Use of generic ritonavir-boosted darunavir and dolutegravir for second line antiretroviral therapy is cost-effective in Zambia: a 10-year modelling analysis

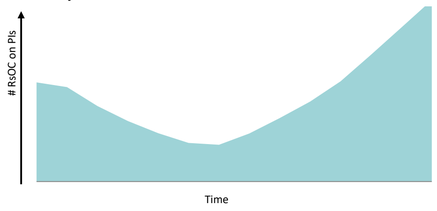
J. Campbell[1], J. Estill[2], Z. Panos[3], J. Harwell[4], C. Chimhundu[3], H. Shakwelele[5], P. Haimbe[5], C. Amole[3], S. Sivile[6], L. Mulenga[6]

[1]Clinton Health Access Initiative (CHAI) Analytics and Implementation Research, USA, [2]Estill Epidemiology Consulting, Tallinn, Estonia, Institute of Global Health, University of Geneva, Geneva, Switzerland, [3]CHAI, HIV Access Program, USA, [4]CHAI, Clinical Sciences Team, USA, [5]CHAI Zambia, Lusaka, Zambia, [6]Zambia Ministry of Health, Lusaka, Zambia

Abstract: EPE244

Background

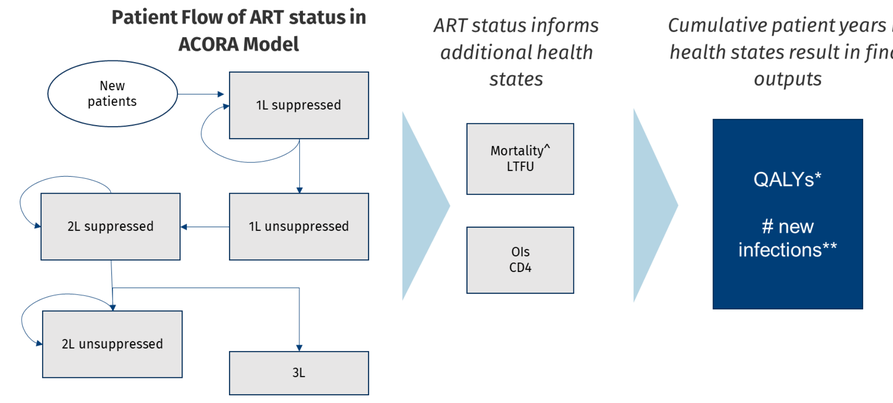
- Darunavir (DRV) is a best-in-class protease inhibitor (PI) commonly used in high-income markets; WHO 2019 guidelines recommend DRV/r as an alternate second line (2L) regimen
- DRV/r has shown better viral suppression compared to lopinavir-ritonavir (LPV/r) and atazanavir-ritonavir (ATV/r), resulting in fewer Recipients of Care (RsOC) requiring more expensive third line (3L) treatment
- Studies have shown DRV/r is better tolerated compared to LPV/r with fewer discontinuations due to adverse events, which may be expected to reduce loss to follow up (LTFU)
- Recently a generic fixed-dose-combination of ritonavir boosted DRV became available at affordable prices to LMIC, slightly cheaper than LPV/r
- Zambia has over one-million adults on antiretroviral therapy (ART), with almost 50 thousand accessing 2L treatment and is one of the first national HIV programs to offer DRV/r as an alternative to LPV/r and ATV/r
- The introduction of DRV/r, along with dolutegravir (DTG) in 2L offers optimization opportunities



The use of PIs in 2L is expected to decline in the short term with an upswing of DTG, PI volume is expected to increase in the medium/ long term

Methods: ACORA model

The Applied Cost and Outcomes Research Analysis (ACORA) Model is a Markovian state transition model designed to estimate treatment costs and RsOC health outcomes for cost-effectiveness analysis



*Inverse values of disability weights from the Global Burden of Diseases are applied to health states to estimate quality adjusted life years.
**HIV transmission rates per 100PYs are applied to health states off ART/discontinued, and if on ART – suppressed or unsuppressed. *Attia et. al. - Sexual transmission of HIV according to viral load and antiretroviral therapy: a systematic review and meta-analysis. 2009*
^ Mortality is dependent on CD4 band and ART status. *Parameters adapted from Optima Consortium for Decision Science / Optima HIV model*

The ART cohort transitions through health states including: ART status, viral load suppression status, CD4 cell count, opportunistic infections (OI). Published utility weights were applied to health states to estimate quality-adjusted-life-years (QALYs).

