Clinical impact and cost-effectiveness of making third-line antiretroviral therapy available in sub-Saharan Africa: A model-based analysis in Côte d'Ivoire

Appendix

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APPENDIX

Appendix A1: Extended list of input parameters

Table A1-1: Additional input parameters
Table A1-2: Characteristics at observed 2nd-line ART failure

Appendix A2: HIV secondary transmission rates

Table A2: HIV secondary transmission rates
Technical appendix A2: HIV secondary transmission calculation

Appendix A3: Main outcomes, undiscounted life expectancy and costs

Table A3: Outcomes of different treatment strategies in patients with observed 2nd-line antiretroviral therapy failure: base case analysis and analyses in different contexts of monitoring (Undiscounted life expectancy and cost)

Appendix A4: Extended one-way sensitivity analysis

Table A4: One-way sensitivity analysis on main input parameters, details

Appendix A5: 10-year survival with the four strategies in a cost-effectiveness analysis of 3rd-line ART in Côte d'Ivoire

Legend to figure A5:

C-ART2: Continue 2nd-line ART
AR-ART2: Adherence reinforcement, continue 2nd-line ART
IS-ART3: Immediate 3rd-line ART
AR-ART3: Adherence reinforcement, 3rd-line ART if failure persists
Percentage alive: percentage of patients still alive over time, among those who were diagnosed as failing 2nd-line
Time (years): time since 2nd-line failure was documented

Table A1-1: Additional input parameters

	Base case value	*Ref*	Sensitivity analysis	
			Range	Type
Sex, female, %	75%	[1]	-	
Pre-ART characteristics				
Age, mean (SD) years	37 (9)	[1]	[28 to 46]	*CI*
CD4, mean (SD) cells/µl	154 (102)	[1]	[52 to 256]	*CI*
Plasma HIV-1 RNA distribution, %		[2]		
>100,000	53		-	
30,001-100,000	22		-	
10,001-30,000	13		-	
3,001-10,000	5		-	
501-3,000	3		-	
49-500	4		-	
< 50	0			
Morbidity and mortality	*Published in:*	[3]		
ART efficacy and toxicity				
1st-line ART (1)				
HIV-1 RNA suppression at 6 months, %	80	[1]	[50 to 90]	ExtrV
Virologic failure after 6 months, per 100 PY	15	[1]	[7 to 22]	*CI*
Monthly CD4 increase, mean (SD) cell/µl (2)				
Between 0 and 2 months	77 (19)	[1]	[58-97]	*CI*
≥ 3 months	4 (1)	[1]	-	
ART toxicity (3)				
Minor	11	[4]	-	
Major				
Toxicity-related switch to 2nd line, %	5	[5]	[0 to 10]	ExtrV
Toxicity-related mortality, %	0.6	[4,5]	-	

Table A1-1 (Continued)

	Base Case Value	*Ref*	Sensitivity Analyses	
			Range	Type
2nd-line ART (1)				
HIV-1 RNA suppression at 6 months, %	80	1	[50 to 90]	ExtrV
Virologic failure after 6 months, per 100 PY	15	1	[7 to 22]	*CI*
Monthly CD4 increase, mean (SD) cell/µl (2)				
Between 0 and 2 months	77 (19)	1	[58-97]	*CI*
≥ 3 months	4 (1)	1	-	
ART Toxicity (3)				
Minor	27	6	-	
Major				
Toxicity-related switch to other 2nd line, %	7	7	[0 to 10]	ExtrV
Toxicity-related mortality, %	0.24	6,7	-	
3rd-line ART (1)				
HIV-1 RNA suppression at 6 months, %	80	1	[50 to 90]	ExtrV
Virologic failure after 6 months, per 100 PY	15	1	[7 to 22]	*CI*
Monthly CD4 increase, mean (SD) cell/µl (2)				
Between 0 and 2 months	77 (19)	1	[58-97]	*CI*
≥ 3 months	4 (1)	1	-	
ART Toxicity (3)				
Minor	24	8	-	
Major				
Toxicity-related switch to other 3rd line, %	1	8	[0 to 5]	ExtrV
Toxicity-related mortality, %	0.03		-	

