Government of Malawi

Ministry of Health

Using **ATV/r** for second line treatment in Malawi

Last updated: May 2012

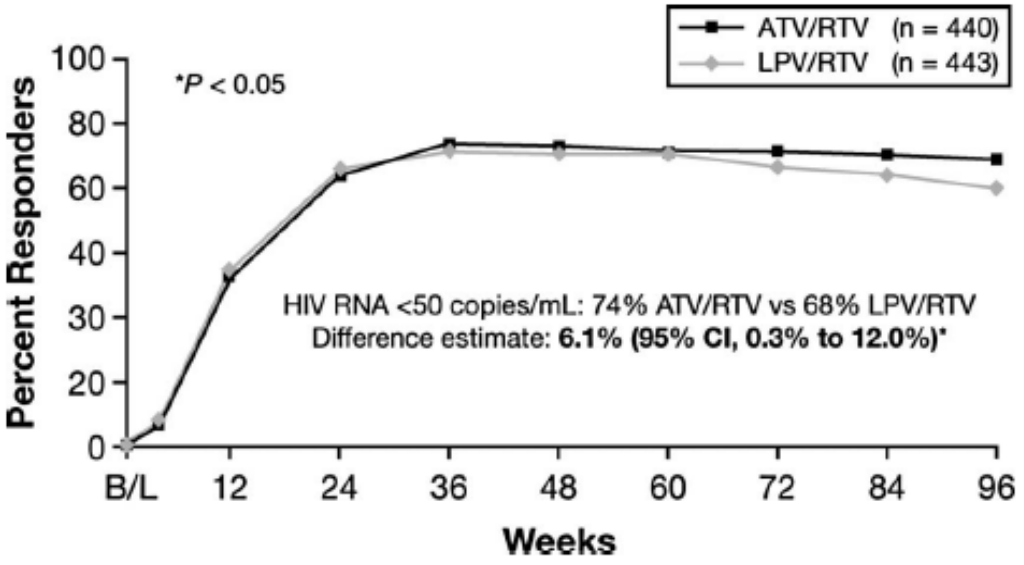
Introduction: Atazanavir boosted by ritonavir (ATV/r) is a WHO-recommended protease inhibitors for 2L treatment

	Characteristics of ATV/r
Convenience	1 pill, once-daily *(vs. 2 pills twice daily for LPV/r)* *Simpler administration can improve adherence*
Current ceiling price	$25 per pack *(vs. $33.25/pack for LPV/r)* *Approximately 25% savings*
Efficacy	Comparable efficacy to LPV/r with lower risk of elevated cholesterol and improved tolerability
Packaging	1 bottle, 30 tablets each

Efficacy: ATV/r demonstrates comparable efficacy in treatment-naïve patients

In head to head studies with LPV/r once-daily ATV/r demonstrated comparable efficacy and safety over 96 weeks.

- "Noninferiority of ATV/r to LPV/r was confirmed at 96 weeks.
- ATV/r had a better lipid profile and fewer gastrointestinal adverse events than LPV/r." *



* Molina JM. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1–infected patients: 96-week efficacy and safety results of the CASTLE Study. *J Acquir Immune Defic Syndr.* 2010;53:323-332

Side-effects: How does ATV/r compare to LPV/r in terms of tolerability

- Both ATV/r and LPV/r are considered to be well-tolerated
- In general, clinical studies have reported **lower toxicities for ATV/r**
- The main adverse effects associated with ATV/r are nausea, jaundice, and diarrhea
- ATV/r jaundice from unconjugated hyperbilirubinemia is largely a cosmetic issue and not related to hepatitis or liver damage. Therefore, ATV/r jaundice is **NOT a true toxicity**
- This has been supported by results from a large prospective analysis of the MASTERS cohort: "In most cases, ATV hyperbilirubinemia appeared to be an innocent phenomenon as far as the risk of a subsequent increase in liver enzyme level is concerned."

Side-effects: How does ATV/r compare to LPV/r in terms of tolerability

- Compared to other PIs, ATV/r is associated with a **lower risk of elevated lipids**.
- The major adverse effects associated with LPV/r are gastrointestinal intolerance, particularly diarrhea. In one study, Toxicity Grades 2-4 treatment-related diarrhea was more common in patients taking LPV/r compared to those taking ATV/r.
- More significantly, LPV/r is also associated with elevated lipids including cholesterol and triglycerides

Side-effects: Anecdotal experience from ATV/r roll-out in other countries

Nigeria

- 8 out of 1,159 **(0.6%)** reported cases of Hyperbilirubinemia – only one case of unconjugated hyperbilirubinaemia
- No reported cases of discontinuation
- Anecdotal evidence points to improved patient experience with ATV/r

