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The heterogeneous rise of HIV drug resistance in Southern Africa

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Stancon 2019, Cambridge UK

HIV in Africa

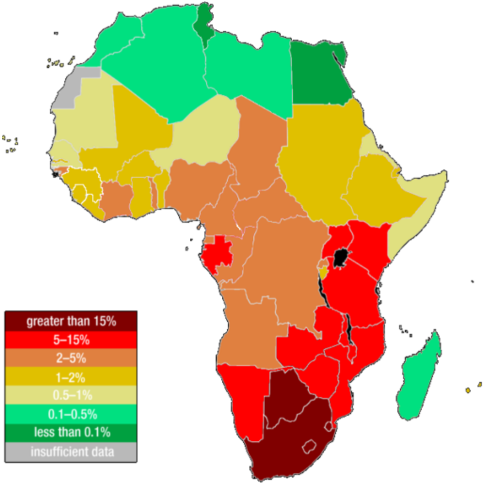

Figure 1: Proportion of persons living with HIV Africa in 2017 (UNAIDS)

ART roll-out since the early 2000s

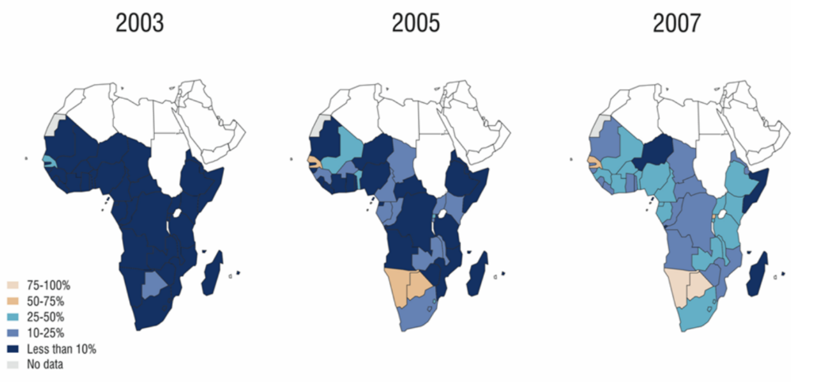

Figure 2: Proportion of person living with HIV on antiretroviral therapy (UNAIDS)

Combination antiretroviral therapy (ART):

- 2 nucleoside analog reverse-transcriptase inhibitors (NRTI)
- 1 non-nucleoside reverse-transcriptase inhibitor (NNRTI)

NNRTI resistance

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HIV resistance to NNRTI poses a growing threat to the success of ART:

- low genetic barrier to resistance[1]
- poor adherence, bad prescription practices, supply chains...

[1] Stanford University, HIV drug resistance database

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Assessed by monitoring pretreatment drug resistance (PDR):

- resistance mutations measured at the moment of treatment initiation
- acquired by transmission

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Growing NNRTI resistance in Africa

Systematic review of PDR surveys in adults[2]:

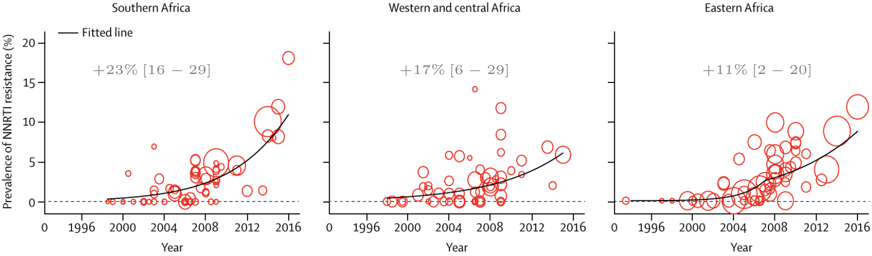

Figure 3: NNRTI PDR by year of sampling (yearly increase in odds of PDR)[3]

⇒ Descriptive analysis of the evolution of PDR by continental region

[2]Gupta et al. (*The Lancet Infectious Diseases*, 2017)

Comments

Regional estimates may mask large between-country heterogeneity

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Regional estimates may mask large between-country heterogeneity

The level of resistance in a population is dependent on ART uptake:

- especially relevant for between-country comparison
- timing and scale of ART roll-out differ by country

