EVIDENCE SUMMARY

Title: Evidence review of the use of cabotegravir as pre-exposure prophylaxis for HIV.

Date: 15 May 2022
Updated: 29 August 2024 (inclusion of NEMLC due diligence commentary on donated stock)

Reviewers: Jeremy Nel, Lise Jamieson
Affiliation and declaration of interests: JN (Division of Infectious Diseases, Department of Medicine, University of the Witwatersrand); LJ (Health Economics and Epidemiology Research Office (HE2RO), University of Witwatersrand). JN and LJ have no conflicts of interest relating to cabotegravir, but JN has received speaker's fees from Mylan, Cipla, J&J relating to HIV topics.

Background:
Pre-exposure prophylaxis (PrEP) is an effective prevention option for any sexually active person who might be exposed to HIV through contact with HIV in the genital tract or blood. In South Africa to date, the only available PrEP formulation has been an oral fixed-dose combination consisting of tenofovir and emtricitabine (TDF-FTC). Clinical trial data suggests that the efficacy of this regimen is critically dependent on adherence levels however.(1) Programmatic data suggests a high rate of early discontinuation of TDF-FTC-based PrEP in real-world settings, and roll out in South Africa has been poor.(2)

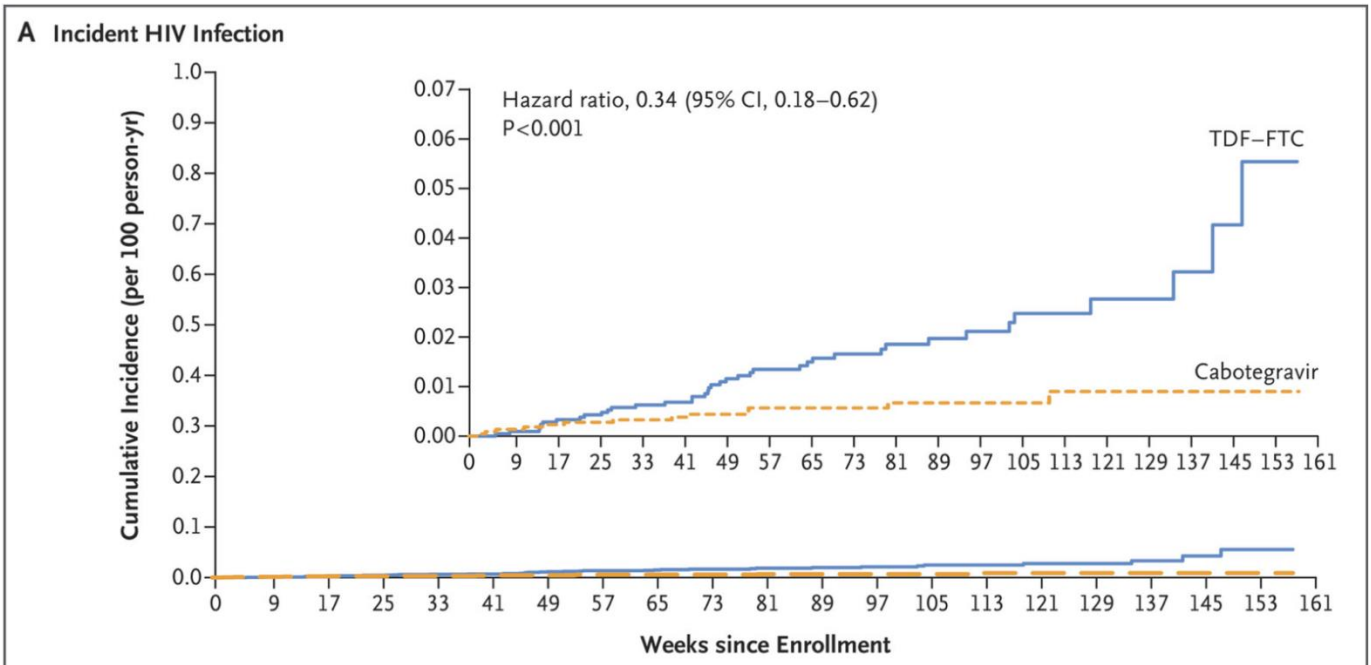
Cabotegravir (CAB) has been formulated as an injectable nanoparticle suspension with a long half-life that permits dosing every eight weeks. Its use as PrEP has recently been the subject of 2 published phase 3 randomised control trials. This evidence summary outlines the key findings of these 2 trials. Both compared long-acting injectable CAB to oral TDF-FTC, and the trials had almost identical designs. They differed primarily in the population under study - HPTN 083 evaluated the drugs in HIV-negative cisgender men and transgender women, whereas HPTN 084 assessed the drugs in HIV-negative women. In each case, there were three phases to the trial: (1) an oral-lead in phase where oral CAB or TDF-FTC was given (in addition to placebo), (2) an injection phase where participants received long-acting CAB injections 8-weekly (plus daily oral placebo) or daily TDF-FTC (plus 8-weekly placebo injection), and (3) a tail phase for those who stopped injections early for any reason (e.g. tolerability, or pregnancy). The role of the oral lead-in phase was to assess drug tolerability prior to potentially receiving a long-acting form of the drugs. Only patients who demonstrated at least 50% adherence to the oral lead in doses (as determined by pill count) were permitted to move to the injection phase. The overall goal of the trials was to assess incident HIV infection in each trial.

