Clinical consequences of delaying implementation of long-acting antiretroviral therapy for people with HIV and persistent viremia in the US

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BACKGROUND

- Small studies have shown Long-acting injectable cabotegravir/ rilpirivine (LA-CAB/RPV) can achieve viral suppression among people with HIV (PWH) with persistent viremia and adherence challenges, when intensive support services (ISS) are available.
- US guidelines recommend CAB/RPV for PWH with viremia only in limited situations, with concerns of developing resistance; at least one new trial is being planned.
- **OBJECTIVE**: to project the clinical outcomes from implementing LA-CAB/RPV now for PWH with persistent viremia and intermittent care engagement (ICE), compared to delaying implementation while awaiting trial data.

METHODS

- Model: the validated Cost-Effectiveness of Preventing AIDS Complications (CEPAC) microsimulation model.
- Population: PWH in the US with persistent viremia and ICE.
- Two approaches (both with ISS to maximize adherence):
  1) Daily integrase strand transfer inhibitor (INSTI)-based oral ART;
  2) LA-CAB/RPV
- Four CAB/RPV implementation (1-time)/uptake (over time) scenarios:
  1) *Current practice* (1% modeled population on CAB/RPV);
  2) *100% implementation* (100% modeled population on CAB/RPV) with 0-5yr delay;
  3) *New trials* scenarios:
     A) 1yr *Single-arm trial* (*SAT*) with 5% uptake/yr thereafter;
     B) 3yr *Randomized controlled trial* (*RCT*) with 15% uptake/yr thereafter;
  4) *Immediate uptake* of 1-20% uptake/yr.
- Outcomes: virologically-suppressed-person-years (VSPY), person-years (PY) with viremia, and deaths over model time of 5 yrs.

Table 1. Select model input parameters

Parameter	Value	Source
Mean Age (SD), years	47 (10)	1
Initial CD4 count (SD), cells/μL	150 (75)	1
HIV RNA suppression rate 6 months after ART initiation		
INSTI-ISS	23%	2-7
CAB/RPV-ISS	65%	8,9
PI-ISS (after CAB/RPV non-suppression)	9%	7,10
Probability of suppression on CAB/RPV at 6 months after discontinuing treatment due to non-adherence	32.5%	9, Assumption
Monthly probability of non-suppression on CAB/RPV	0.27%	8
Disengagement from care on CAB/RPV at 12 months	22%	2
Relative background non-HIV-related mortality vs. the general population	9	11
Modeled population size	34,500	Assumption
Time horizon	5 years	12, Assumption

1. Christopoulos *AMEAS* 2023
2. Flash *OFID* 2019
3. SAX *Lancet* 2017
4. Raffi *Lancet* 2013
5. Clotet *Lancet* 2014
6. Gallant *Lancet* 2017
7. Cheng *Medicine* 2018
8. Margolis *Lancet* 2017
9. Hsu *OFID* 2023
10. Gordon *APCS* 2015
11. Shebl *PLOS ONE* 2023
12. Flexner *CROI* 2024

Intensive support services to ensure on-time injections and other efforts to make long-acting ART more widely available should be strengthened while awaiting additional trial results.

- Sensitivity analysis: 1) One-way. 2) Two-way: impact of different trial delay and uptake. 3) Multivariate: implication of developing resistance in a 'pessimistic scenario' with 3 different *'resistance multipliers':* i) probability of non-suppression on CAB/RPV doubled, ii) probability of suppression on CAB/RPV after discontinuing treatment due to non-adherence halved, and iii) probability of suppression on PI on after CAB/RPV non-suppression halved.

RESULTS

Implementation scenarios (Table 2)