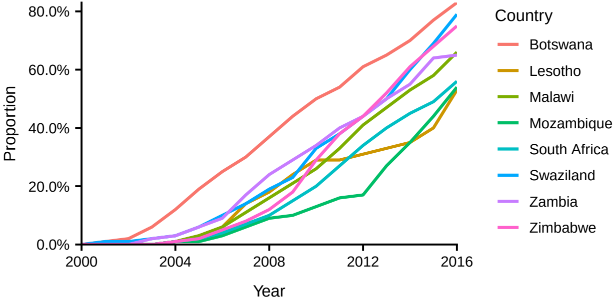
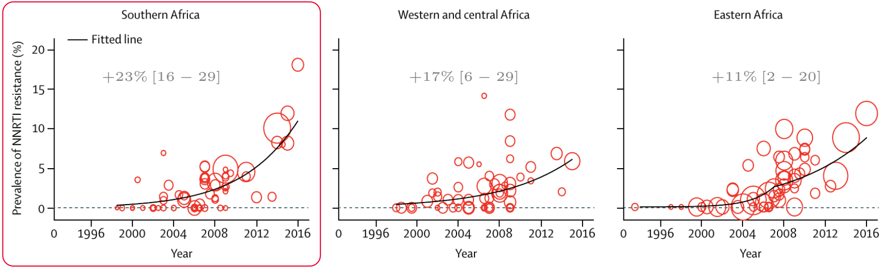


Figure 4: Proportion of person living with HIV on ART in Southern Africa (UNAIDS)

Reanalysis for Southern Africa



Objectives:

1. develop a mechanistic model describing the processes leading to PDR (mutation, transmission, treatment, measurement in surveys)

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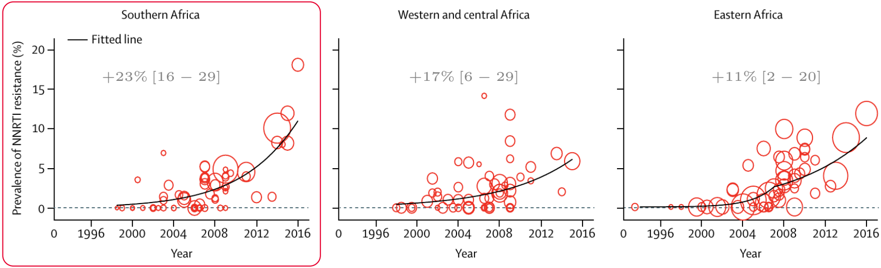

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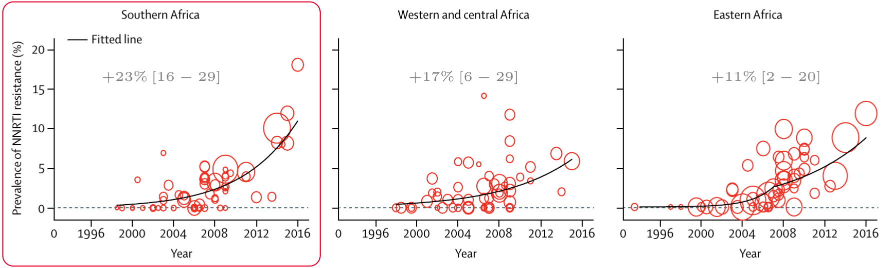

Objectives:

1. develop a mechanistic model describing the processes leading to PDR (mutation, transmission, treatment, measurement in surveys)
2. account for the main characteristics of HIV transmission and treatment
3. in every country of Southern Africa

Modelling strategy

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We want a multivariate model able to fit jointly, in each country:

- the adult prevalence of HIV ($\mathbb{A}$)
- the number of HIV-infected adults under ART ($\mathbb{B}$)
- the AIDS-related mortality ($\mathbb{C}$)
- the size of the adult population ($\mathbb{D}$)

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- pretreatment drug resistance in adults ($\mathbb{E}$)

Systematic review

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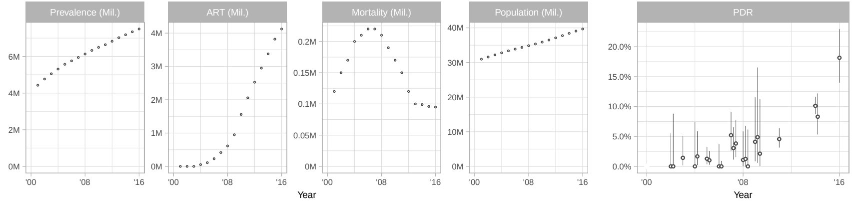
Systematic review