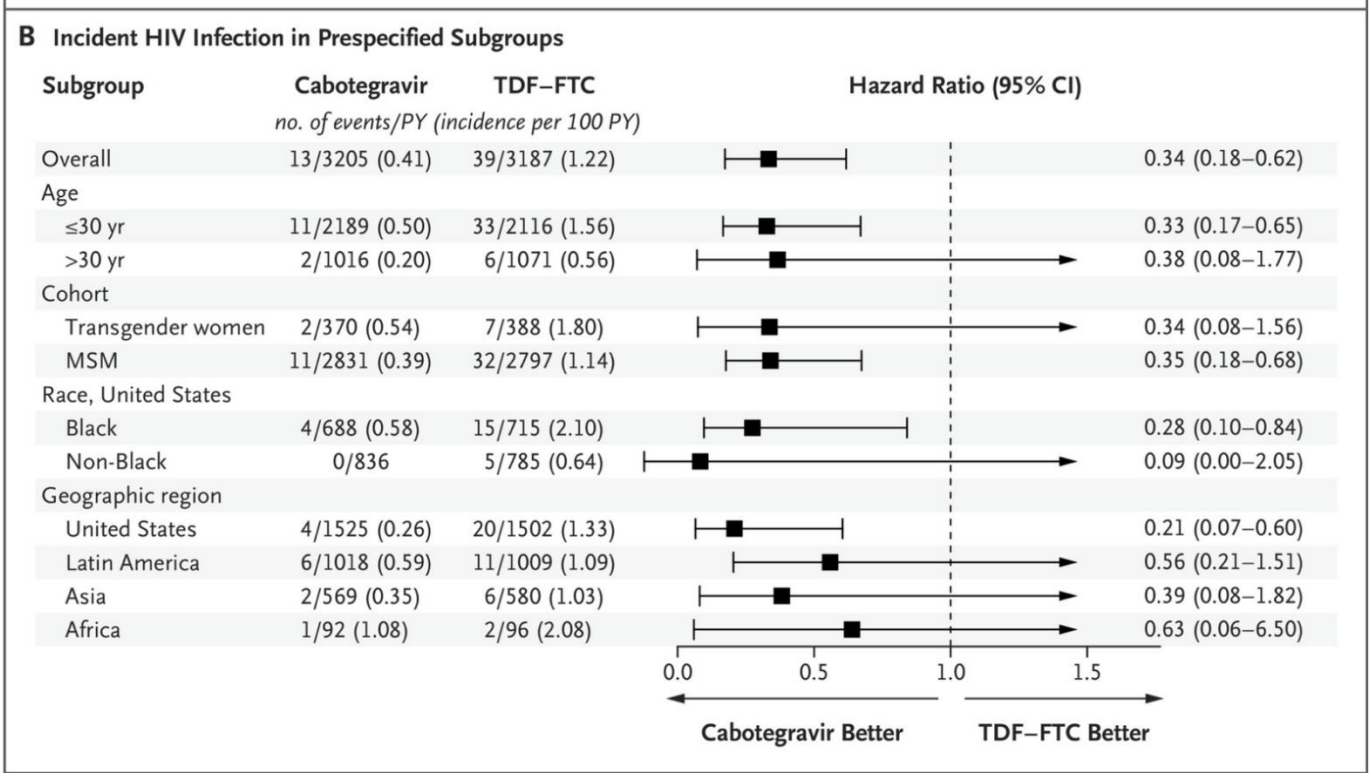
HPTN 083(3)
4570 patients underwent randomisation and baseline characteristics were similar between the two groups. Participant retention was 87% at one year, with a median follow-up of 1.4 years (IQR 0.8-1.9). The injection phase consisted of 8-weekly injections starting from week 5 and lasting until week 185.