Results shown include 2L and 3L costs only (removing costs due to first line treatment). Incremental cost effectiveness ratios (ICER) and average cost effectiveness ratios (ACER) were calculated.

Methods: scenarios and inputs

Scenarios: We defined 4 pragmatic second-line options based on proactive switching and sequencing

ACORA Model 2L Optimization Scenarios

	Scenario	Scenario Details	Schematic
SOC	Status Quo	• No DRV/r in second-line • Existing 2L split of LPV/r and ATV/r is maintained for 1L failures	1L Failure → Fail → ATV/r / LPV/r
(C1)	Proactive switch of LPV/r to DRV/r, no ATV/r switches	• Patients on LPV/r switched to DRV/r (except for those on RIF-based TB treatment) • Patients on ATV/r stay on ATV/r	ATV/r → No change; LPV/r → Switch → DRV/r
(C2)	Proactive switch of both LPV/r and ATV/r to DRV/r	• Patients on LPV/r (except for those on RIF-based TB treatment) and ATV/r switched to DRV/r	ATV/r → DRV/r; LPV/r → Switch → DRV/r
(C3)	Proactive switch to DTG in 2L	• All existing 2L patients on PIs moved to DTG • When 1L DTG fails, move patients to DRV/r in 2L • When 1L non-DTG-based regimens fail, move to 2L DTG	ATV/r → Switch → DTG → Fail → DRV/r; LPV/r → DTG → DRV/r; 1L TLD → Fail → DRV/r; 1L NNRTI → Switch → DTG → Fail → DRV/r

Notes on regimens:

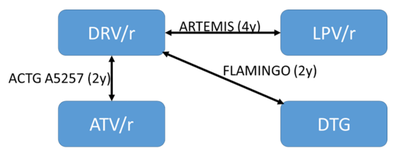
** 2L regimens are paired with AZT/3TC*

** 3L regimen: TDF/3TC+DTG+DRV/r (600/100)x2*

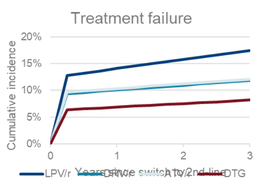
All TB co-infections will use LPV/r in 2L

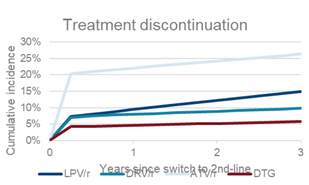
ARVs: Drug defining areas that drive health state transitional probabilities*:

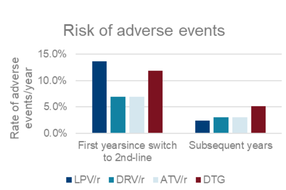
1. Failures – defined as viral failure rates
2. Discontinuations, or loss to follow up – defined as discontinuations due to serious adverse events



Sources for inputs were derived from published clinical trials, in the absence of a four-way head of the 4 drugs, we standardized results to account for results taken from multiple studies



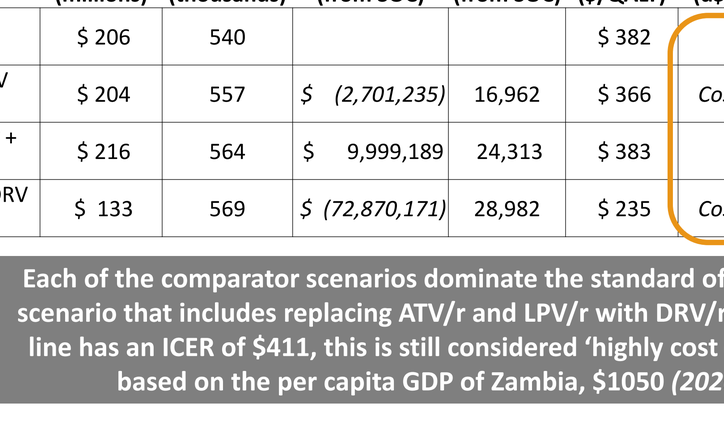




Regimen	$USD	Regimen	$USD
AZT/3TC+LPV/r	$ 294	TDF/3TC+DTG+DRV/r (600/100)x2	$ 756
AZT/3TC+ATVr	$ 231	TLD	$ 63
AZT/3TC+DVRr	$ 280	AZT/3TC+DTG	$ 99

Zambia program data: In January 2021 there were 1.121 million adult and adolescent RsOC:
1L – 96% [94% on DTG, 6% on NNRTI], 2L- 4% [69% LPV/r, 31% ATV/r]