E.g. for the Republic of South Africa (RSA):



Model 1

Starting with a simple system of ODEs:

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \tau \mathbf{1}_\tau(t, t_0) I$$
$$\frac{dR}{dt} = \tau \mathbf{1}_\tau(t, t_0) I$$

With the step function $\mathbf{1}_\tau(t, t_0)$ depending on the year of ART roll-out t_0:

$$\mathbf{1}_\tau(t, t_0) = \begin{cases} 0 & \text{if } t < t_0 \\ 1 & \text{otherwise} \end{cases}$$

Initial values $S(0), I(0), T(0)$ are set using data from 2000

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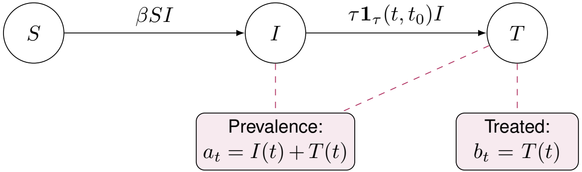

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Model 1

We fit the model to yearly estimates of HIV prevalence ($\mathbb{A}$) and of the number of adults on ART ($\mathbb{B}$) using independent normal distributions[3]:

$$\Pr\left(\begin{bmatrix}\sqrt{\mathbb{A}_t}\\ \sqrt{\mathbb{B}_t}\end{bmatrix} \;\middle|\; \beta, \tau, \sigma_a, \sigma_b\right) = \mathcal{N}\left(\begin{bmatrix}\sqrt{a_t}\\ \sqrt{b_t}\end{bmatrix}, \begin{bmatrix}\sigma_a^2 & 0\\ 0 & \sigma_b^2\end{bmatrix}\right)$$

where:

- β is the parameter governing transmission
- τ is the parameter governing treatment initiation
- σ_a and σ_b are the error parameters related to $\mathbb{A}$ and $\mathbb{B}$
- $\begin{bmatrix}a_t\\ b_t\end{bmatrix} = g(\beta, \tau, t, t_0)$ is the output of the ODE system at time t

[3] after variance-stabilizing square-root transformation, see Yu (*Stat. & Prob. Letters*, 2009)

Model 1

We choose weakly informative priors for all parameters:

$$\beta \sim \text{Expon}(5) \qquad \tau \sim \text{Expon}(5) \qquad \sigma_a \sim \text{Expon}(1) \qquad \sigma_b \sim \text{Expon}(1)$$

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We check the adequacy of these choices by simulating from the priors[4]:

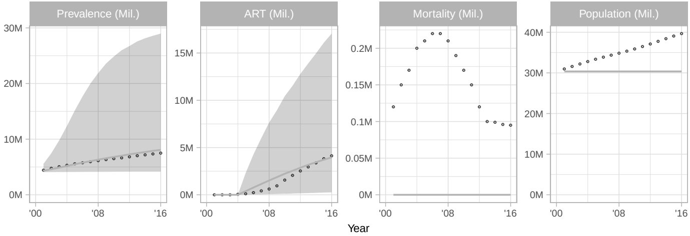

Figure 5: *Prior predictive check*[7] for model 1 in the RSA

[4] Gabry et al. (*Journal of the Royal Statistical Society*, 2019)

Model 1

We fit the model in `Stan` and get the following posterior distributions:

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
beta[1]	0.0612	0.0004	0.0005	0.0603	0.061	0.0613	0.0615	0.0619	2	17482
tau[1]	0.0580	0.0002	0.0003	0.0576	0.058	0.0581	0.0581	0.0583	2	1568
sigma[1,1]	1.6139	0.0426	0.0602	1.5320	1.584	1.6113	1.6416	1.7009	2	13410
sigma[1,2]	3.2192	0.4293	0.6072	2.3062	3.028	3.2776	3.4683	4.0155	2	64905

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sigma[1,1]	1.6139	0.0426	0.0602	1.5320	1.584	1.6113	1.6416	1.7009	2	13410
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That correspond to the following fit:

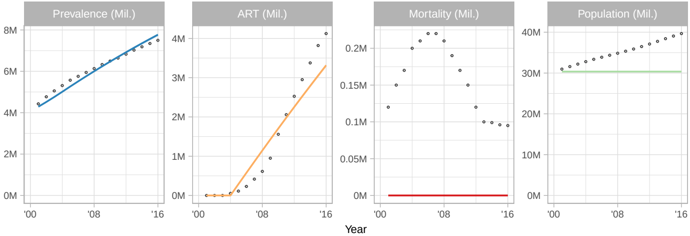

Figure 6: Fit of model 1 to $\mathbb{A}$ and $\mathbb{B}$ (in RSA)