Uganda

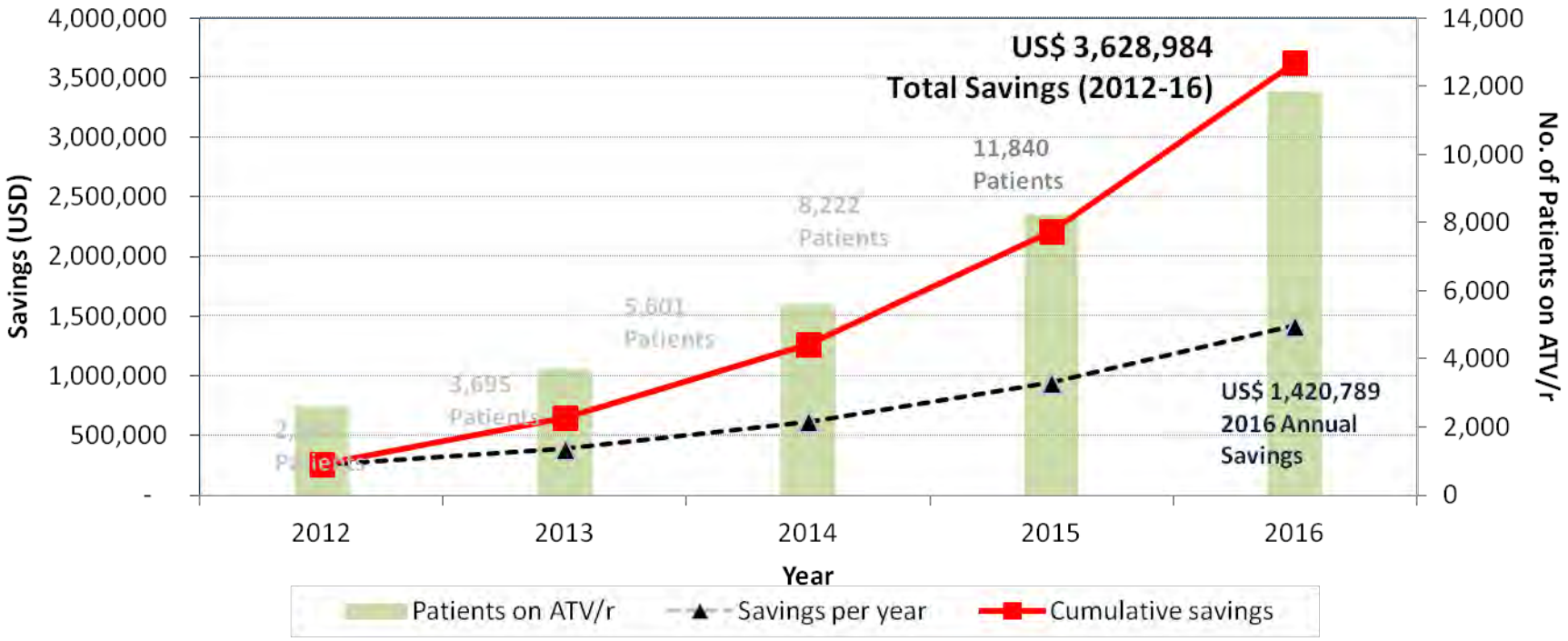
- 6 out of 445 **(1.4%)** reported cases of Hyperbilirubinemia – only one case of unconjugated hyperbilirubinaemia
- No case of discontinuation

Conclusion: Concerns over jaundice appear to be overblown given very positive experience with ATV/r in other African countries

Cost analysis: Based on ceiling prices, ATV/r FDC is 25% cheaper than the LPV/r FDC

- MOH procures LPV/r at **$33.25 per pack**
- CHAI ceiling price of ATV/r FDC is **$25.00 per pack**
- This translates into savings of **$99 per patient** per year (pppy)
- These **savings are expected to grow** based on the entrance of future SRA-approved suppliers for ATV/r FDC

Cost analysis: Based on ceiling prices, ATV/r FDC is 25% cheaper than the LPV/r FDC



- Second-line treatment will be a significant cost driver going forward
- By end of 2014 (end of GF RCC Phase 2) potential cumulative savings from a shift to ATV/r expected to be **$1,262,648.** These savings translate into the equivalent of **8,000 new patients on TDF/3TC/EFV** for an entire year at its current price
- By end of 2016 (4.5 years) a total savings of **$3,628,984.** Cumulative savings translate into over **24,000 new patients** on TDF for one year

Rolling out ATV/r: Patients currently on LPV/r should be able to proactively switch to ATV/r

- ATV is unique among PI's in that its signature resistance mutation, I50L, confers resistance to ATV but increased susceptibility to many other PI's, including LPV/r. However, mutations that accumulate with use of other PI's will confer resistance to ATV/r.
- Patients who are having issues with ATV/r and hyperbilirubinaemia can be switched back to LPV/r safely.