Table A1-1 (Continued)

	Base case value	*Ref*	Sensitivity analysis	
			Range	Type
6-months adherence reinforcement and 2nd-line				
HIV-1 RNA suppression at 6 months, % (4)	30	Assump	[15 to 45]	*CI*
Virologic failure after 6 months, per 100 PY	15	1	[7 to 22]	*CI*
Monthly CD4 increase, mean (SD), cell/µl (2)				
Between 0 and 2 months	77 (19)	1	[58 to 97]	*CI*
≥ 3 months	4 (1)	1	-	
Monitoring and follow-up				
Interval between clinic visits, months	3	Assump	[1 to 6]	ExtrV
Interval between HIV RNA or CD4 tests, months	6	Assump	[3 to 12]	ExtrV
Loss to follow-up, per 100 PY				
0 - 12 months on 1st-line	12	9	[6 to 18]	*CI*
> 12 months on 1st-line, and on 2nd-line	9	9	[4 to 15]	*CI*
Costs, USD				
Drugs, per month				
1st-line ART	16	10	-	
2nd-line ART	42	10	[21 to 63]	*CI*
3rd-line ART	164	11	[82 to 246]	ExtrV
1st- and 2nd-line ART toxicity (6)	69	12-14	-	
6-month adherence reinforcement (7)	153	Assump	[77 to 230]	*CI*
Laboratory monitoring, per test				
CD4 test	28	15	[14 to 43]	*CI*
HIV RNA test	99	15	[49 to 148]	*CI*
Follow-up				
Outpatient hospital care, per visit	4	14	-	
Routine care, per month				
Mean CD4 ≥ 200/ cell/µl	38	14	-	
Mean CD4 < 200 / cell/µl	28	14	-	

Footnotes to Table A1-1

ART: antiretroviral therapy; SD: standard deviation; PY: person-years; USD: US dollars; Ref: references, Assump: assumption; CI: confidence interval; ExtrV: extreme values.

Confidence intervals were derived from input data or estimated by multiplying the base case value by 0.5 for the lower bound and 1.5 for the upper bound.

(1) 1st-line ART: tenofovir or zidovudine + emtricitabine or lamivudine + efavirenz; 2nd-line ART: tenofovir or zidovudine + emtricitabine or lamivudine + lopinavir/ritonavir; alternative 2nd-line in patients with major LPV/r toxicity: tenofovir or zidovudine + emtricitabine or lamivudine + atazanavir/ritonavir; 3rd-line ART: 2 nucleoside reverse transcriptase inhibitors + raltegravir + darunavir/ritonavir.

(2) In the base case analysis, we assumed no plateau effect and a continued increase of CD4. In sensitivity analysis, we assumed that there was a plateau effect, with no CD4 count increase in patients on ART after 5 years of treatment.

(3) The probability of toxicity inducing ART switching was estimated at 12 months. The drug toxicity-related mortality was calculated by multiplying the probability of major toxicity [5,7,8], by the fatal toxicity rate [4,6] (1st-line: 0.047 x 0.133; 2nd-line: 0.069 x 0.035; 3rd-line: 0.01 x 0.035).

(4) We assumed that 60% patients with documented 2nd-line failure harbored a virus still sensitive to lopinavir/ritonavir,[16] and that 50% of these patients would reach virologic success after the adherence reinforcement phase.

(5) We assumed that in case of major toxicity on 2nd-line ART, patients switch to a sub-regimen associating 2NRTI and ritonavir boosted-atazanavir.

(6) ART major toxicity cost included 6 days of inpatient hospital care cost, which was estimated by multiplying the outpatient hospital care by 2.8 the ratio of inpatient to outpatient visits from the WHO Choice.[12-14]

(7) The adherence reinforcement involved 6 adherence training sessions (one/month) and weekly SMS reminders.