Model 2

We improve the adequacy of the model to the non-linear rise of the number of adults on ART by replacing the step function by a logistic function:

$$\mathbf{1}_\tau(t, t_0, \nu, \xi) = \frac{1}{1 + e^{-\xi(t - t_0 - \nu)}}$$

where:
- t_0 is the year of ART roll-out in the country (here 2004)
- ξ is a logistic growth rate (i.e. the steepness)
- ν is a shift in years (i.e. time to reach 50% of maximum)

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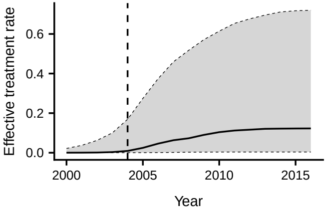
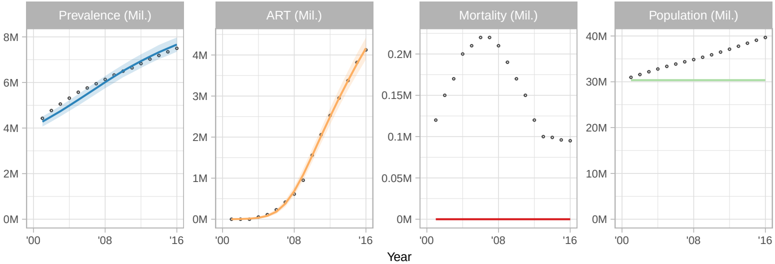


Figure 7: Prior predictive check on the effective treatment rate, i.e. $\tau \mathbf{1}_\tau(t, t_0, \nu, \xi)$

Model 2

We follow the same procedure and obtain:

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
beta[1]	0.0598	0.0000	0.0007	0.0583	0.0593	0.0598	0.0602	0.0612	3791	1.0001
tau[1]	0.1060	0.0001	0.0044	0.0978	0.1030	0.1058	0.1088	0.1151	2000	1.0029
xi[1]	0.8460	0.0012	0.0527	0.7499	0.8092	0.8432	0.8789	0.9579	1993	1.0025
nu[1]	9.3009	0.0044	0.1892	8.9338	9.1753	9.2999	9.4240	9.6829	1816	1.0031
sigma[1,1]	26.9860	0.0422	2.6567	22.2979	25.0947	26.8145	28.6770	32.6426	3966	0.9997
sigma[1,2]	29.5964	0.0450	2.8041	24.6788	27.6000	29.4228	31.3488	35.5833	3891	0.9998



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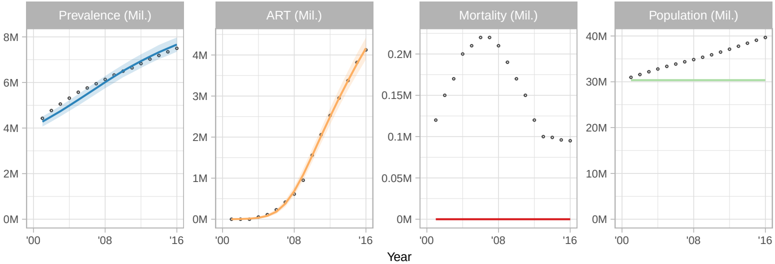

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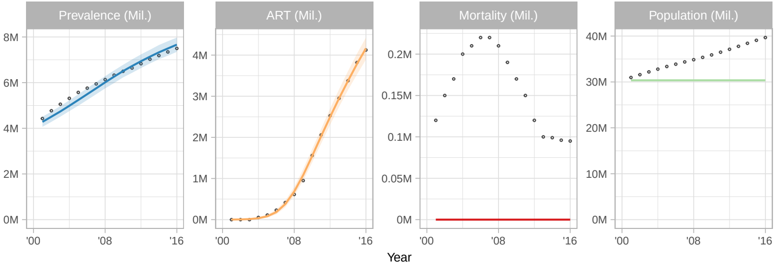

Figure 8: Fit of model 2 to $\mathbb{A}$ and $\mathbb{B}$ (in RSA)

