A potential transition from a concentrated to a generalized HIV epidemic

the case of Madagascar

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Nov 27th, 2025

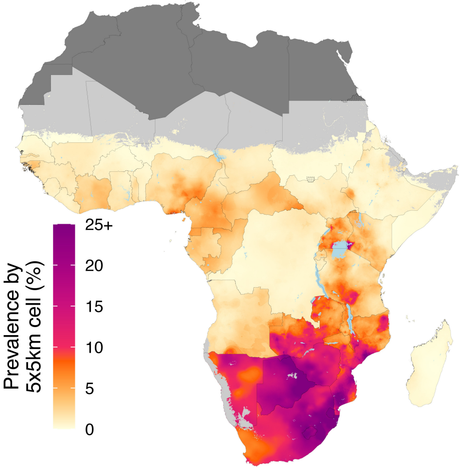
Some facts

- 37.6 million [30.2 million–45.0 million] people globally were living with HIV in 2020.
- 1.5 million [1.1 million–2.1 million] people became newly infected with HIV in 2020.
- 690 000 [480 000–1 million] people died from AIDS-related illnesses in 2020.
- 77.5 million [54.6 million–110 million] people have become infected with HIV since the start of the epidemic
- 34.7 million [26.0 million–45.8 million] people have died from AIDS-related illnesses since the start of the epidemic.

Global HIV & AIDS statistics

https://www.unaids.org/en/resources/fact-sheet

- Why different countries and sub-regions show disparate HIV epidemic profiles?



npr.org

Data...

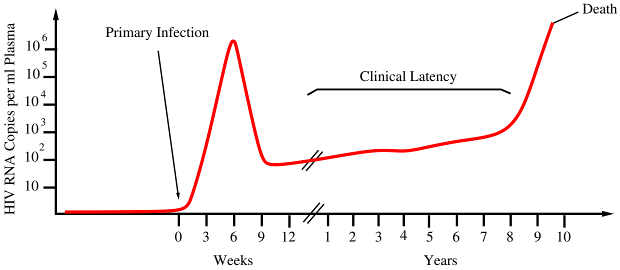
1. Little Data on Prevalence within SWs across main cities in Madagascar

	Sexual Worker Population				HIV Prevalence					
	2014		2017		2012			2016		
	Min	Max	Min	Max	%	CI		%	CI	
Antananarivo	28925	35021	4908	12647	0.2	0.0	0.6	1.8	0.4	4
Antsiranana	2978	6812	4489	10749	0.0	0.0	0.0	2.9	0.8	6.5
Mahajanga	2290	5637	571	1516	3.0	0.8	6.2	22.7	13.9	31.2
Toamasina	4289	12336	3638	15120	**1.8**	0.2	3.9	**5.4**	2.9	8.1
Fianarantsoa	3415	7795	743	2961	0.9	0.0	1.4	1.2	0.0	3.3
Toliary	4190	11367	1956	7530	1.2	0.0	3.9	2.7	0.7	5.1
Taolagnaro	1392	5059	830	2419	0.0	0.0	0.0	4.1	0.7	9.6
Moramanga	1648	2807	460	1388	0.3	0.0	0.5	0.6	0.0	5.7
Antsirabe	3677	9328	2150	6164	0.0	0.0	0.0	0.0	0.0	0.0
Morondava	1648	3672	502	1733	6.5	3.2	10.0	7.0	3.2	11.3
Nosy Be	7268	14830	2029	4048	—	—	—	9.5	4.5	15.3

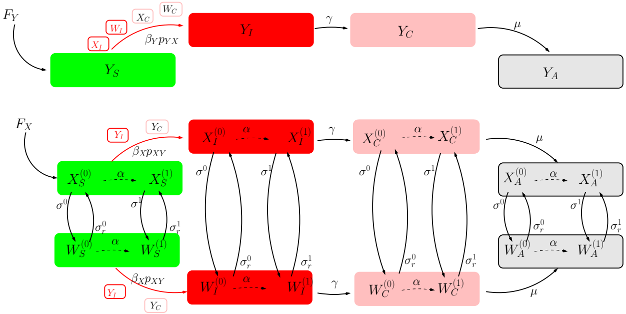
Data after the Institut National de la Statistique, Antananarivo, at 2018

2. Demographic data (detailed life tables from 2000)

Data from several public sources (WHO, CIA, Worlddometers)



Death
Primary Infection
Clinical Latency
HIV RNA Copies per ml Plasma
10
10^2
10^3
10^4
10^5
10^6
0 3 6 9 12
1 2 3 4 5 6 7 8 9 10
Weeks
Years



F_Y
X_C W_C
W_I
X_I
$\beta_Y p_{YX}$
Y_S
Y_I
γ
Y_C
μ
Y_A
F_X
Y_I Y_C
$\beta_X p_{XY}$
$X_S^{(0)}$ α $X_S^{(1)}$
$W_S^{(0)}$ α $W_S^{(1)}$
$X_I^{(0)}$ α $X_I^{(1)}$
$W_I^{(0)}$ α $W_I^{(1)}$
$X_C^{(0)}$ α $X_C^{(1)}$
$W_C^{(0)}$ α $W_C^{(1)}$
$X_A^{(0)}$ α $X_A^{(1)}$
$W_A^{(0)}$ α $W_A^{(1)}$
σ^0 σ^1 σ_r^0 σ_r^1
$\beta_X p_{XY}$
Y_I Y_C
γ μ