Rolling out ATV/r: If possible, patients viral load should be checked to ensure viral suppression prior to making switch

- If a patient has viral suppression on an LPV/r containing regimen, ATV/r will also be effective.
- However, making a switch to ATV/r in patients who are currently failing second-line may not be helpful since a virus that is resistant to LPV/r will also be resistant to ATV/r.
- LPV/r resistance requires several specific mutations and is not easy to acquire. Most patients currently failing LPV/r are not likely to have true PI resistance and are, instead, failing due to suboptimal adherence or failure to other drug classes. For this reason it is generally **safe to switch patients to ATV/r even if a viral load is not available because adherence may improve**.
- If a patient subsequently develops resistance via the development of the I50L mutation, other PI's including LPV/r may be sequenced as part of a third-line regimen.

Rolling out ATV/r: Both ATV/r and LPV/r can be used among pregnant women

- The 2010 WHO ART Guidelines indicate that both ATV/r and LPV/r can be used among pregnant women; however, the WHO PMTCT Guidelines do not provide specific recommendations as there have been limited studies on the use of ATV/r in PMTCT.
- In February 2011, the U.S. FDA approved new labeling for ATV for use in pregnancy, stating that it should always be given with RTV and that dose modifications were required only when used TDF or an H2 receptor antagonist.
- According to the U.S. FDA's Pregnancy Category Ratings for drug risks to the fetus, **ATV/r is considered "Category B" while LPV/r is listed as "Category C".** (Category B drugs are deemed safer than Category C drugs).

Rolling out ATV/r: Both ATV/r and LPV/r can be used among pregnant women (cont'd…)

- One study suggests that LPV/r in pregnancy increases the risk of preterm delivery; however, the effect of LPV/r and other PIs on the risk of preterm delivery is still debatable. Additionally, LPV/r drug levels are reduced in the third trimester of pregnancy.
- For ATV/r, one study suggests that drug levels remain constant throughout all stages of pregnancy and effectively prevents mother to child transmission.
- A concern with ATV/r is maternal hyperbilirubinemia. Elevated bilirubin is observed in women receiving ATV/r and could theoretically put an infant at risk of developing kernicterus, a form of brain damage caused by excessive jaundice; however, no clinical cases of kernicterus have been observed in conjunction with ATV/r use. Furthermore, ATV/r has not been found to impact the fetus in clinical trials.

Rolling out ATV/r: Both ATV/r and LPV/r can be used among pregnant women (cont'd…)

- Both ATV/r and LPV/r have been used in pregnant women without evidence of toxicity to either the mother or the fetus though there is comparably less experience using ATV/r in this population. As of July 2010, the ARV Pregnancy Registry documented approximately 450 cases of pregnant women with ATV exposure in the first trimester and 675 cases with LPV exposure. **The rate of birth defects were similar for ATV/r and LPV/r (2.5% and 2.1%, respectively) and to the rate for the general population.**
- In summary, both ATV/r and LPV/r are described as acceptable to use in pregnancy if the benefits for the mother and the baby outweigh the potential risks.

Rolling out ATV/r: A two-phase approach proactively switching 2L patients to ATV/r

- Training plan
- Update guideline appendix
- Provide circular to health facilities and job aid to health workers
- 2 Phase approach (procure ATV/r in next procurement cycle)
  - 1st phase (beginning 2013)
    - Switch 50% of existing 2L patients to ATV/r over 6-month period
    - Initiate new 2L patients on to ATV/r
    - Hold off procurement of LPV/r to reduce existing stock
  - 2nd phase (mid 2013)
    - Switch remaining 50% of existing 2L patients to ATV/r
    - Retain stock of LPV/r for 5% of total 2L patients

Appendix: Calculation of cost-savings (accumulated and annual) for ATV/r switch

	2012	2013		2014		2015		2016	
Patients on:	**2nd Half**	**1st Half**	**2nd Half**	**1st Half**	**2nd Half**	**1st Half**	**2nd Half**	**1st Half**	**2nd Half**
TDF/3TC + LPV/r (a) (USD)	2,667	3,371	4,193	5,113	6,234	7,514	*9,017*	*10,820*	*12,984*
AZT/3TC + LPV/r (b) (USD)	54	86	130	185	260	354	*425*	*510*	*612*
Total Cost (USD)	**2,721**	**3,457**	**4,322**	**5,299**	**6,493**	**7,868**	**9,442**	**11,330**	**13,596**
Average patients per year	2,721		3,890		5,896		8,655		12,463
Percent switch to ATV/r	95%		95%		95%		95%		95%
Patients on ATV/r	2,585		3,695		5,601		8,222		11,839
Savings per person per year (USD)	**100**		**105**		**110**		**115**		**120**
Savings per year (USD)	**258,491**		**388,015**		**616,141**		**945,548**		**1,420,789**
Cumulative savings (USD)	**258,491**		**646,506**		**1,262,648**		**2,208,196**		**3,628,984**

Note that as more SRA approved manufacturers enter the market expected, savings per patient expected to grow $5 per year