Model 3

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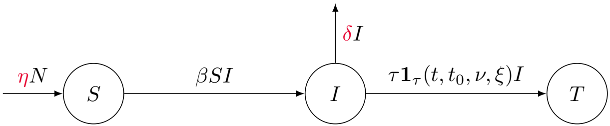
We add population growth and AIDS-related mortality:



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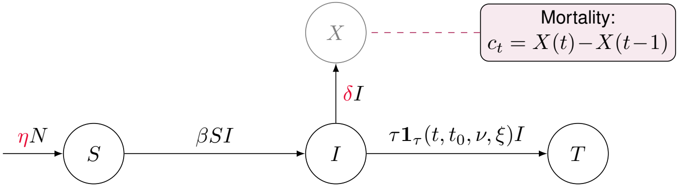

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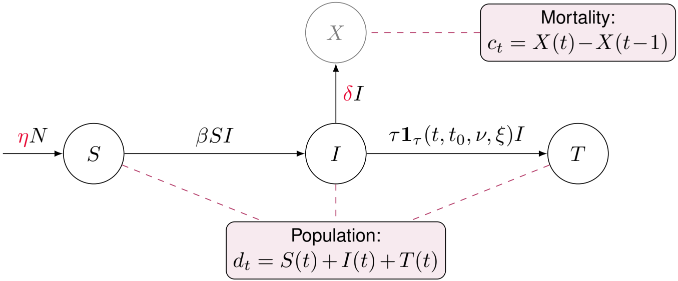

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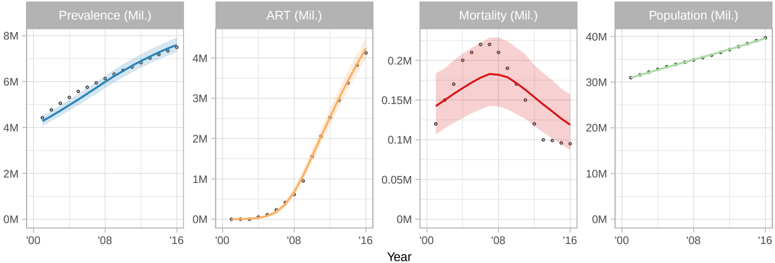
beta[1]	0.0985	0.0000	0.0014	0.0958	0.0976	0.0985	0.0995	0.1014	2048	1.0003
tau[1]	0.1112	0.0001	0.0048	0.1025	0.1079	0.1110	0.1142	0.1212	2088	1.0009
xi[1]	0.8381	0.0011	0.0516	0.7447	0.8022	0.8363	0.8705	0.9470	2081	0.9998
nu[1]	9.4155	0.0044	0.1889	9.0598	9.2870	9.4128	9.5431	9.8072	1867	1.0003
delta[1]	0.0342	0.0000	0.0011	0.0320	0.0334	0.0342	0.0349	0.0365	2000	1.0003
eta[1]	0.0242	0.0000	0.0002	0.0238	0.0241	0.0242	0.0243	0.0246	2033	1.0003
sigma[1,1]	27.2853	0.0433	2.6379	22.5539	25.4524	27.1472	28.9237	32.9611	3714	1.0003
sigma[1,2]	30.1005	0.0503	3.0478	24.7784	27.8969	29.8980	31.9773	36.5806	3669	0.9999
sigma[1,3]	24.6105	0.0410	2.5323	20.1948	22.8419	24.3955	26.2101	30.0860	3820	1.0015
sigma[1,4]	6.2926	0.0151	0.9469	4.6973	5.6303	6.2078	6.8565	8.4115	3956	1.0002



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eta[1]	0.0242	0.0000	0.0002	0.0238	0.0241	0.0242	0.0243	0.0246	2033	1.0003
sigma[1,1]	27.2853	0.0433	2.6379	22.5539	25.4524	27.1472	28.9237	32.9611	3714	1.0003
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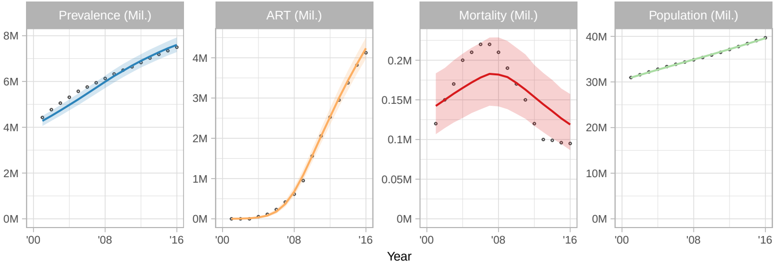