Table A1-2: Characteristics at 2nd line ART failure documentation

	Base case	Scenario analysis	
	Routine CD4, targeted VL	Routine CD4, no VL [1]	Routine CD4 and VL [2]
Age at observed 2nd-line failure, mean (SD) years	44.2 (10)	44.1 (9.9)	41.3 (9.4)
CD4 at observed 2nd-line failure, mean (SD) cells/µl	240 (195)	240 (210)	495 (255)
Plasma HIV-1 RNA distribution at observed 2nd-line failure, % [3]			
>100,000	53.2	50.3	38.1
30,001-100,000	22.3	21.1	21.5
10,001-30,000	12.9	12.1	16.6
3,001-10,000	5.3	4.9	11.0
501-3,000	3.0	2.6	9.2
49-500	3.3	2.9	3.6
< 50	0.0	6.2	0.0
Mean time from 1st-line ART initiation to true 1st-line failure, years	2.9	2.8	3.1
Mean time from 1st-line ART initiation to observed 1st-line failure, years	5.2	5.2	3.9
Mean time from 2nd-line ART initiation to true 2nd-line failure, years	2.9	2.8	3.1
Mean time from 2nd-line ART initiation to observed 2nd-line failure, years	5.4	5.3	3.8

Footnotes to Table A1-2

VL: viral load; SD: standard deviation; ART: antiretroviral therapy

(1) **Routine CD4, no viral load:** In these settings we assumed that viral load testing was not available, and that CD4 count was done every 6 months. The 2nd-line failure was diagnosed according to WHO criteria for immunological failure.[17] All patients diagnosed with immunological failure were included in the analysis. All projections of outcomes started when immunological failure was diagnosed.

(2) **Routine CD4 and viral load:** In these settings we assumed that CD4 count and viral load testing were done routinely every 6 months. The 2nd-line failure was diagnosed as a plasma viral load >1000 copies/ml or return to the set-point viral load level. All patients diagnosed with virologic failure were included in the analysis. All projections of outcomes started after virological failure was confirmed.

(3) The model displays set-point plasma viral load distribution. The percentages of patients with plasma viral load <1000 included the patients who were diagnosed as failing because they returned to their set-point viral load level (501-3,000; 500-49).

Mean time to true 1st-line ART failure: mean time from ART initiation to 1st-line ART failure, irrespective of whether the latter is diagnosed or not.

Mean time to observed 1st-line ART failure: mean time between ART initiation and the time when ART failure is documented.

Mean time to true 2nd-line ART failure: mean time between 2nd-line ART initiation and 2nd-line ART failure, irrespective of whether the latter is diagnosed or not.

Mean time to observed 2nd-line ART failure: mean time between 2nd -line ART initiation and the time when ART failure is documented.

Table A2: HIV secondary transmission rate (adapted from Attia et al, AIDS 2009) [18]

HIV RNA current level	Secondary HIV transmission per 100 person-years
>100,000 copies/mL	9.03
30,001 – 100,000 copies/mL	9.03
10,001 – 30,000 copies/mL	8.12
3,001 – 10,000 copies/mL	4.17
501 – 3,000 copies/mL	2.06
21 – 500 copies/mL	0.16
0 – 20 copies/mL	0.16

Technical appendix A2: HIV secondary transmission calculation

The secondary outcome was the cumulative number of secondary HIV cases 10 years after 2nd-line ART failure. This outcome was calculated based on a direct model output (updated level of plasma viral load) and on a parameter from the literature (viral load strata-specific risk of HIV transmission). The cumulative number of secondary HIV cases was defined as the number of HIV-negative people that would become HIV-infected due to the transmission of virus by an index patient who had failed 2nd-line. The number of secondary HIV cases during a given one-month period was estimated by multiplying the HIV transmission rate for a level of plasma viral load, as published in the literature,[18] by the corresponding number of people at this level of plasma viral load at the end of this month, as given by the model. The number of secondary cases at 10 years was calculated as the sum of the monthly cases.

