National Essential Medicines List Pharmacoeconomics and Budget impact analysis
Component: HIV infection

Date: 01 February 2023
Medication: Cabotegravir (injectable)
Indication: For the prevention of HIV infection in HIV negative individuals at risk of HIV acquisition

1 INTRODUCTION

This document is an annexure to the medicine review of injectable cabotegravir (CAB) for pre-exposure prophylaxis (PrEP) for the prevention of HIV infection. The review showed that CAB had superior efficacy to the standard-of-care oral PrEP formulation, tenofovir/emtricitabine (TDF/FTC). Efficacy of CAB was evaluated through two well-conducted randomized clinical trials (HPTN 083 and HPTN 084). These trials have shown CAB to be highly effective in preventing HIV infection, reducing the risk of HIV acquisition by 66% (95% confidence interval (CI) 38%-82%) in men who have sex with men (MSM) and transgender women, and by 89% (95%CI 68%-96%) in young women, compared to oral TDF/FTC, after 12 months of follow-up. Further follow-up for the latter (in young women) have confirmed similar results after 24 months of follow up.

This efficacy advantage appears to be driven by a greater proportion of time with therapeutic drug levels (in turn driven by greater adherence). There were no significant differences in adverse events between CAB and TDF/FTC regimens, with the exception of injection site reactions. The latter were more common in the CAB arm, but were generally mild and occurred less frequently with subsequent injections.

Currently there is no price for CAB as this product has not yet been negotiated for the South African market. This report describes a cost-effectiveness analysis that compares the scaling up of CAB compared to scaling up TDF/FTC, with different assumptions for coverage and duration on PrEP, with the base-case being the current low TDF/FTC roll-out. Our analysis also includes a threshold analysis with the aim of estimating the optimal price at which CAB remains as cost-effective as TDF/FTC.

This report is a summary of the modelling study by Jamieson et al [1], which aimed to evaluate the cost-effectiveness of scaling up CAB vs. scaling up TDF/FTC, compared to a baseline of the current TDF/FTC roll-out programme.

2 PHARMACOECONOMICS MODEL – METHODS AND SCENARIOS

The impact of CAB and TDF/FTC was estimated using Thembisa (version 4.4, C++), a **deterministic compartmental HIV transmission model of the South African HIV epidemic** [2]. The model population is stratified by age, sex, sexual experience, sexual behaviour, marital status, HIV testing history and male circumcision status. More detailed information about the model can be access at www.thembisa.org.

We modelled the **impact over a 20-year time horizon (2022-2041)** separately for TDF/FTC and CAB with target populations female sex workers (FSW), MSM, adolescent girls and young women (AGYW) (aged 15-24 years), and heterosexual adolescent boys and young men (ABYM) (aged 15-24 years). We **assumed two coverage levels for scaling up PrEP** (TDF/FTC and CAB) for each population (**high and medium coverage**), assuming a higher uptake by CAB users, based on studies showing a higher stated preference for injectable products compared to TDF/FTC [3–5].

PrEP coverage was assumed to increase linearly over a 3-year period. Based on South African PrEP implementation programme data [2], **TDF/FTC coverage is assumed to be low at baseline** (between 0.5% and 3% of the relevant target populations), and the average duration on TDF/FTC is assumed to be 5 months for AGYW and ABYM, and 11 months for

MSM, and there is no TDF/FTC uptake in CAB scenarios. We assume a 1-month supply of TDF/FTC at last visit will provide an additional month of protection.

For CAB the average duration in the programme was modelled under two sub-scenarios:

1) **minimum duration scenario**, in which users remain in the programme for a similar time as they would on TDF/FTC (i.e. 5 months for AGYW and ABYM, and 11 months for MSM);
2) **maximum duration scenario**, in which users remain on PrEP for longer than TDF/FTC, i.e. 12 months (AGYW, ABYM) or 24 months (MSM).

3 CLINICAL INPUTS AND COSTS

Effectiveness

TDF/FTC effectiveness, accounting for both efficacy and adherence, is assumed to be 85% for adolescent boys and young men (ABYM) and MSM, and 65% for adolescent girls and young women (AGYW) and female sex workers (FSW) [6,7].