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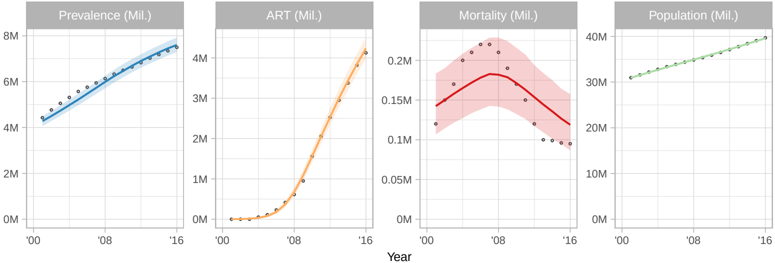

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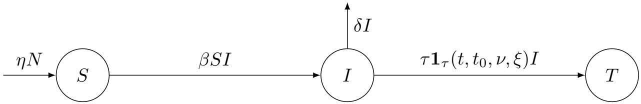
Model 4

Occurrence and transmission of NNRTI resistance:



Model 4

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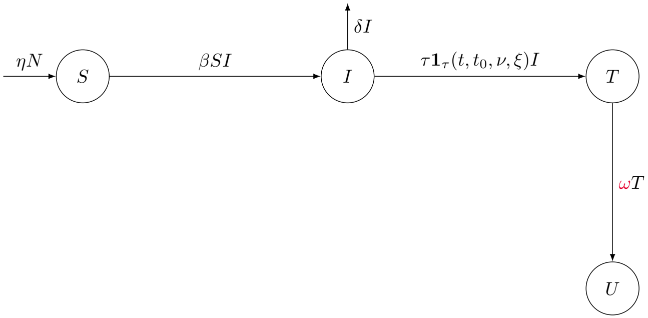

Model 4

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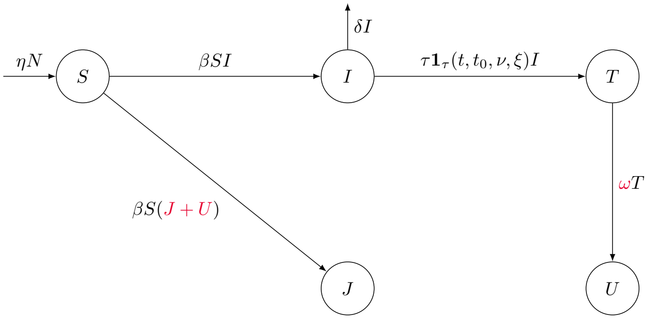

Model 4

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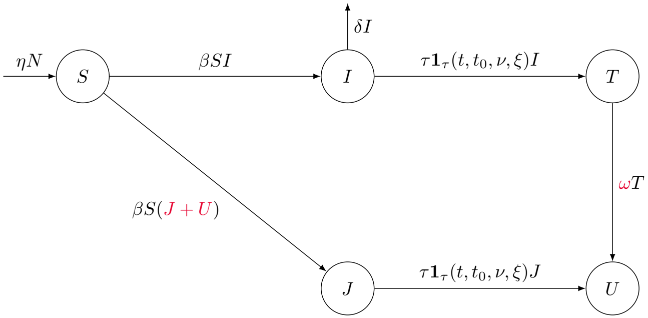

Model 4

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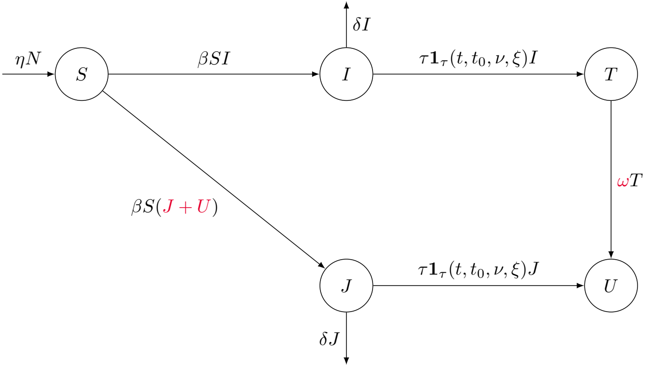