The percentage of secondary HIV cases averted was defined as the ratio of the cumulative number of secondary HIV cases in each strategy compared to the cumulative number of HIV secondary cases in strategy C-ART2. The secondary HIV cases were not included in the cost-effectiveness analysis.

Table A3. Outcomes of different treatment strategies in patients with observed 2nd-line antiretroviral therapy failure: base case analysis and analyses in different contexts of monitoring (undiscounted life expectancy and lifetime cost)

	Primary outcomes					Secondary outcomes	
	Clinical			Economic			
	% alive at 2 years	% alive at 10 years	LE (months) [4]	Lifetime cost (2011 USD) [4]	ICER (USD /YLS)	% cases averted at 2 years [5]	% cases averted at 10 years [5]
Base case analysis: routine CD4, viral load testing to confirm failure [1]							
Continue 2nd-line ART (C-ART2)	75.8	6.0	54.5	5,120	-	-	-
Adherence reinforcement, continue 2nd-line ART (AR-ART2)	80.4	16.9	74.0	6,840	1,100	22.2	5.7
Adherence reinforcement, 3rd-line ART if failure persists (AR-ART3)	85.5	37.2	110.6	17,160	3,400	37.8	16.8
Immediate switch to 3rd-line ART (IS-ART3)	87.9	35.4	106.5	19,890	Dominated	59.2	15.1
Context analyses							
Routine CD4, viral load unavailable [2]							
Continue 2nd-line ART (C-ART2)	75.6	8.0	57.0	5,140	-	-	-
Adherence reinforcement, continue 2nd-line ART (AR-ART2)	80.0	18.7	76.3	6,850	1,100	22.1	5.5
Adherence reinforcement, 3rd-line ART if failure persists (AR-ART3)	85.3	38.0	111.9	17,160	3,500	37.6	16.1
Immediate switch to 3rd-line ART (IS-ART3)	87.7	36.6	108.8	20,000	Dominated	59.0	14.8
Routine CD4 and routine viral load [3]							
Continue 2nd-line ART (C-ART2)	90.8	28.1	93.7	9,180	-	-	-
Adherence reinforcement, continue 2nd-line ART (AR-ART2)	92.2	38.4	113.2	10,970	1,100	22.9	9.4
Adherence reinforcement, 3rd-line ART if failure persists (AR-ART3)	94.1	57.5	152.7	24,850	4,200	52.8	31.4
Immediate switch to 3rd-line ART (IS-ART3)	94.6	55.3	145.5	26,080	Dominated	61.0	25.5

Footnotes to Table A3

ART: antiretroviral therapy; LE: life expectancy; USD: US dollars; YLS: years of life saved.

Cases averted: number of cases from secondary HIV transmission that were averted in strategies AR-ART2, AR-ART3, and IS-ART2, compared to C-ART2.

(1) **Routine CD4, viral load testing to confirm failure:** In the base case we assumed that viral load testing was available and was use to confirm immunological failure. CD4 count was done every 6 months. line failure was diagnosed according to WHO criteria for immunological failure [17]. All patients diagnosed with immunological failure were included in the analysis. All projections of outcomes started when immunological failure was diagnosed and then confirmed by viral load (See Table A1-2 in technical appendix).

(2) **Routine CD4, viral load unavailable:** In these settings we assumed that viral load testing was not available, and that CD4 count was done every 6 months. 2nd-line failure was diagnosed according to WHO criteria for immunological failure.[17] All patients diagnosed with immunological failure were included in the analysis. All projections of outcomes started when immunological failure was diagnosed. As immunological criteria are imperfectly predictive of virological failure, 93.7% of the patients included in the analysis had true virologic failure (i.e. a plasma viral load >1000 copies/ml) and 6.3% had no virologic failure (i.e. a plasma viral load <1000 copies/ml) (see Table A1-2 in technical appendix).