CAB effectiveness, compared to TDF/FTC, was assumed to be 66% in men and 89% in women [8,9]. For modelling purposes we need to estimate their effectiveness compared to no PrEP; we modified the trial results to approximate a 95% effectiveness for CAB (i.e. 0.95 = 1-(1-0.85) x (1-0.66) for men; 0.96 = 1-(1-0.65) x (1-0.89) for women).

Costs

Costs were analysed from the perspective of the provider, the South African government, and reported in 2021 South African Rand (ZAR).

The **average cost of PrEP provision was estimated using an ingredients-based approach.** Briefly, PrEP is provided in primary healthcare clinics and includes rapid HIV testing, counselling, provision of condoms, syndromic screening for sexually transmitted infections with treatment referral, adherence counselling, training, outreach, mobilisation, monitoring and evaluation costs. The cost of TDF/FTC is R68.65 per month.

The cost of CAB provision was structured using similar methodology with adjustments (increasing professional nurse time for the injection administration, removing creatinine testing). Since the cost of drug is currently unknown, in our initial modelling we varied the price between 1-to-5-fold the 2-monthly price of TDF/FTC.

Table 1. Key assumptions on duration, coverage, effectiveness and cost of CAB and TDF/FTC

	TDF/FTC		**CAB**			
			Minimum duration		***Maximum duration***	
	Medium coverage	**High coverage**	**Medium coverage**	**High coverage**	**Medium coverage**	**High coverage**
Duration	5mo (AGYW, FSW, ABYM); 11mo (MSM)		*Same as for TDF/FTC*		12mo (AGYW, FSW, ABYM); 24mo (MSM)	
Coverage	5% (AGYW, ABYM); 15% (FSW, MSM)	10% (AGYW, ABYM); 30% (FSW, MSM)	25% (FSW, MSM); 20% (AGYW); 10% (ABYM)	50% (FSW, MSM); 40% (AGYW); 20% (ABYM)	40% (FSW, MSM); 35% (AGYW); 20% (ABYM)	67% (FSW, MSM); 60% (AGYW); 35% (ABYM)
Effectiveness	65% (AGYW, FSW); 85% (ABYM, MSM)		95% (all populations)			
Cost per person initiated*	R1,113-R1,145 (AGYW, FSW, ABYM); R1,692 (MSM)		R1,146-1,190 (AGYW, FSW, ABYM); R1,777 (MSM)		R1,911-2,006 (AGYW, FSW, ABYM, MSM 1st year); R1,528 (MSM 2nd year)	

*For comparison reasons we assume the cost of CAB is the same as for TDF/FTC (2-month supply)

Cost-effectiveness

We analysed cost-effectiveness over a 20-year time horizon (2022-2041), over a baseline of currently available HIV interventions in South Africa. Outcomes of interest were cost per life year saved and cost per HIV infection averted. Further, using the modelling output- the total cost of the HIV programme, the cost of provision of PrEP and the impact of each of the PrEP technologies, **we solve for the optimal price at which CAB is as cost-effective as TDF/FTC.**

Sensitivity analysis

Several sensitivity analyses are conducted in Jamieson et al [1]; however, of note there are two key analyses which may be of importance to this review: (1) assuming CAB **coverage would be the same as that of TDF/FTC scenarios**, and (2) the **inclusion of annual PCR testing** in the HIV diagnostic algorithm for CAB provision. We consider the impact of these on the threshold price and the budget impact analysis (BIA).

4 RESULTS

Epidemiological impact

Over the 20-year period, CAB averted up to 52,000 infections averted/year in the high coverage, maximum duration scenario, 42,800 infections averted/year (high coverage, minimum duration), 35,600 infections averted (medium coverage, maximum duration), 26,400 infections averted/year (medium coverage, minimum duration).

TDF/FTC averted at most 16,300-9,000 infections annually in high and medium coverage scenarios.

Overall CAB scenarios averted 15%-28% of new HIV infections over baseline (current TDF/FTC roll-out) compared to 4%-8% with the scaling up of TDF/FTC, over the 20-year period (Table 2).

Costs and cost-effectiveness

Under the assumption that CAB drug costs were equal to that of TDF/FTC for the same 2-month period (i.e. cost of 1 injection = cost of 2 months of TDF/FTC):

- the incremental cost of CAB to the HIV programme was higher than TDF/FTC (5%-14% vs 2%-4%) over the 20-year period, due to higher assumed uptake of CAB.
- The cost per infection averted was R88,414-R96,558 (TDF/FTC) and R65,306-R84,419 (CAB) over the 20-year period.