Efficacy

HIV infection was acquired after enrolment by 52 participants – 13 in the CAB group (incidence 0.14 per 100 person-years) and 39 in the TDF-FTC group (incidence 1.22 per 100 years). The hazard ratio for infection in the CAB arm was 0.34 (95% CI 0.18-0.62). The effect was consistent across all prespecified subgroups. The trial was stopped early for efficacy at the first pre-planned interim analysis. Of the 13 infections in the CAB group, 4 were deemed to have occurred before enrolment, 5 occurred in patients who had not taken a recent dose of CAB, 3 occurred in the oral

lead-in phase, and 4 occurred in participants who had received the injectable form of CAB, and were adherent to the regimen. CAB drug levels were normal in these four patients.





CAB resistance mutations

Integrase gene resistance was detected in 5 patients in the CAB arm (1 with baseline infection and 4 with incident infection). Of note, none of these cases occurred in the "tail" phase after CAB administration.

Safety

With the exception of injection site reactions, the side-effect profile was very similar between the two arms. Grade 2 or higher adverse events (AEs) occurred in over 90% of both arms, driven primarily by decreased creatinine clearance (in ~71% of participants overall). Serious AEs occurred in 5.3% of each arm. There were 11 deaths in the study – 7 in the TDF-FTC arm (1 thought to be related to the drug) and 4 in the CAB arm (none thought to be related to the drug). Injection site reactions were reported in 81% of the CAB arm (vs 31% of the TDF-FTC arm), were mostly mild-moderate in severity, and occurred mostly with the initial doses. 2.4% of participants in the CAB arm permanently discontinued the injections due to an injection-related AE. A mean annualised increase in weight of 1.23 kg (95% CI 1.05-1.42) was seen in the CAB arm, compared to 0.37kg (0.18-0.55) in the TDF-FTC arm.

Refer to table 1 for the summary of findings for the HPTN 083(3) trial.

HPTN 084(4)

3224 participants were enrolled; baseline characteristics were again well-balanced between the two arms. Participant retention was 90% at one year, and 86% at two years, and the median follow-up period was 1.24 years (IQR 0.92-1.56). The injection phase consisted of 8-weekly infections from week 5 to week 153.

Efficacy

40 incident HIV infections occurred in the trial – 4 in the CAB group (incidence 0.2 per 100 person-years, 95% CI 0.06-0.52)) and 36 in the TDF-FTC group (incidence 1.85 per 100 person years, 95% CI 1.3-2.57). The hazard ratio was 0.12 (95% CI 0.05-0.31, p<0.0001). Of the 4 incident cases in the CAB arm, 3 occurred prior to receiving any CAB injections, and the 4th case occurred after a delayed visit of 16 weeks between injections. Outcomes were consistent across prespecified subgroups. As with HPTN 083, the trial was stopped early due to efficacy.

