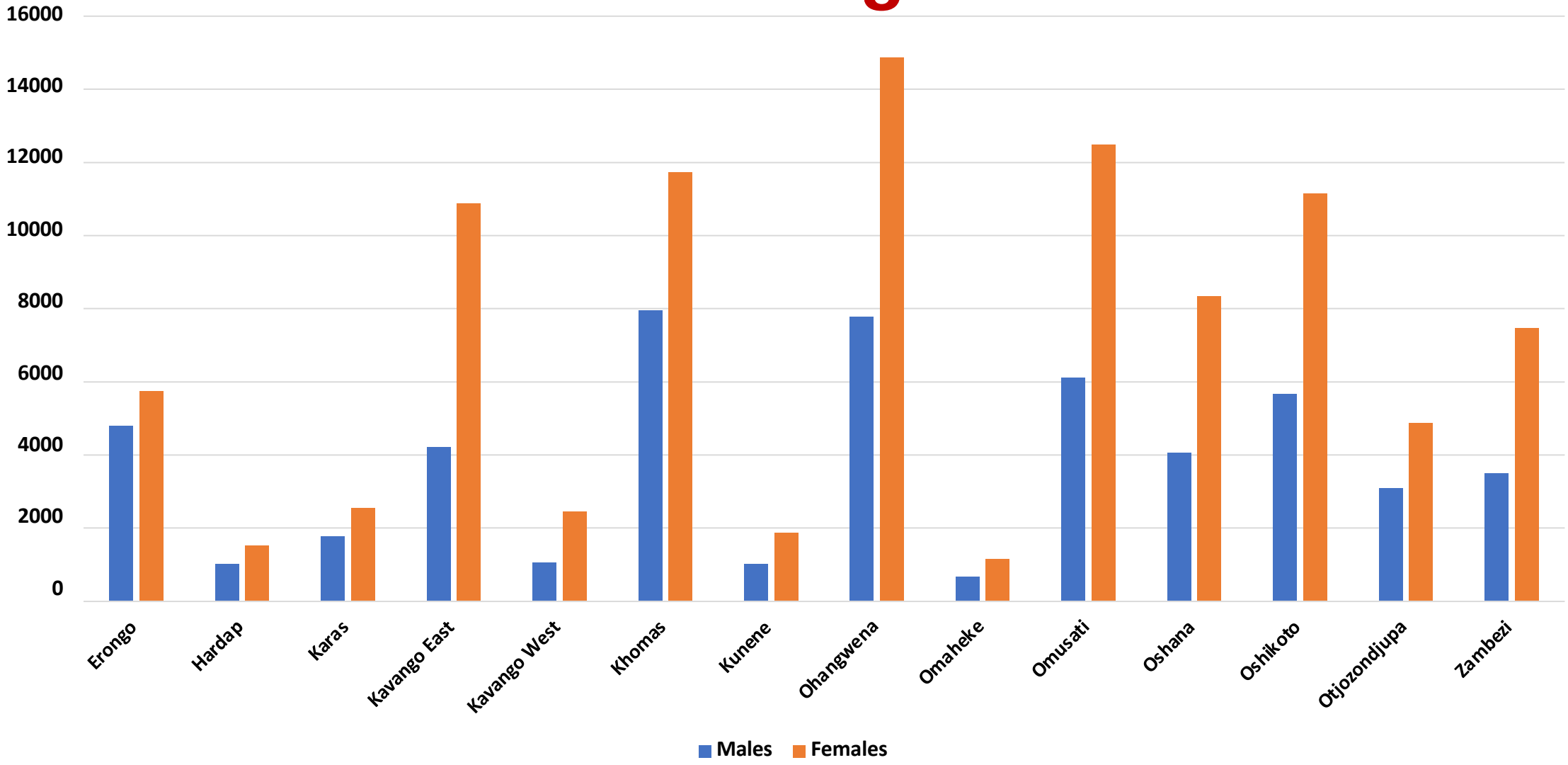
TLD Transition Status (December 2020): Are all Genders initiating TLD?