Sexual encounters...

$$Y_S + X_I^{(0)} \xrightarrow{\beta_{YX}\, p_{YX}\, \chi\, f_0\, f_X} Y_I + X_I^{(0)}$$

$$Y_S + X_I^{(1)} \xrightarrow{\beta_{YX}\, p_{YX}\, \chi\, f_1\, f_X} Y_I + X_I^{(1)}$$

$$Y_S + X_C^{(0)} \xrightarrow{\beta_{YX}\, p_{YX}\, f_0\, f_X} Y_I + X_C^{(0)}$$

$$Y_S + X_C^{(1)} \xrightarrow{\beta_{YX}\, p_{YX}\, f_1\, f_X} Y_I + X_C^{(1)}$$

$$Y_S + W_I^{(0)} \xrightarrow{\beta_{YX}\, p_{YX}\, \chi\, f_0\, f_W} Y_I + W_I^{(0)}$$

$$Y_S + W_I^{(1)} \xrightarrow{\beta_{YX}\, p_{YX}\, \chi\, f_1\, f_W} Y_I + W_I^{(1)}$$

$$Y_S + W_C^{(0)} \xrightarrow{\beta_{YX}\, p_{YX}\, f_0\, f_W} Y_I + W_C^{(0)}$$

$$Y_S + W_C^{(1)} \xrightarrow{\beta_{YX}\, p_{YX}\, f_1\, f_W} Y_I + W_C^{(1)}$$

$$\frac{dY_S}{dt} = F_Y - \beta_Y \, p_{YX} \, x \, Y_S - \delta \, Y_S$$

$$\frac{dY_I}{dt} = \beta_Y \, p_{YX} \, x \, Y_S - \delta \, Y_I - \gamma \, Y_I$$

$$\frac{dY_C}{dt} = \gamma \, Y_I - \mu \, Y_C - \delta \, Y_C$$

$$\frac{dY_A}{dt} = \mu \, Y_C - (1+m) \, \delta \, Y_A$$

$$\boxed{x = f_0 \, x_0 + (1 - f_0) \, x_1}$$

$$x_0 = \frac{f_W \, (\chi \, W_I^{(0)} + W_C^{(0)}) + (1 - f_W)(\chi \, X_I^{(0)} + X_C^{(0)})}{N_f}$$

$$x_1 = \frac{f_W \, (\chi \, W_I^{(1)} + W_C^{(1)}) + (1 - f_W)(\chi \, X_I^{(1)} + X_C^{(1)})}{N_f}$$

$$
\begin{aligned}
\frac{dX_S^{(1)}}{dt} &= -\beta_X\, p_{XY}\, y\, X_S^{(1)} - \delta\, X_S^{(1)} + \alpha\, X_S^{(0)} - \sigma^1\, X_S^{(1)} + \sigma_r^1\, W_S^{(1)} \\
\frac{dX_I^{(1)}}{dt} &= \beta_X\, p_{XY}\, y\, X_S^{(1)} - \delta\, X_I^{(1)} + \alpha\, X_I^{(0)} - \gamma\, X_I^{(0)} - \sigma^1\, X_I^{(1)} + \sigma_r^1\, W_I^{(1)} \\
\frac{dX_C^{(1)}}{dt} &= \gamma\, X_I^{(1)} - \mu\, X_C^{(1)} - \delta\, X_C^{(1)} + \alpha\, X_C^{(0)} - \sigma^1\, X_C^{(1)} + \sigma_r^1\, W_C^{(1)} \\
\frac{dX_A^{(1)}}{dt} &= \mu\, X_C^{(1)} - (1+m)\,\delta\, X_A^{(1)} + \alpha\, X_A^{(0)} - \sigma^1\, X_A^{(1)} + \sigma_r^1\, W_A^{(1)}
\end{aligned}
$$

$$
\boxed{y = \frac{\chi\, Y_I + Y_C}{N_m}}
$$

Model Parameter	Symbol	V_0	V_1	Refs.
Demographic parameters				
Recruitment rate into active sexual age	F_Y	0.00	$5\ 10^4$	[8]
Recruitment rate into active sexual age	F_X	0.00	$5\ 10^4$	[8]
Natural mortality percapita rate (X)	δ_X	0.01	0.05	[8]
Natural mortality percapita rate (Y)	δ_Y	0.01	0.05	[8]
Aging rate into the AF stage	α	0.08	0.12	
Transition rate into the SW stage (YF)	σ^0	0.00	0.05	
Reverse rate from the SW stage (YF)	σ_r^0	0.00	0.05	
Transition rate into the SW stage (AF)	σ^1	0.00	0.05	
Reverse rate from the SW stage (AF)	σ_r^1	0.00	0.05	
Disease transmission parameters				
Total male sexual contact rate	β_Y	96.0	120.0	[7]
Total female sexual contact rate	β_X	96.0	120.0	[7]
Sexual worker β_X factor $[(1+\eta)\beta_X]$	η	0.00	19.00	
Male-to-Female transmission probability	p_{XY}	0.00	0.005	[7, 5, 4]
Female-to-Male transmission probability	p_{YX}	0.00	0.001	[7, 5, 4]
Transition rate from I into C stage	γ	0.5	6.00	[3]
Transition rate from C into A stage	μ	0.05	0.20	[1]
Disease-induced mortality factor $[(1+m)\delta]$	m	0.00	99.00	
Infectious phase (I) transmission factor	χ	1.00	100.00	[6]
Male sexual preference factor (for SW)	f_W	0.00	0.99	
Male sexual preference factor (for YF)	f_0	0.00	0.99	

Table 1: Model Parameters for the *SICA* model. V_0 and V_1 define reasonable parameter ranges for each parameter value. Subscripts X and Y stand for female and male, respectively. YF, young female; AF, adult female; SW, sexual worker. All rates are given in year^{-1}. Mortality and recruitment rates are directly estimated from life table information. Transmission probabilities are given per coital act and represent basal values. The χ factor controls how much these are incremented when a healthy individual has a sexual encounter with an individual in the acute infection phase (I).