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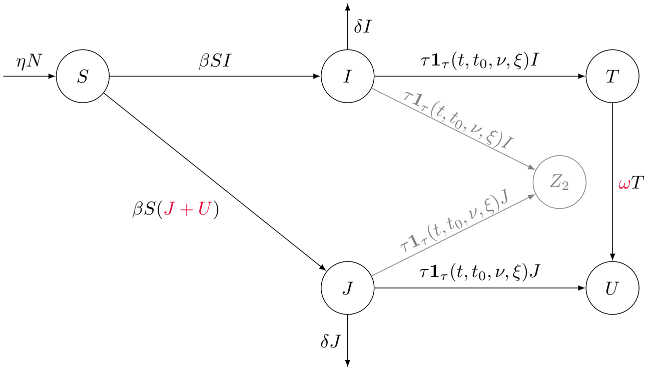

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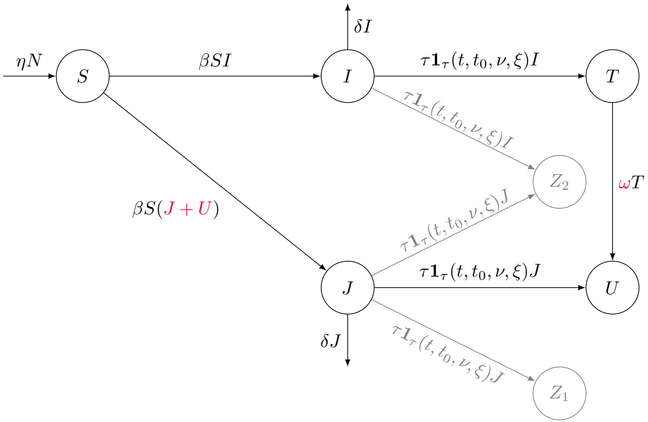

Model 4

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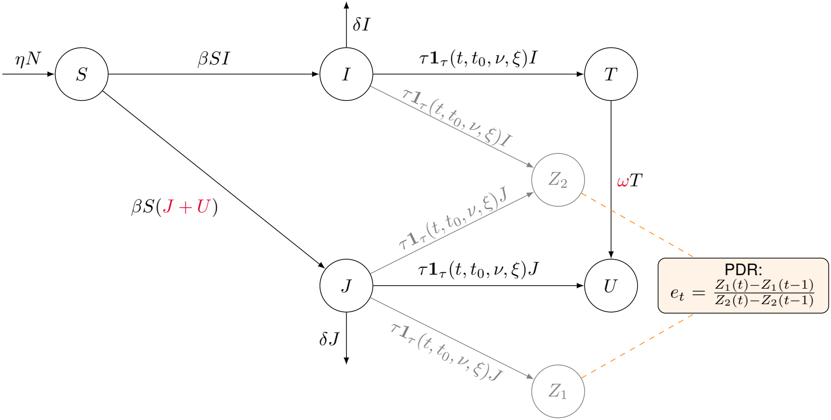
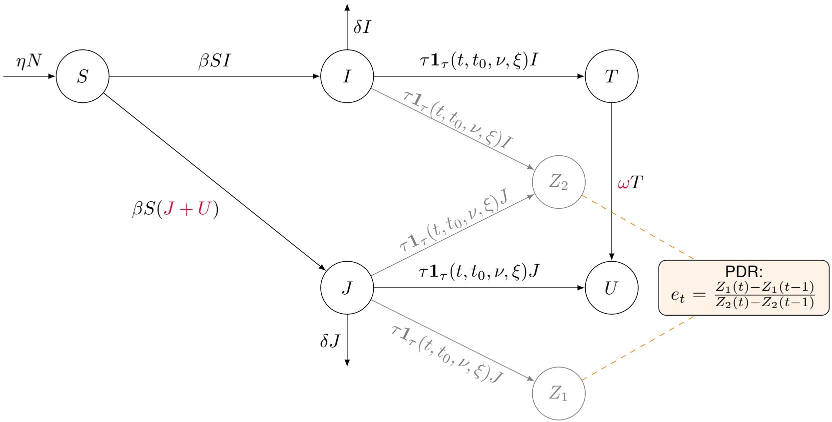


Model 4

Occurrence and transmission of NNRTI resistance:



We also add a parameter ι for the initial proportion of resistance (in 2000)