(3) **Routine CD4 and routine viral load:** In these settings we assumed that CD4 count and viral load testing were done routinely every 6 months. 2nd-line failure was diagnosed as a plasma viral load >1000 copies/ml. All patients diagnosed with virologic failure were included in the analysis. All projections of outcomes started after virological failure was confirmed (See Table A1-2 in technical appendix).

(4) The life expectancy and the lifetime cost were undiscounted.

(5) In these cohorts with observed second-line failure, the estimated number of secondary HIV cases at 2 and 10 years with the C-ART2 strategy were 148/1,000 persons and 347/1,000 persons in the base case, 140/1,000 persons and 326/1,000 persons in the context of routine CD4, viral load unavailable and 133/1,000 persons and 435/1,000 persons in the context of routine CD4 and routine viral load.

Table A4: One-way sensitivity analysis on main input parameters

	Inputs for SA	Incremental cost effectiveness ratio (ICER) $/YLS			
		C-ART2	AR-ART2	AR-ART3	IS-ART3
Pre-ART characteristics					
Mean age, years	CI				
28		-	1,083	3,555	Dominated
46		-	1,096	3,654	Dominated
Mean CD4, cells/µl	CI				
52		-	1,094	3,570	Dominated
256		-	1,076	3,643	Dominated
ART efficacy and toxicity during initialization phase					
1st-line ART (1)					
HIV-1 RNA suppression at 6 months, %	ExtrV				
50		-	1,097	3,542	Dominated
90		-	1,082	3,631	Dominated
Virologic failure after 6 months, per 100 PY	CI				
7		-	1,086	3,621	Dominated
22		-	1,085	3,593	Dominated
Monthly CD4 increase 1st and 2nd months, mean cell/µl	CI				
58		-	1,090	3,572	Dominated
97		-	1,081	3,632	Dominated
Toxicity-related switch to 2nd line , %	ExtrV				
0		-	1,085	3,610	Dominated
10		-	1,085	3,611	Dominated
2nd-line ART (1)					
HIV-1 RNA suppression at 6 months, %	ExtrV				
50		-	1,101	3,524	Dominated
90		-	1,078	3,639	Dominated
Virologic failure after 6 months, per 100 PY	CI				
7		-	1,082	3668	Dominated
22		-	1,090	3,562	Dominated
Monthly CD4 increase 1st and 2nd months, mean cell/µl	CI				
58		-	1,090	3,582	Dominated
97		-	1,082	3,623	Dominated
Toxicity-related switch to other 2nd line, %	ExtrV				
0		-	1,087	3,604	Dominated
10		-	1,084	3,618	Dominated
1st and 2nd-line ART					
No CD4 increase ≥ 60 months (2)	ExtrV	0	1,094	3,529	Dominated

Table A4 (Continued)

	Inputs for SA	Incremental cost effectiveness ratio (ICER) $/YLS			
		C-ART2	AR-ART2	AR-ART3	IS-ART3
Characteristics at 2nd-line ART failure documentation					
CD4 count, mean cells/µl	ExtrV				
50		-	1,128	3,438	Dominated
400		-	1,041	3,841	Dominated
Plasma HIV-1 RNA distribution	ExtrV				
100% patients >100,000 cp/ml		-	1,089	3,574	Dominated
100% patients 3,000-10,000 cp/ml		-	1,075	3,647	Dominated
Characteristics after 2nd-line failure documentation					
6-month adherence reinforcement phase					
HIV-1 RNA suppression at 6 months, % (3)	ExtrV				
15		-	1,250	3,541	13,400
45		-	1,002	3,765	Dominated
Virologic failure after 6 months, per 100 PY	CI				
7		-	1,059	3581	Dominated
22		-	1,108	3,592	Dominated
Monthly CD4 increase 1st and 2nd months, mean cell/µl	CI				
58		-	1,097	3589	Dominated
97		-	1,078	3,546	Dominated
3rd-line ART (1)					
HIV-1 RNA suppression at 6 months, %	ExtrV				
50		-	1,086	4,462	Dominated
90		-	1,085	3,443	Dominated
Virologic failure after 6 months, per 100 PY	CI				
7		-	1,087	3,374	217,000
22		-	1,085	3,786	Dominated
Monthly CD4 increase 1st and 2nd months, mean cell/µl	CI				
58		-	1,085	3,690	Dominated
97		-	1,084	3,535	Dominated
Toxicity-related switch to other 3rd-line, %	ExtrV				
0		-	1,084	3,609	Dominated
5		-	1,087	3,600	Dominated
6-month adherence reinforcement and 3rd-line ART					
No CD4 increase ≥ 60 months (2)	ExtrV	-	1,094	3,606	Dominated