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Aging rate into the AF stage	α	0.08	0.12	
Transition rate into the SW stage (YF)	σ^0	0.00	0.05	
Reverse rate from the SW stage (YF)	σ_r^0	0.00	0.05	
Transition rate into the SW stage (AF)	σ^1	0.00	0.05	
Reverse rate from the SW stage (AF)	σ_r^1	0.00	0.05	
Disease transmission parameters				
Total male sexual contact rate	β_Y	96.0	120.0	[7]
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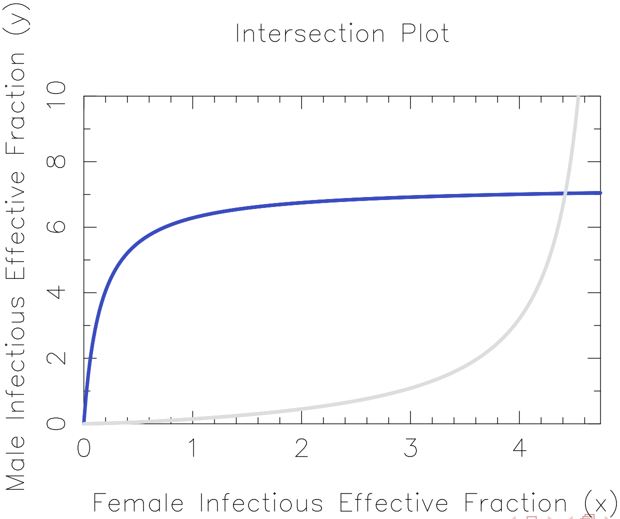
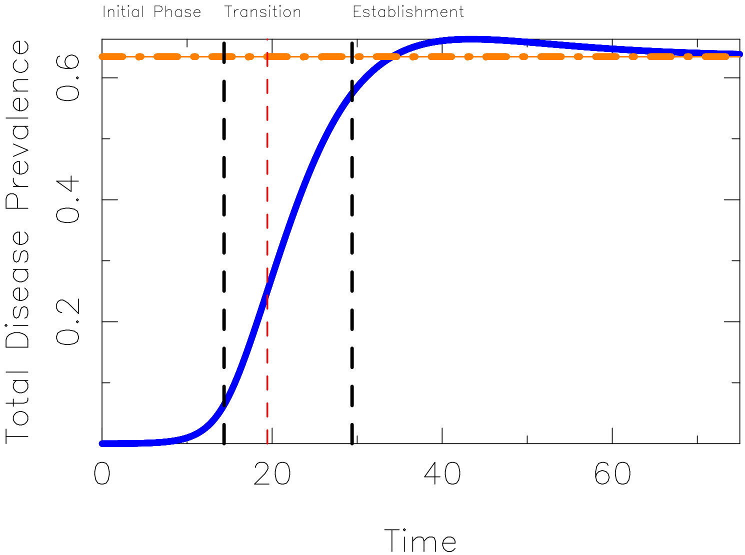
Table 2: Model Parameters for the *SICA* model. V_0 and V_1 define reasonable parameter ranges for each parameter value. Subscripts X and Y stand for female and male, respectively. YF, young female; AF, adult female; SW, sexual worker. All rates are given in year^{-1}. Mortality and recruitment rates are directly estimated from life table information. Transmission probabilities are given per coital act and represent basal values. The χ factor controls how much these are incremented when a healthy individual has a sexual encounter with an individual in the acute infection phase (I).

Some model analysis...




Initial Phase
Transition
Establishment
Total Disease Prevalence
0.2
0.4
0.6
0
20
40
60
Time

$$
\begin{aligned}
\frac{dY}{dt} &= F_Y - \delta_Y Y \\
\frac{dX^{(0)}}{dt} &= F_X - \sigma^0 X^{(0)} + \sigma_r^0 W^{(0)} - \alpha X^{(0)} - \delta_X X^{(0)} \\
\frac{dW^{(0)}}{dt} &= \sigma^0 X^{(0)} - \sigma_r^0 W^{(0)} - \alpha W^{(0)} - \delta_X W^{(0)} \\
\frac{dX^{(1)}}{dt} &= \alpha X^{(0)} + \sigma_r^0 W^{(1)} - \sigma^0 X^{(1)} - \delta_X X^{(1)} \\
\frac{dW^{(1)}}{dt} &= \alpha W^{(0)} + \sigma^0 X^{(1)} - \sigma_r^0 W^{(1)} - \delta_X W^{(1)}
\end{aligned} \tag{1}
$$

Further simplification...

$$
\begin{aligned}
\frac{dY}{dt} &= F_Y - \delta_Y Y \\
\frac{dX}{dt} &= F_X - \delta_X X
\end{aligned} \tag{2}
$$