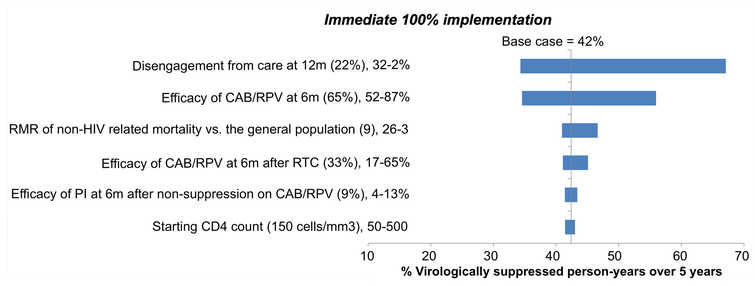
- *Current practice* projects 40,630 VSPY and 17,880 deaths at 5yrs.
- *Immediate 100% implementation* increases VSPY by 28,690 and averts 3,980 deaths. Each year of delay to *100% implementation* produces 5,740 fewer VSPY and 800 more deaths.
- *SAT* yields 1,490 more VSPY and 200 fewer deaths than *Current practice*; *RCT* yields 1,100 more VSPY and 90 fewer deaths.
- *Immediate uptake* yields similar gains in VSPY to *SAT* and *RCT* at ~3% uptake/yr and ~2% uptake/yr (Fig 2).

One-way sensitivity analysis: Most influential parameter on VSPY in *Immediate 100% implementation* is the probability of disengagement from care (Fig 1). Similar results are observed in all scenarios.

Table 2. Model-projected outcomes in different CAB/RPV implementation scenarios

Pre-trial scenarios			
	VSPY	PY with viremia	Deaths
Current practice	40,630	86,290	17,880
Immediate 100% implementation	69,320	74,890	13,900
***100% implementation* scenarios – impact of years delayed**			
	Compared to Immediate 100% implementation		
Delay	Decrease in VSPY	Increase in PY with viremia	Increase in deaths
1-year	10,990	2,260	1,240
2-year	15,510	3,500	1,930
3-year	19,630	5,120	2,660
4-year	23,380	7,160	3,420
***New trials* scenarios**			
	Compared to current practice		
	Increase in VSPY	Decrease in PY with viremia	Decrease in deaths
Single-arm trial (SAT)	1,490	1,020	200
Randomized controlled trial (RCT)	1,100	910	90
***Immediate uptake* scenarios**			
	Compared to current practice		
% uptake/year	Increase in VSPY	Decrease in PY with viremia	Decrease in deaths
3% uptake/year	1,430	890	200
10% uptake/year	4,770	2,970	680
20% uptake/year	9,520	5,910	1,350

Figure 1. One-way Sensitivity analysis on *Immediate 100% implementation* scenario for the outcome of virologically suppressed person-years.



Two-way sensitivity analysis: tradeoff between delay and uptake (Fig 2).

Figure 2. Virologically suppressed person-years gained over 5 years, compared to *Current practice*. [a] SAT, [b] RCT.

Uptake/year, %	Years of delay to trial end: 0	1	2	3	4
20	9,520	5,960	3,300	1,470	400
15	7,150	4,470	2,480	[b] 1,100	300
10	4,770	2,980	1,650	740	200
5	2,390	[a] 1,490	830	370	99
3	1,430	890	500	220	60
2	960	600	330	150	40
1	480	300	170	70	20

10,000 8,000 6,000 4,000 2,000 0

Increase in virologically suppressed person-years

Multivariate sensitivity analysis: Controlling for disengagement from care, in a 'pessimistic scenario' of developing resistance, CAB/RPV is still the strategy that has higher VSPY (Table 3).

Table 3. Model outcomes of a 'pessimistic scenario' of developing resistance

	Probability of disengagement from care	VSPY	PY with viremia	Deaths
Current practice	0.5x base case	52,820	77,660	16,710
Immediate 100% implementation x 3 *resistance multipliers*	0.5x base case	78,700	67,860	13,170
Current practice	2x base case	25,260	96,270	19,580
Immediate 100% implementation x 3 *resistance multipliers*	2x base case	41,340	96,200	16,030

LIMITATIONS

- The number of PWH with persistent viremia in the US who might be eligible for CAB/RPV with ISS is uncertain.
- The timing and uptake of CAB/RPV after a trial, either single-arm or RCT, is uncertain.
- These results do not apply to PWH not engaged in care at all since some connection with health care is needed for CAB/RPV initiation and continued engagement.

CONCLUSIONS

- Immediate implementation of CAB-RPV in PWH with persistent viremia and intermittent care engagement would lead to substantially more years with viral suppression and fewer deaths compared to waiting for more evidence.
- Intensive support services to ensure on-time injections and other efforts to make this therapy more widely available should be strengthened while awaiting additional trial results.

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