Table A4 (Continued)

	Inputs for SA	Incremental cost effectiveness ratio (ICER) $/YLS			
		C-ART2	AR-ART2	AR-ART3	IS-ART3
Monitoring and follow-up					
Interval between clinic visits, months	ExtrV				
1		-	1,086	3,594	Dominated
6		-	1,086	3,592	Dominated
Interval between HIV RNA or CD4 tests, months	ExtrV				
3		-	1,123	3,790	Dominated
12		-	1,057	3,422	39,500
Loss to follow-up, per 100 PY [4]	ExtrV				
x0.5 base case values		-	1,105	3,806	Dominated
x1.5 base case values		-	1,091	3,477	Dominated
Costs, USD					
Drugs, per month					
2nd-line ART	ExtrV				
21		-	894	3,848	Dominated
63		-	1,279	3,359	Dominated
3rd-line ART	ExtrV				
82		-	1,086	1,827	Dominated
246		-	1,086	5,377	Dominated
6-month adherence reinforcement [5]	ExtrV				
77		-	1,018	3,606	Dominated
230		-	1,156	3,600	Dominated
Laboratory monitoring, per test					
CD4 test	ExtrV				
14		-	1,061	3,572	Dominated
43		-	1,112	3,621	Dominated
Plasma HIV-1 RNA test	ExtrV				
49		-	1088	3,605	Dominated
148		-	1,084	3,605	Dominated

Footnotes to Table A4

SA: sensitivity analysis; ART: antiretroviral therapy; PY: person-years; USD: US dollars; Ref: references; CI: confidence intervals; ExtrV: extreme values; C-ART2: continue 2nd-line ART; AR-ART2: adherence reinforcement, continue 2nd-line ART; IS-ART3: immediate 3rd-line ART; AR-ART3: adherence reinforcement, 3rd-line ART if failure persists.

Confidence intervals were derived from input data or estimated by multiplying the base case value by 0.5 for the lower bound and 1.5 for the upper bound.

(1) 1st-line ART was tenofovir or zidovudine + emtricitabine or lamivudine + efavirenz; 2nd-line ART was tenofovir or zidovudine + emtricitabine or lamivudine + lopinavir/ritonavir; 3rd-line ART was 2 nucleoside reverse transcriptase inhibitors + raltegravir + darunavir/ritonavir.