For CAB to remain as cost-effective as TDF/FTC, the cost of the drug would need to be between 1- and 2-fold that of TDF/FTC (2 months' supply).

Table 2: Impact and cost-effectiveness of CAB-LA compared to baseline* and oral TDF/FTC compared to baseline, over a 20-year time horizon (2022-41)

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to TDF/FTC drug†	Total cost of the HIV programme (2021 ZAR)		Incremental cost effectiveness (2021 ZAR)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Baseline (BL)	3.02		37.34			603			
Medium PrEP coverage									
TDF/FTC	2.89	4%	37.00	1%	N/A	615	2%	88,414	33,725
CAB-LA minimum duration	2.58	15%	36.19	3%	1x	632	5%	65,306	24,912
					2x	649	8%	105,335	40,182
					3x	667	11%	145,364	55,451
					4x	685	13%	185,393	70,721
					5x	702	16%	225,423	85,991
CAB-LA maximum duration	2.44	19%	35.81	4%	1x	647	7%	75,330	28,889
					2x	675	12%	123,385	47,319
					3x	704	17%	171,441	65,749
					4x	732	21%	219,497	84,178
					5x	760	26%	267,552	102,608
High PrEP coverage									
TDF/FTC	2.78	8%	36.68	2%	N/A	627	4%	96,558	36,483
CAB-LA minimum duration	2.31	24%	35.41	5%	1x	663	10%	84,419	31,327
					2x	699	16%	133,611	49,582
					3x	734	22%	182,802	67,836
					4x	769	27%	231,993	86,090
					5x	804	33%	281,185	104,345
CAB-LA maximum duration	2.17	28%	35.03	6%	1x	688	14%	99,108	36,665
					2x	740	23%	159,432	58,982
					3x	791	31%	219,757	81,300
					4x	843	40%	280,081	103,617
					5x	894	48%	340,406	125,934

*Baseline scenario: current roll-out of TDF/FTC as standard of care PrEP (see Table 1 for comparative coverage levels by population).
† Drug cost only, excluding cost of provision (staff, lab monitoring, consumables and overhead). Abbreviations: HIV=Human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, CAB-LA = long-acting injectable cabotegravir, ZAR = South African Rand, BL = Baseline, PrEP = pre-exposure prophylaxis

We estimated the **threshold price for CAB per injection** to be between R132 (high coverage, maximum duration) to R211 (medium coverage, minimum duration) if it was to remain as cost-effective as TDF/FTC (Table 3).

Table 3: Estimated cost threshold per CAB injection to ensure CAB remains as cost-effective as oral TDF/FTC (2021 ZAR)

	Minimum duration scenario		Maximum duration scenario	
Cost per CAB injection solving for	***Medium coverage***	***High coverage***	***Medium coverage***	***High coverage***
CAB cost/HIV infection averted = TDF/FTC cost/HIV infection averted	R211	R169	R172	R132
CAB cost/life year saved = TDF/FTC cost/life year saved	R211	R174	R171	R136

Sensitivity analyses and the impact on the threshold price

When assuming CAB coverage would be the same as that of TDF/FTC scenarios (refer to Table 1), the threshold price increases to R219 to R282 per injection (Table 4).

If we include an annual PCR testing in the HIV diagnostic algorithm for CAB provision, the threshold price decreases to between R7 to R90 per injection (Table 4). As the cost of providing CAB services increases (inclusion of PCR), the need to decrease the cost of the injection becomes greater in order to reduce the ICER of CAB to align with the ICER of TDF/FTC.