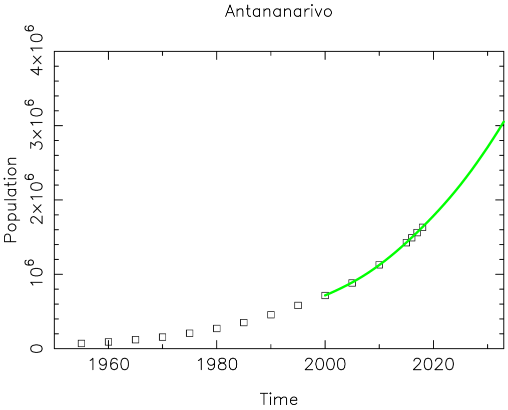


Figure 1: Demographic trends in Antananarivo. Solid green line: the numerical integration of the demographic model taking the population in 2000 as the initial condition, and time-dependent parameters F_Y, F_X, δ_X, δ_Y, all estimated from life table data (2000-2016). Squares represent population data.

Source: `http://www.worldometers.info/world-population/madagascar-population/`

The R_0, the reproductive number...

The NGM [2] can be reduced to:

$$\mathbf{K} = \begin{bmatrix} 0 & k_{(1,3)} & k_{(1,4)} & k_{(1,5)} & k_{(1,6)} \\ k_{(3,1)} & 0 & 0 & 0 & \\ k_{(4,1)} & 0 & 0 & 0 & \\ k_{(5,1)} & 0 & 0 & 0 & \\ k_{(6,1)} & 0 & 0 & 0 & \end{bmatrix}$$

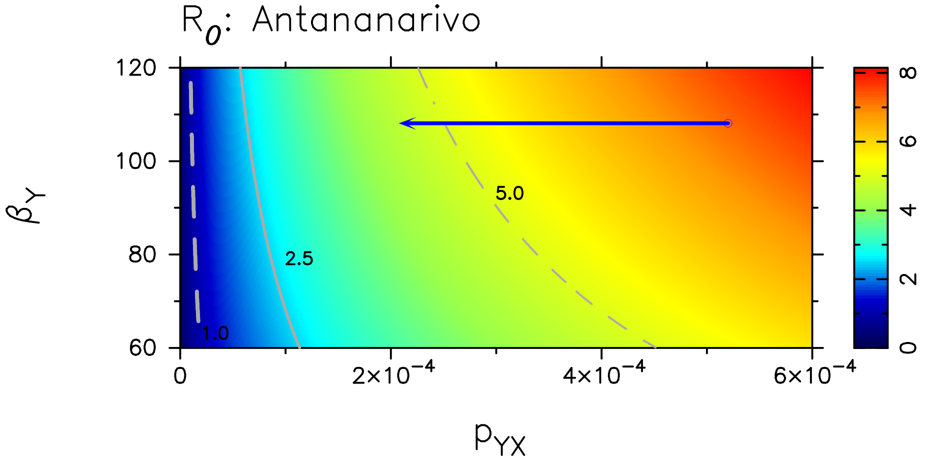
The characteristic equation thus reads:

$$\det(\mathbf{K} - \lambda \mathbf{I}) = -\lambda^{\mathbf{3}} \left(\lambda^{\mathbf{2}} - \mathbf{k}_{(\mathbf{1},\mathbf{3})}\mathbf{k}_{(\mathbf{3},\mathbf{1})} - \mathbf{k}_{(\mathbf{1},\mathbf{4})}\mathbf{k}_{(\mathbf{4},\mathbf{1})} - \mathbf{k}_{(\mathbf{1},\mathbf{5})}\mathbf{k}_{(\mathbf{5},\mathbf{1})} - \mathbf{k}_{(\mathbf{1},\mathbf{6})}\mathbf{k}_{(\mathbf{6},\mathbf{1})}\right)$$

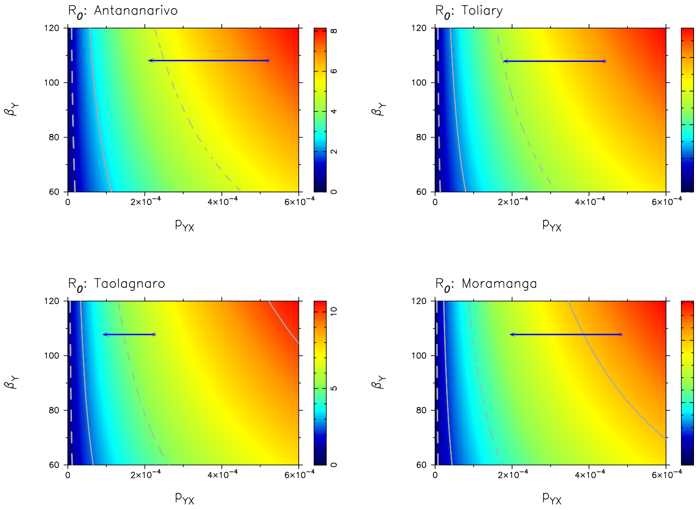
which leads to a final closed expression for R_0:

$$\boxed{R_0 = \sqrt{k_{(1,3)}k_{(3,1)} + k_{(1,4)}k_{(4,1)} + k_{(1,5)}k_{(5,1)} + k_{(1,6)}k_{(6,1)}}}$$