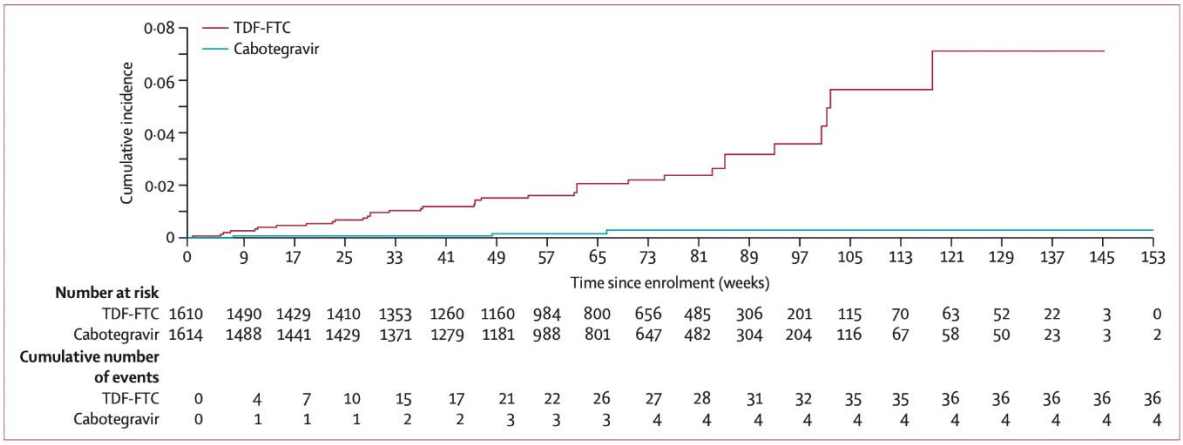


***Figure 3*: Cumulative HIV incidence by study group**
Kaplan-Meier estimates of HIV infection are shown. Four HIV infections were observed in the cabotegravir group (HIV incidence 0·20 per 100 person-years [95% CI 0·06–0·52]) and 36 in the TDF-FTC group (1·85 per 100 person-years [1·3–2·57]). Participants in the cabotegravir group had an 88% lower risk of HIV infection than those in the TDF-FTC group (hazard ratio 0·12 [0·05–0·31]; p<0·0001). TDF-FTC=tenofovir disoproxil fumarate plus emtricitabine.

CAB resistance mutations

No major *integrase* resistance mutations were detected in any of the four "breakthrough" infections in the CAB group.

Safety

Safety findings were very similar to those in HPTN 083, and with the exception of injection-site reactions (which were more common in the CAB group, 38% vs 10%), these were well-balanced between groups. Grade 2 or worse AEs occurred in 92% of participants (again driven by a change in creatinine clearance that was not clinically significant in the majority of cases), and grade 3 or worse AEs in 17%. Serious AEs occurred in 2.0% of each arm. No injection-site reactions led to discontinuation. There were 3 deaths in the CAB arm (vs 0 in the TDF-FTC arm) but none were thought by blinded assessors to be linked to the drug. Weight gain was again more prominent in the CAB arm, but the difference was relatively small (2.4 kg per year vs 2.1 kg per year).

Refer to table 2 for the summary of findings for the HPTN 083(4) trial.

Table 1: Summary of findings for the HPTN 083 trial

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LA-CAB	TDF-FTC	Hazard (95% CI)	Absolute (95% CI)		
Incident HIV (follow-up: mean 1.4 years; assessed with: per 100 person-years)												
1	RCT	serious[a]	not serious	not serious	not serious	strong association	0.41 per 100 person years	1.22 per 100 person years	**HR 0.34** (0.18 to 0.62)	**8 fewer per 1,000 person years** (from 10 fewer to 5 fewer)	⊕⊕⊕⊕ High	CRITICAL
Grade 2 or higher Adverse Events (follow-up: mean 1.4 years)												
1	RCT	serious[a]	not serious	not serious	not serious	none	2106/2280 (92.4%)	2116/2282 (92.7%)	**RR 1.00** (0.98 to 1.01)	**0 fewer per 1,000 person years** (from 19 fewer to 9 more)	⊕⊕⊕◯ Moderate	IMPORTANT

CI: confidence interval; **LA-CAB:** long-acting carbotegravir; **RCT**: randomised controlled trial; **RR:** risk ratio

Explanations

a. Trial stopped early for benefit

Table 2: Summary of findings for the HPTN 084 trial

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LA- CAB	TDF-FTC	Hazard (95% CI)	Absolute (95% CI)		
Incident HIV (follow-up: mean 1.24 years; assessed with: 100 patient years)												
1	RCT	serious[a]	not serious	not serious	not serious	very strong association	0.2 per 100 person years	1.85 per 100 person years	**HR 0.12** (0.05 to 0.31)	**16 fewer per 1,000 person years** (from 18 fewer to 13 fewer)	⊕⊕⊕⊕ High	CRITICAL
Grade 2 or higher Adverse Events (follow-up: mean 1.24 years)												
1	RCT	serious[b]	not serious	not serious	not serious	none	1487/1614 (92.1%)	1486/1610 (92.3%)	**HR 1.00** (0.95 to 1.05)	**0 fewer per 1,000** (from 11 fewer to 9 more)	⊕⊕⊕◯ Moderate	IMPORTANT

CI: confidence interval; **LA-CAB:** long-acting carbotegravir; **RCT**: randomised controlled trial; **RR:** risk ratio

a. Trial stopped early due to efficacy. Limited number of events.

b. Trial stopped early due to efficacy.