Table 4: Estimated cost threshold per CAB injection to ensure CAB remains as cost-effective as oral TDF/FTC (2021 ZAR) – under sensitivity analyses

	Minimum duration scenario		Maximum duration scenario	
Cost per CAB injection solving for	***Medium coverage***	***High coverage***	***Medium coverage***	***High coverage***
CAB coverage the same as that of TDF/FTC				
CAB cost/HIV infection averted = TDF/FTC cost/HIV infection averted	R282	R272	R245	R222
CAB cost/life year saved = TDF/FTC cost/life year saved	R281	R270	R239	R219
Annual PCR testing				
CAB cost/HIV infection averted = TDF/FTC cost/HIV infection averted	R90	R48	R47	R7
CAB cost/life year saved = TDF/FTC cost/life year saved	R90	R53	R46	R12

5 PUBLISHED HEALTH ECONOMICS

There are a limited number of published cost-effectiveness studies on CAB, particularly for South Africa. Glaubius et al [10] found a risk-prioritized strategy cost-effective (<$1600 per life-year gained) over 10 years under a threshold of 3x gross domestic product, compared to no PrEP. Van Vliet et al [11] found CAB cost-effective at a price of <$16/year over 40 years under an arbitrary threshold of <$519/disability-adjusted life year averted.

A modelling study done in the United States found that the CAB injection would need to be between 1- and 2-fold the price of TDF/FTC for it to remain as cost-effective [12] .

6 BUDGET IMPACT ANALYSIS

The cost of CAB for the South African market is currently unknown. The expected volume/uptake is also uncertain. We therefore present two scenarios, both of which aim to get to the lowest range of the cost: 1) medium coverage with minimum duration on CAB (i.e. the same duration users would have been on TDF/FTC (see Table 1), 2) assuming the same coverage and duration for CAB as for TDF/FTC (as per our sensitivity analysis). Assumptions for coverage, duration and cost are noted in the table below for each scenario.

Under a conservative scenario where we expect the lowest scale-up of CAB modelled, we can expect between 383,000 and 611,000 initiates per year at a cost of R700 million to R1.1 billion per year (Table 5). If we expect a higher uptake of CAB compared to TDF/FTC, an estimated 1.1 million to 1.7 million users will initiate CAB annually at a cost of R1.6 billion to R2.5 billion per year.

Table 5. Cost of CAB provision (2021 ZAR) from 2023/24 to 2027/28

Medium coverage; minimum duration on CAB ***Coverage**: 25% (FSW, MSM); 20% (AGYW);10% (ABYM)* ***Duration**: 5mo (AGYW, FSW, ABYM); 11mo (MSM)* ***Cost**: R211/injection; **Total cost of provision (incl drugs)**: R1,445-R1,488 (AGYW, FSW, ABYM); R2,313 (MSM)*					
	2023/24	**2024/25**	**2025/26**	**2026/27**	**2027/28**
Number of users initiated	1,085,900	1,555,955	1,574,404	1,620,995	1,671,383
Cost of providing CAB (billions)	1.627	2.328	2.352	2.421	2.496
Incremental cost to programme* (billions)	1.240	1.774	1.759	1.773	1.782
Same coverage and duration on CAB as TDF/FTC ***Coverage**: 5% (AGYW, ABYM); 15% (FSW, MSM)* ***Duration**: 5mo (AGYW, FSW, ABYM); 11mo (MSM)* ***Cost**: R282/injection; **Total cost of provision (incl drugs)**: R1,734-R1,754 (AGYW, FSW, ABYM); R2,829 (MSM)*					
	2023/24	**2024/25**	**2025/26**	**2026/27**	**2027/28**
Number of users initiated	383,893	562,880	576,831	593,806	611,248
Cost of providing CAB (billions)	0.701	1.026	1.049	1.080	1.111
Incremental cost to programme* (billions)	0.421	0.628	0.631	0.636	0.638

*compared to baseline scenario with continued low TDF/FTC coverage; incremental cost accounts for down-the-line impacts of averted HIV infections, including the reduction in the need for HIV treatment.

7 CONCLUSION

CAB will be as cost-effective compared to scaling up TDF/FTC in the same population if the price can range between R132-R211 per injection, dependent on the underlying coverage and duration assumptions. Lowering the CAB coverage to equal that of TDF/FTC scale-up, we estimate a slight increase in this threshold price (up to R282/injection). Changing the HIV diagnostic algorithm to include PCR testing annually, will cause the threshold price to decrease significantly (R7-R90/injection).

8 REFERENCES

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Version	Date	Reviewer(s)	Conclusion
First	01 Feb 2023	Lise Jamieson	CAB will be as cost-effective compared to scaling up TDF/FTC in the same population if the price can range between R132-R211 per injection, dependent on the underlying coverage and duration assumptions.