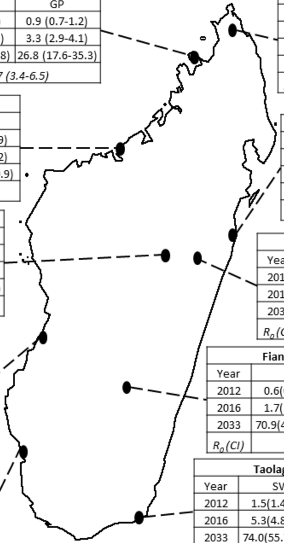
	Toliary	Taolagnaro	Moramanga
	Disease transmission parameters		
β_Y	108.282 ± 6.935	107.897 ± 6.775	108.158 ± 6.738
β_X	108.308 ± 6.955	108.342 ± 6.871	107.776 ± 6.900
η	6.248 ± 4.875	10.788 ± 4.389	14.804 ± 2.887
m_δ	50.306 ± 28.286	46.779 ± 29.143	50.387 ± 28.043
f_W	0.498 ± 0.221	0.400 ± 0.187	0.521 ± 0.237
f_0	0.522 ± 0.260	0.509 ± 0.273	0.804 ± 0.182
p_{XY}	0.003 ± 0.001	0.003 ± 0.001	0.003 ± 0.001
p_{YX}	0.001 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
γ	1.882 ± 1.005	2.415 ± 0.955	3.159 ± 0.564
μ	0.098 ± 0.050	0.105 ± 0.051	0.133 ± 0.051
χ	35.894 ± 24.942	49.076 ± 23.731	72.181 ± 18.285
R_0	5.110 ± 1.878	4.161 ± 0.841	7.323 ± 2.291



R_0: Antananarivo
120
100
80
60
0
2×10^{-4}
4×10^{-4}
6×10^{-4}
p_{YX}
β_Y
1.0
2.5
5.0
0
2
4
6
8



R0: Antananarivo
R0: Toliary
R0: Taolagnaro
R0: Moramanga
βY
pYX
120
100
80
60
0
2×10−4
4×10−4
6×10−4



Nosy Be, % (CI)		
Year	SW	GP
2012	2.9(2.8-3.2)	0.9 (0.7-1.2)
2016	9.8(9.0-10.3)	3.3 (2.9-4.1)
2033	72.5(45.8-88.8)	26.8 (17.6-35.3)
$R_0(CI)$	*4.97 (3.4-6.5)*	

Antsiranana, % (CI)		
Year	SW	GP
2012	1.0(0.1-1.1)	0.1 (0.1-0.3)
2016	3.8(3.5-3.9)	0.6 (0.4-1.0)
2033	75.4(57.9-87.3)	17.7 (10.9-25.5)
$R_0(CI)$	*4.96 (3.5-5.5)*	

Mahajanga, % (CI)		
Year	SW	GP
2012	6.9(6.5-7.4)	0.6 (0.4-0.9)
2016	22.3 (21.0-23.5)	2.0 (1.6-3.2)
2033	83.7(58.9-95.6)	17.6 (7.9-30.9)
$R_0(CI)$	*8.61 (4.8-12.4)*	

Toamasina, % (CI)		
Year	SW	GP
2012	1.7(1.5-1.8)	0.3 (0.1-0.6)
2016	5.7(5.3-6.1)	1.0 (0.6-1.8)
2033	80.5(58.4-91.7)	23.0 (13.9-33.0)
$R_0(CI)$	*5.27 (3.3-7.3)*	

Antananarivo, % (CI)		
Year	SW	GP
2012	0.6(0.6-0.7)	0.1 (0.0-0.2)
2016	2.3(2.1-2.4)	3.4 (0.2-0.7)
2033	80.5(63.7-89.9)	24.6 (12.5-33.8)
$R_0(CI)$	*6.58 (2.7-10.3)*	

Moramanga, % (CI)		
Year	SW	GP
2012	0.8(0.7-0.9)	0.05 (0.04-0.08)
2016	2.9(2.6-3.2)	0.2 (0.1-0.2)
2033	75.5(55.1-89.2)	9.3 (4.7-15.8)
$R_0(CI)$	*9.39 (4.9-13.9)*	

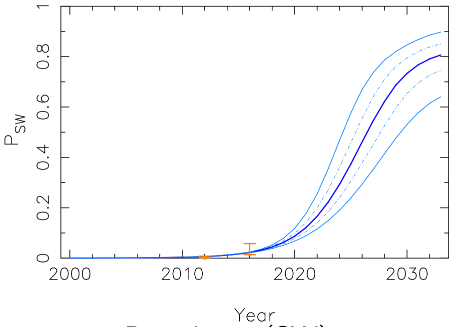
Morondava, % (CI)		
Year	SW	GP
2012	3.0(2.9-3.2)	0.6 (0.3-0.9)
2016	8.1(7.6-9.0)	1.5 (1.0-2.4)
2033	70.8(47.6-89.0)	20.0 (14.1-27.7)
$R_0(CI)$	*6.41 (4.2-8.6)*	

Fianarantsoa, % (CI)		
Year	SW	GP
2012	0.6(0.5-0.6)	0.1 (0.05-0.2)
2016	1.7(1.6-1.8)	0.3 (0.2-0.4)
2033	70.9(47.9-79.8)	15.1 (11.0-20.4)
$R_0(CI)$	*6.30 (4.0-8.6)*	