Conclusions

Two well-conducted RCTs both demonstrated the markedly superior efficacy of CAB relative to TDF-FTC; both trials were stopped early for efficacy. 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. Given the long pharmacokinetic "tail" of CAB, there is a theoretical concern that non-adherence might drive the development of integrase-inhibitor drug resistance (due to there being a prolonged period of sub-therapeutic drug levels with non-adherence). This was not borne out by either trial however, although the absolute number of incident HIV cases is still very low.

Of note:

- CAB data for pregnant women is extremely limited, and so the safety and efficacy in this subgroup has not been established. This is being researched currently via an open-label extension to HPTN083.
- As the trials were stopped early, long-term safety data is not available yet; the median follow-up was 1.4 years in HPTN083 and 1.24 in HPTN084, instead of the planned 3 years. This longer-term data being collected via open-label extensions to both trials.
- Routine HIV diagnostics such as "rapid" HIV antibody testing and ELISA assays were found to be associated with delayed diagnosis of incident HIV infections in both studies, and so HIV viral load testing may need to be performed instead to ensure that incident infections are rapidly detected. This is in contrast to HIV PrEP with tenofovir/emtricitabine, where screening for HIV by rapid tests or ELISA is adequate. Delayed diagnosis of incident HIV likely contributed to the development of drug resistance in several cases.
- There are important drug-drug interactions, including with rifampicin, that might limit CAB's use in programmatic settings.
- The total budgetary cost of CAB remains to be fully assessed, as the price is not currently known.

As no safety concerns were identified during the oral lead-in phase in these prevention studies and also in treatment studies, it is possible that this can be omitted. However, clinical data for this is currently lacking. It is being researched in an open-label extension to HPTN083 and HPTN084.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			
Recommendation: Although the efficacy of CAB is high, and the safety profile acceptable, the PHC/Adult Hospital Level Committee suggests not to use CAB as PrEP for HIV, until such time as the price becomes known, and the evidence of efficacy for regimens that do not include an oral lead-in phase are available. *Rationale:* Two phase 3 RCTs both found that PrEP with long-acting injectable CAB had greater efficacy than oral tenofovir plus emtricitabine. A model to assess budgetary impact and cost-effectiveness analysis has been developed, however until a price is confirmed, a final recommendation cannot be made. **Level of Evidence: High certainty evidence** **Review indicator:** Evidence of efficacy in regimens that do not require oral lead-in doses, information on cost.					
NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022): Accepted **UPDATED NEMLC RECOMMENDATION (e-ratified, 30 MARCH 2023):** Updated recommendation following completion of the budget impact analysis (March 2023) ratified by NEMLC, as above.					
Monitoring and evaluation considerations					
Research priorities					

NEMLC COMMENTS ON DONATED STOCK (29 AUGUST 2024)

The Committee noted that donated stock of CAB from USAID has been accepted by the NDoH, in accordance with the SAHPRA's medicine donations policy. The donation will be for a 2-year period. The NEMLC raised the following concerns regarding this donation of CAB for PrEP which were addressed by the programme as detailed below:

IMPLEMENTATION CONSIDERATIONS:

- The standard ART regimen in South Africa is dolutegravir based. Defaulting while on CAB therapy could result in HIV acquisition with potential integrase inhibitor resistance. Monitoring and support to minimize the risk of defaulting CAB therapy is recommended. Programme guidance and training on screening candidates who are most likely to benefit from therapy is advised. NEMLC notes the plan for screening, monitoring, and support, as outlined in the guidelines provided by the programme including the development of a comprehensive job aid. NEMLC notes that people who seroconvert will be identified, and transitioned to ARV therapy with adequate monitoring as appropriate.
- Clients on CAB therapy who have a breakthrough infection are at high risk of false negative HIV test results if standard HIV antibody- and/or antigen-based diagnostic tests are used. It is suggested that nucleic acid testing be considered instead (e.g. HIV viral load), possibly for a limited assessment period in view of the cost implications with expanded viral load testing. NEMLC notes the testing strategy outlined in the programme guidelines, as it stands. NEMLC also understands that alternative strategies are being implemented currently in pilot sites, and that the programme may amend their strategy, based on findings from these pilot sites.
- Adequate monitoring of both benefits and harms is strongly recommended to inform decision making once the donated stock is depleted. NEMLC notes that facilities identified as pilot sites will be required to record CAB uptake on a tracker register as part of three different PrEP products offered at these sites. Data on uptake, retention and switches will be recorded in a standardized format at each site and collated monthly.