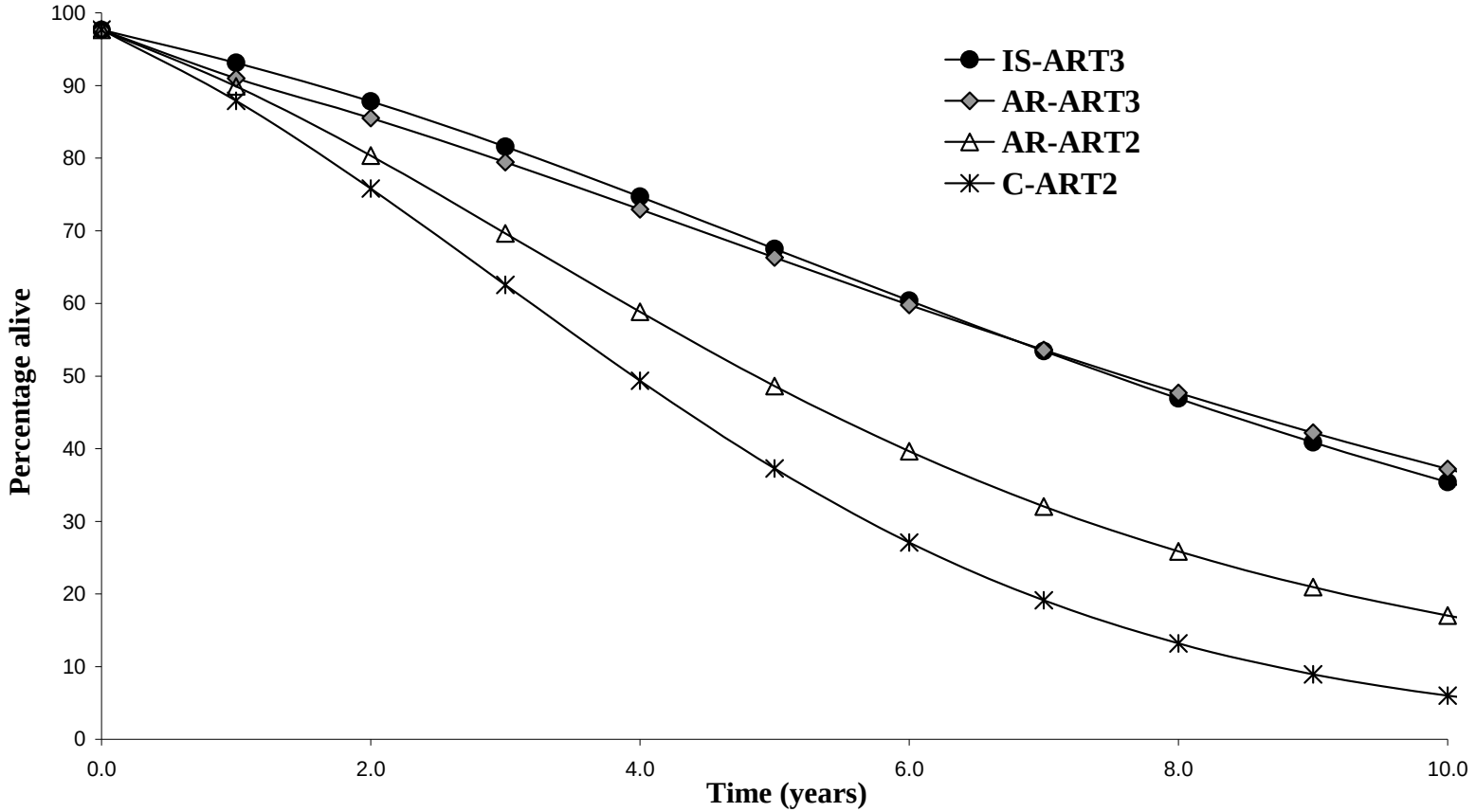
(2) In the base case analysis, we assumed a continued increase of CD4 with no plateau effect. In sensitivity analysis, we assumed that there was a plateau effect, with no CD4 count increase, in patients on ART after 5 years of treatment.[19]

(3) We assumed that 60% patients failed 2nd-line while harbouring a virus still sensitive to lopinavir/ritonavir [16], and that about 50% of these patients would reach virologic success after the adherence reinforcement phase.

(4) We varied both the probability of loss to follow-up from 0 to 12 months and after 12 months.

(5) The adherence reinforcement involved 6 adherence training sessions (one/month) and weekly SMS reminders.

Figure A5: 10-year survival with the four strategies in a cost-effectiveness analysis of 3rd-line ART in Côte d'Ivoire



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