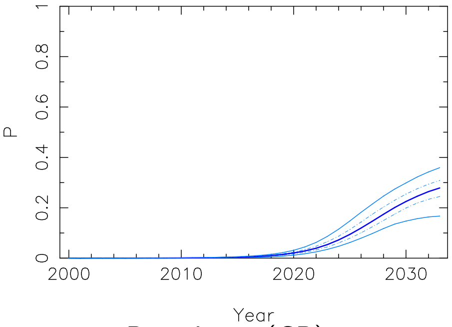
Toliary, % (CI)		
Year	SW	GP
2012	0.9(0.8-1.0)	0.2 (0.1-0.3)
2016	3.1(2.9-3.3)	0.6 (0.4-1.1)
2033	78.1(55.9-88.2)	22.6 (15.9-30.7)
$R_0(CI)$	*5.87 (4.4-7.4)*	

Taolagnaro, % (CI)		
Year	SW	GP
2012	1.5(1.4-1.6)	0.2 (0.2-0.3)
2016	5.3(4.8-5.6)	1.0 (0.8-1.3)
2033	74.0(55.7-87.6)	18.9 (12.1-25.8)
$R_0(CI)$	*4.43 (3.5-5.3)*	

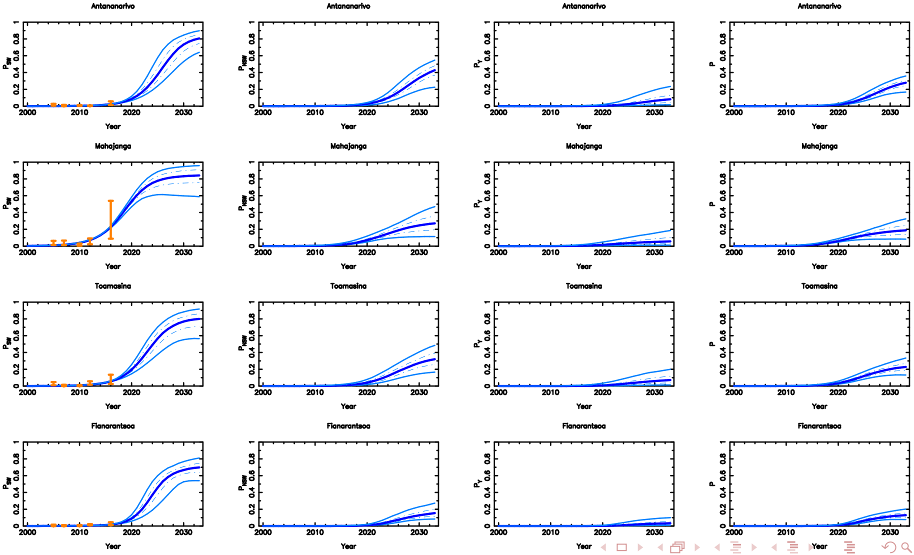
Model Projections (Antananarivo)



Prevalence (SW)



Prevalence (GP)


Antananarivo
Mahajanga
Toamasina
Fianarantsoa
P_{SW}
P_{NSW}
P_{Y}
P
Year
0
0.2
0.4
0.6
0.8
1
2000
2010
2020
2030

1. Our approach allows for HIV prevalence projections up to year 2033 across most important cities in Madagascar.
2. Estimated R_0 across cities in 2000, when incidence was extremely low, lies within real-life estimations reported for HIV (between 4 and 9).
3. Our model consistently predicts sigmoid-like prevalence curves (with turning points within years 2020-2022) that reach a stable prevalence of HIV infection by 2033, within 9 to 24 percent in certain/most cities, similar to other high-prevalence regions in Southern Africa.
4. Our results suggest that the late/delayed transition in Madagascar may have been due late introduction of HIV.
5. Madagascar may be currently undergoing a transition from a concentrated to a generalized HIV epidemic, where young women would play a central key role
6. A complex interplay between cultural (i.e., widespread practice of circumcision and women social vulnerability) and geopolitics (geographical and political population isolation) play a major role in determining the transition

List of References I

[1] P. Bacchetti and A. R. Moss. Incubation period of AIDS in San Francisco. *Nature*, 338(6212):251–253, 1989.