Results: 10-year costs and cost-effectiveness*



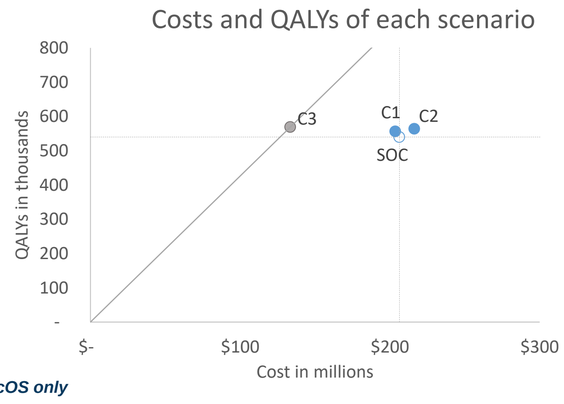
Replacing LPV/r and ATV/r with DRV/r alone does not significantly change total costs over 10-years; however, utilizing DRV/r with DTG in second-line for eligible RsOC shows a large savings of 25%, or $73 million, over the forecast period.

Scenario	Total Cost (millions)	Total QALYs (thousands)	Diff Cost (from SOC)	Diff QALYs (from SOC)	ACER ($/QALY)	ICER (d$/dQALY)	Result
SOC	$ 206	540			$ 382		Dominated
C1 - DRV for LPV	$ 204	557	$ (2,701,235)	16,962	$ 366	*Cost saving*	Cost effective
C2 - DRV for LPV + ATVr	$ 216	564	$ 9,999,189	24,313	$ 383	$ 411	Dominated
C3 - DTG in 2L + DRV	$ 133	569	$ (72,870,171)	28,982	$ 235	*Cost saving*	**Cost effective**

Each of the comparator scenarios dominate the standard of care. The scenario that includes replacing ATV/r and LPV/r with DRV/r in second line has an ICER of $411, this is still considered 'highly cost effective' based on the per capita GDP of Zambia, $1050 *(2020)*

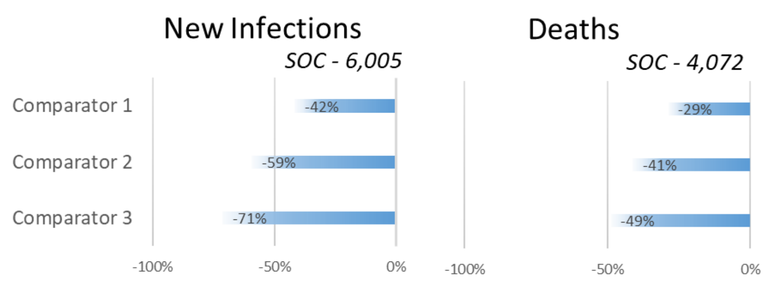
COST EFFECTIVENESS PLANE

Comparator 3 lies far to the left (less costly) than the SOC and the other comparators, while still having slightly higher QALYs. Further, without DTG in second-line, Comparators 1 and 2 show to be cost effective.



**Results include costs and outcomes associated with 2L and 3L RcOS only*

Results: Health Outcomes



There are large improvements on health outcomes from using DTG and DRV/r regimens. New infections can be reduced by over 71% and mortality reduced by 49% over 10 years using drugs with improved efficacy and safety profiles

Discussion and Limitations

- DRV/r yields cost savings and improved outcomes when replacing LPV/r; tuberculosis co-infections will still require LPV/r, as DRV/r is contraindicated with rifampicin.
- There is a slight increase in costs when DRV/r also replaces ATV/r, though this scenario is still considered to be highly cost-effective. Including DTG in 2L results in the greatest amount of cost savings.
- There are significant improvements in infections averted and deaths averted with adapting DRV/r and DTG in 2L.
- Zambia's HIV guidelines have been revised in 2021 to include DTG for eligible 2L RsOC and DRV/r as alternative PI following 1L DTG treatment failure, and these will be launched in 2022. These revisions are expected to lead to financial savings and improved health outcomes.
- Zambia will be phasing in DRV/r in 2022, to generate lessons and inform further guideline revisions and scaleup.
- **Limitations:**
  - Parameters on 2L disease progression for different regimens are mostly based on multi-country studies, often from high-income countries that would be used as first-line treatment.
  - We did not disaggregate the model by sex, age, pregnancy status, or other types of health status like obesity.
  - Regimen changes within the same line are not possible in the model.

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