Total on TLD: 149803 (Males = 52712, Females = 97091)

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pDTG Transition April 2022

Region	Active on care: < 6 years	Active on care: 6 - 9 years	Active on care: 10 - 19 years	Total Active	Number on DTG: < 6 years	Number on DTG: 6 - 9 years	Number on DTG: >10 - 19 years	Total DTG	%
Erongo	27	25	242	294	25	24	235	284	96.5
Kavango West	47	91	366	504	39	78	345	462	91.6
Kunene	44	32	122	198	44	31	121	196	98.9
Oshana	65	108	854	1027	52	87	786	925	90
Ohangwena	164	282	1869	2315	157	272	1838	2267	97.5
Otjozondjupa	44	65	311	420	32	49	289	370	88
Omusati	146	227	1794	2167	130	193	1661	1984	91.5
Karas	44	41	137	222	43	41	123	204	93.2
Zambezi	71	144	677	892	63	118	607	788	88.3
Hardap	31	41	120	192	26	42	109	177	92.1
Omaheke	34	29	84	147	31	28	80	139	94.5
Khomas	51	55	444	550	41	48	415	504	91.6
Oshikoto	127	188	1135	1450	90	140	1045	1275	87.9
Kavango East	121	200	849	1170	69	153	785	1007	86
Total	1016	1528	9004	11548	842	1304	8439	10585	91.6

pDTG Transition June 2022

Region	Active on care: < 6 years	Active on care: 6 - 9 years	Active on care: 10 - 19 years	Total Active	Number on DTG: < 6 years	Number on DTG: 6 - 9 years	Number on DTG: >10 - 19 years	Total DTG	%
Khomas	69	71	602	**742**	56	65	562	**683**	**92.00%**
Kavango West	36	80	396	**512**	35	74	390	**499**	**97.40%**
Kunene	37	36	122	**195**	37	35	122	**194**	**99.40%**
Erongo	35	31	249	**315**	33	30	246	**309**	**98.00%**
Kavango East	118	188	828	**1134**	111	180	802	**1093**	**96.30%**
Otjozondjupa	50	65	319	**434**	45	59	309	**413**	**95.10%**
Ohangwena	165	279	1849	**2293**	165	276	1845	**2286**	**99.60%**
Oshikoto	115	176	1148	**1439**	101	159	1084	**1344**	**93.30%**
Hardap	28	31	104	**163**	26	30	98	**154**	**94.40%**
Oshana	78	113	915	**1106**	73	101	881	**1055**	**95.30%**
Omusati	136	224	1792	**2152**	134	212	1740	**2086**	**96.90%**
Karas	38	44	146	**228**	38	42	140	**220**	**96.40%**
Omaheke	35	29	84	**148**	34	28	80	**142**	**95.90%**
Zambezi	78	114	674	**866**	76	113	658	**847**	**97.80%**
Total	**1018**	**1481**	**9228**	**11727**	**964**	**1404**	**8957**	**11325**	**96.50%**

Key Points

1. Superior Viral Suppression: DTG is a potent integrase inhibitor that has demonstrated superior viral suppression compared to other antiretroviral drugs.
2. Improved Immunological Response: Patients on DTG-based regimens often experience significant improvements in their CD4+ T cell counts.
3. Fewer Side Effects: DTG has been associated with fewer adverse effects compared to older antiretroviral drugs.
4. Lower Risk of Drug Resistance: The high genetic barrier of DTG reduces the risk of developing drug resistance, making it a valuable component in both first-line and second-line treatment options.

Key Points

5.Rapid Viral Load Reduction: DTG has been shown to rapidly decrease viral load within the first few weeks of treatment, leading to a quicker response to therapy and faster viral suppression.

6.Simplified Dosage: DTG is available; Effective in Diverse Populations: Clinical studies have demonstrated the effectiveness of DTG in various populations

7.More than 95% of PLHIV in Namibia are on DTG based regimen.

References

- Adapted from Bertolli et al., Estimating the timing of mother-to-child transmission of human immunodeficiency virus in a breast-feeding population in Kinshasa, Zaire. J Infect Dis. 1996 Oct. 174(4): 722-6.)
- COP2019 Out brief, Namibia, Johannesburg, 14 Mar 2019
- National Guidelines for Antiretroviral Therapy (pocket guide 2021)
- MoHSS DHIS-2 database