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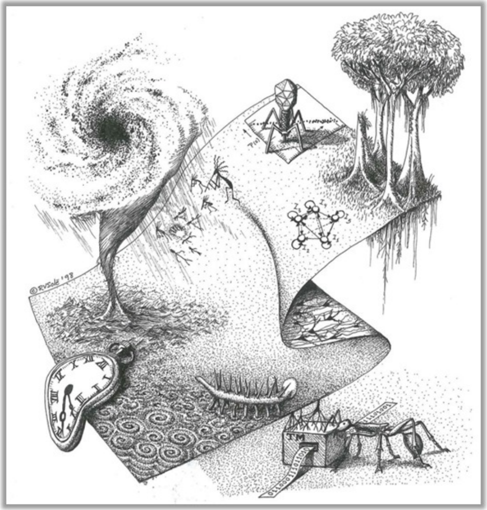
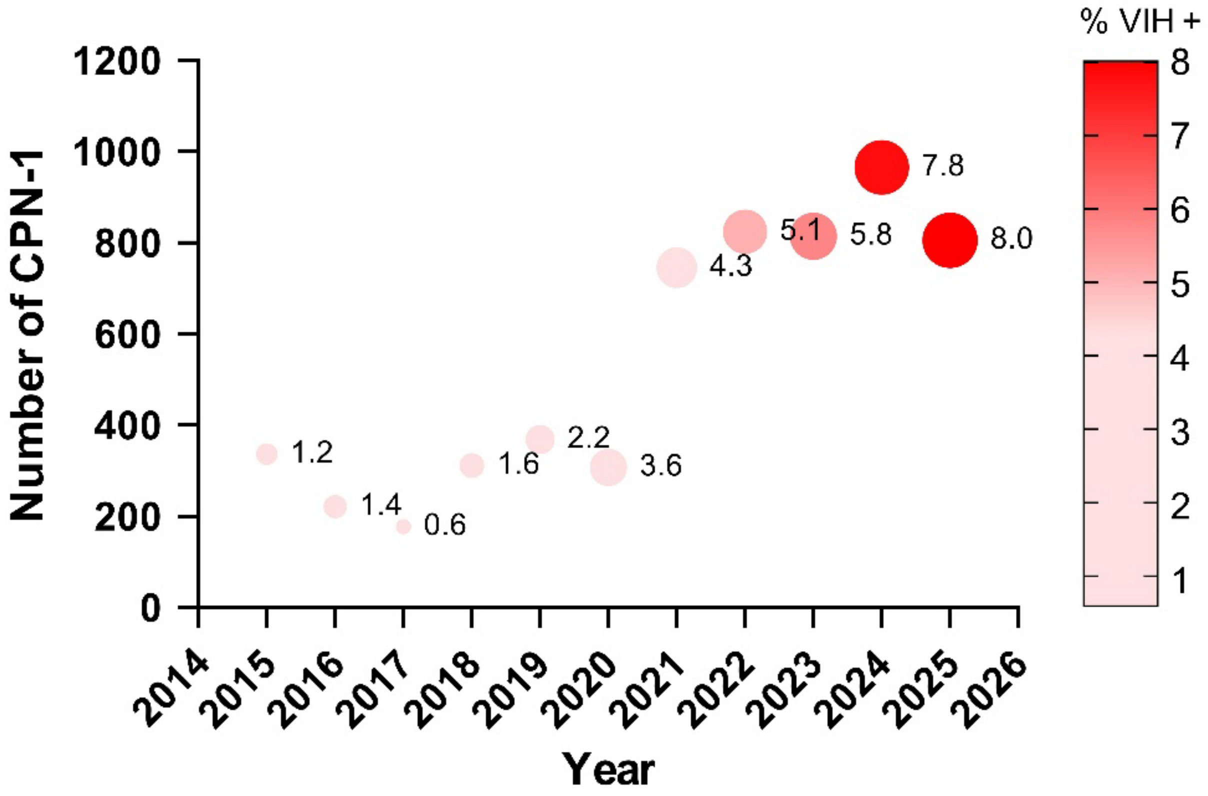


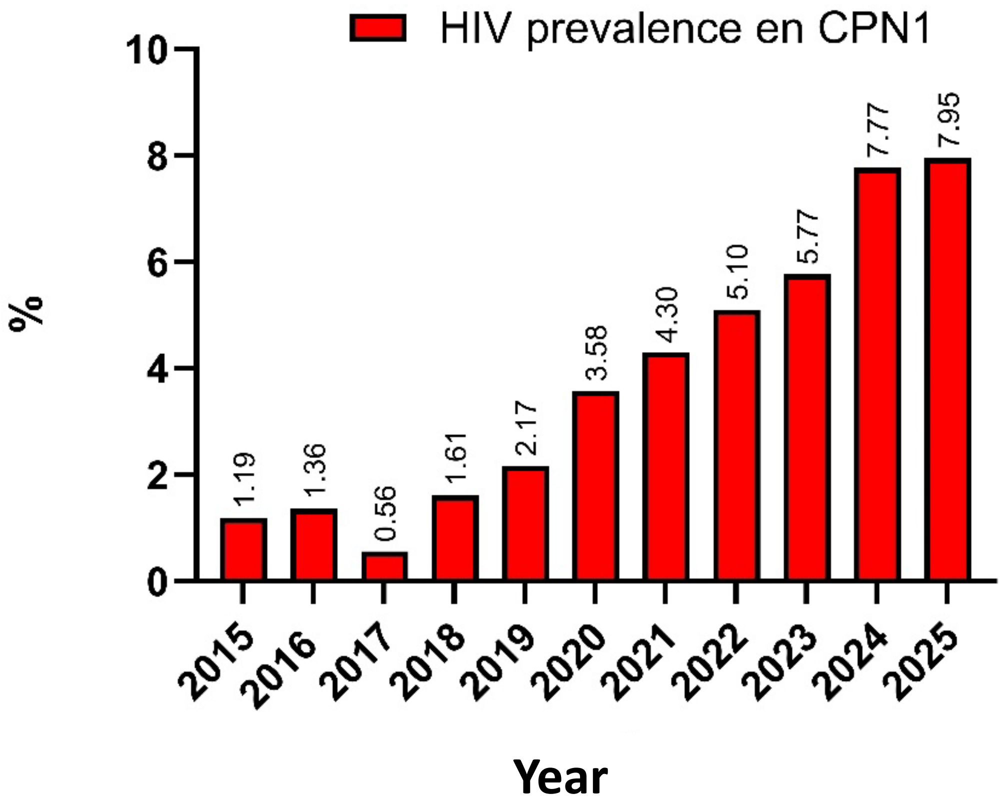
Thank You So Much!