SUSTAINABILITY OF SUPPLY CONSIDERATIONS:

- Concerns regarding continuity of care (once donated stock is depleted) were noted as CAB remains a non-EML medicine, until such time that more affordable generic alternatives become available. NEMLC notes the continuity of care recommendations put forward by the programme - should alternative access to injectable PrEP not be available at the end of the 2-year pilot program, clients will be transitioned to oral PrEP. NEMLC acknowledges though that moving clients at high risk of HIV acquisition to a less effective method of prevention, is not ideal.

Appendix 2: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [x] Moderate [ ] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Two large well-designed RCTs showing substantially better efficacy of CAB over TDF-FTC – see grade tables above
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [x] None [ ]	Men/transgender women: 8 fewer infections per 1000 patient years (95% CI: 5-10) compared to oral TE. Women: 13 fewer infection per 1000 patient years (95% CI 14-18) compared to oral TE.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [x] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Two large well-designed RCTs showing that CAB regimen was generally well-tolerated, and as well tolerated as TDF-FTC - see grade tables above
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [X] None [ ]	CAB compared to TE: Serious AEs were uncommon (2-5%), as were drug discontinuations (0-4%). No deaths were attributable to CAB in either trial.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [x] Favours control [ ] Intervention = Control *or* Uncertain [ ]	Strong reduction in incident HIV at the cost of more injection site reactions, the vast majority of which were mild/moderate and settled with time.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	Feasible, but would require more frequent patient visits to clinic (8-weekly). Would also likely require retraining for healthcare workers on good injection technique.
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [x]	Not registered with SAHPRA and so SEP unknown. A recent cost-effectiveness analysis concluded: "*The cost per CAB-LA injection needed to be less than twice that of a 2-month supply of TDF/FTC to remain as cost-effective, with threshold prices ranging between $9.03/injection [high uptake; CAB taken for median 12 months vs 5 months on TDF/FTC] and $14.47/injection [medium uptake; CAB and TDF/FTV both taken for median 5 months].*"(6) - https://dx.doi.org/10.2139/ssrn.4047136

		See attached budget impact analysis in the appendix. Local price is needed to confirm budget impact and determine affordability.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	Survey data and clinical trial suggest a patient preference for long-acting injectable forms of PrEP.(5)
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	No survey data available pertaining to equity, but the Committee was of the opinion that there would be no impact on health inequity.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	15 May 2022	JN. LJ	Although the efficacy of CAB is high, and the safety profile acceptable, CAB is not recommended as PrEP for HIV, until the medicine is SAHPRA-registered, available at an affordable price and there is updated evidence of efficacy for regimens that do not include an oral lead-in phase are available.
V5.0	28 March 2023	ERC Update	The recommendation has been updated following registration by SAHPRA and completion of the BIA, although a final price is yet to be announced.
V5.1	29 August 2024	NEMLC update	NEMLC comments added in response to donated stock offered by USAID

References

1. Chou R, Evans C, Hoverman A, Sun C, Dana T, Bougatsos C, et al. Preexposure Prophylaxis for the Prevention of HIV Infection: Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2019;321(22):2214-30.
2. Stankevitz K, Grant H, Lloyd J, Gomez GB, Kripke K, Torjesen K, et al. Oral preexposure prophylaxis continuation, measurement and reporting. Aids. 2020;34(12):1801-11.
3. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. New England Journal of Medicine. 2021;385(7):595-608.
4. Delany-Moretlwe S, Hughes JP, Bock P, Ouma SG, Hunidzarira P, Kalonji D, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet. 2022;399(10337):1779-89.
5. Quaife M, Eakle R, Cabrera Escobar MA, Vickerman P, Kilbourne-Brook M, Mvundura M, et al. Divergent Preferences for HIV Prevention: A Discrete Choice Experiment for Multipurpose HIV Prevention Products in South Africa. Medical Decision Making. 2018;38(1):120-33.
6. Jamieson L, Johnson LF, Nichols BE, Delany-Moretlwe S, Hosseinipour MC, Russell C and Meyer-Rath G. The Relative Cost-Effectiveness of Long-Acting Injectable Cabotegravir Versus Oral Pre-Exposure Prophylaxis: A Modelled Economic Evaluation and Threshold Analysis in South Africa Based on the HPTN 083 and 084 Trials. Available at SSRN: https://ssrn.com/abstract=4047136 or http://dx.doi.org/10.2139/ssrn.4047136