Impact

- The modelling exercise has been a catalizer for the creation a working HIV group in Madagascar encompassing local and International NGO's, local Health authorities and local and International research institutions
- This group aims to coordinate and implement research initiatives and interventions to better ascertain the epidemiology of HIV in Madagascar and reinforce the response to the epidemic
- Actually, the results of the modelling study have been disseminated among local and International stakeholders and fòrums to raise the attention among this emerging Public Health threath in Madagascar

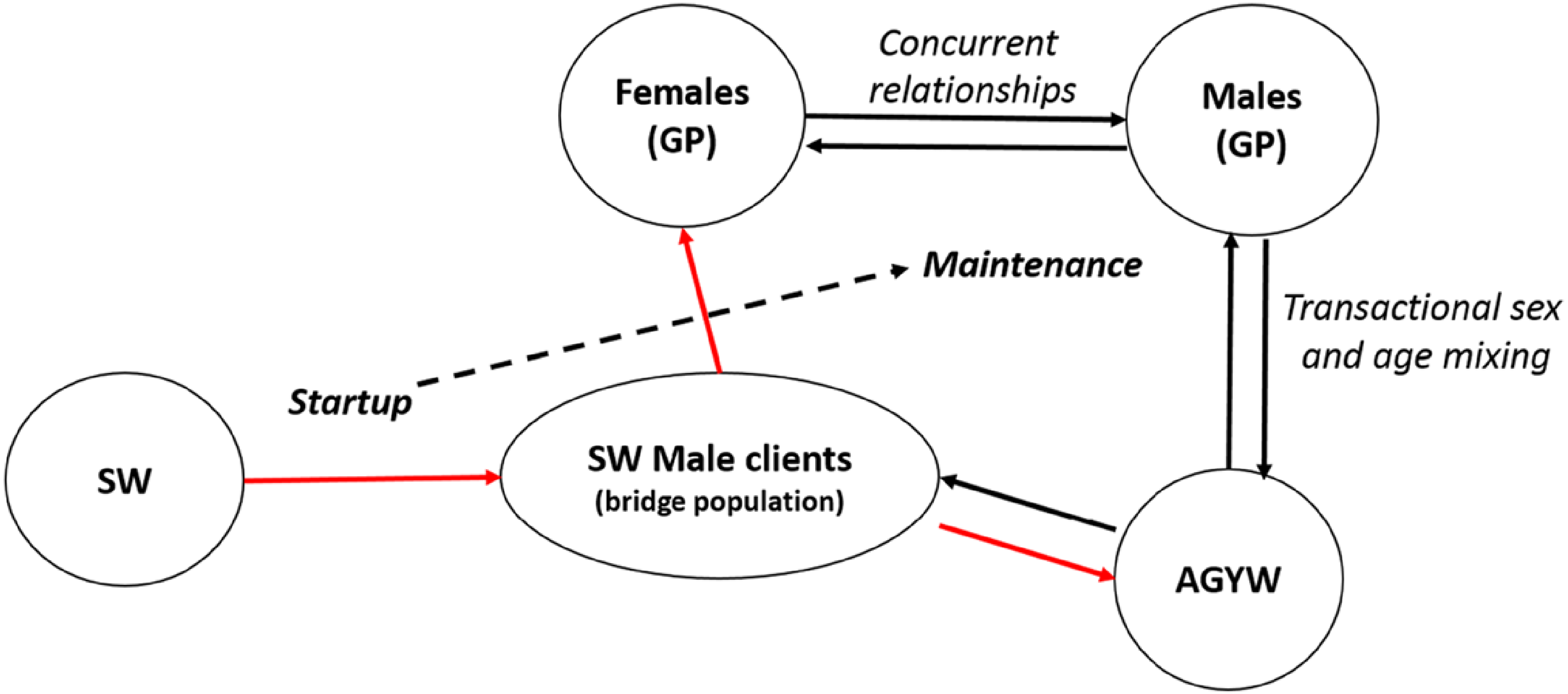
Positivity rate trend among pregnant women in the northern District of Ambanja (Madagascar)





Median age at diagnostic 23-24 years, range 14-42

Conceptual framework of HIV epidemic generalisation



Background and justification

Review

Is Madagascar at the edge of a generalised HIV epidemic? Situational analysis

Mihaja Raberahona ,[1] François Monge,[2] Rijasoa Harivelo Andrianiaina,[3] Mamy Jean de Dieu Randria,[1] Andosoa Ratefiharimanana,[4] Rivo Andry Rakatoarivelo,[5] Lanto Randrianary,[6] Emma Randriamilahatra,[6] Liva Rakotobe,[6] Chiarella Mattern,[7,8] Volatiana Andriananja,[1] Hobimahanina Rajaonarison,[1] Mirella Randrianarisoa,[7] Elliott Rakotomanana,[7] Dolorès Pourette,[8] Hery Zo Andriamahenina,[2] Charlotte Dezé,[9] Narjis Boukli,[10] Laurence Baril,[7] Xavier Vallès [7]

- Very weak epidemiological surveillance
- Limited response to HIV epidemic: 20% HIV coverage of HIV testing among pregnant women, 30% coverage of ARV, etc.
- Response mainly focused to Key Populations, which have high prevalence of HIV
- Uncertain prevalence of HIV among General Population but presence of alarm signs of progression (i.e. Increasing TB-HIV coinfection, late diagnosctics of Advanced AIDS disease among young people, fragmentary empiracal data, etc.
- Widespread presence of all risk factors associated to HIV diffusion (i.e. Age mixing, population mobility transactional sex, multi-partner, inconsistent use of condoms, etc.)

Some empirical data