Model 4

In addition to the indicators $\{\mathbb{A}, \mathbb{B}, \mathbb{C}, \mathbb{D}\}$, we also fit the model to survey data:

$$\Pr(\mathbb{E}_i|\theta) = \text{Binom}(\mathbb{N}_i, e_i)$$

where:
- $\mathbb{E}_i$ is the number of individuals with NNRTI resistance in study i
- $\theta = \{\beta, \tau, \nu, \xi, \delta, \eta, \omega, \iota, \sigma_{a,\dots,d}\}$ represents all 12 parameters
- $\mathbb{N}_i$ is the sample size of study i
- $e_i = g(\theta, t = \mathbb{T}_i, t_0)$ is the model-predicted PDR at the time of survey i

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So that the full likelihood is:

$$\Pr(\mathbb{A}, \mathbb{B}, \mathbb{C}, \mathbb{D}, \mathbb{E}|\theta) = \prod_{t,i} \Pr(\mathbb{A}_t, \mathbb{B}_t, \mathbb{C}_t, \mathbb{D}_t|\theta) \Pr(\mathbb{E}_i|\theta)$$

Model 4

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
beta[1]	0.0937	0.0000	0.0016	0.0906	0.0927	0.0937	0.0947	0.0968	2270	0.9997
tau[1]	0.1134	0.0001	0.0050	0.1042	0.1101	0.1132	0.1163	0.1244	1890	1.0024
nu[1]	9.3673	0.0044	0.1915	8.9925	9.2423	9.3680	9.4878	9.7553	1877	1.0019
xi[1]	0.8474	0.0011	0.0529	0.7496	0.8120	0.8442	0.8803	0.9581	2282	1.0010
eta[1]	0.0242	0.0000	0.0002	0.0238	0.0240	0.0242	0.0243	0.0245	2119	1.0000
delta[1]	0.0347	0.0000	0.0012	0.0324	0.0339	0.0347	0.0354	0.0370	2064	0.9997
omega[1]	0.2023	0.0006	0.0307	0.1473	0.1810	0.2005	0.2210	0.2676	2878	0.9995
iota[1]	0.0183	0.0000	0.0028	0.0132	0.0164	0.0182	0.0201	0.0240	3295	1.0004
sigma[1,1]	37.0132	0.0538	3.3885	30.7901	34.6296	36.8115	39.1864	44.2509	3961	0.9997
sigma[1,2]	30.2510	0.0480	2.9472	24.8307	28.1822	30.0687	32.1629	36.4259	3770	1.0003
sigma[1,3]	25.7334	0.0404	2.6130	21.0834	23.9575	25.5655	27.3904	31.2707	4184	0.9997
sigma[1,4]	6.6229	0.0171	1.0313	4.9126	5.8995	6.5207	7.2135	8.9772	3642	1.0000

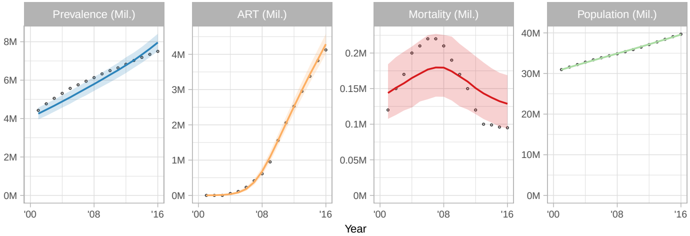

Figure 10: Fit of model 4 to $\mathbb{A}$, $\mathbb{B}$, $\mathbb{C}$ and $\mathbb{D}$ (in RSA)

Model 4

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
beta[1]	0.0937	0.0000	0.0016	0.0906	0.0927	0.0937	0.0947	0.0968	2270	0.9997
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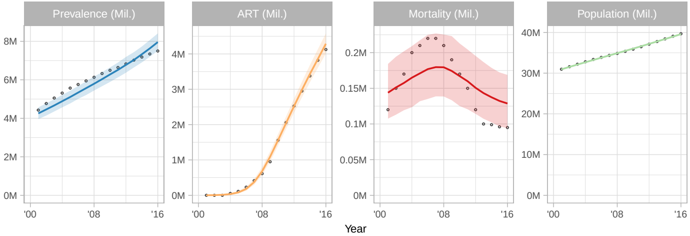

Figure 10: Fit of model 4 to $\mathbb{A}$, $\mathbb{B}$, $\mathbb{C}$ and $\mathbb{D}$ (in RSA)

Model 4

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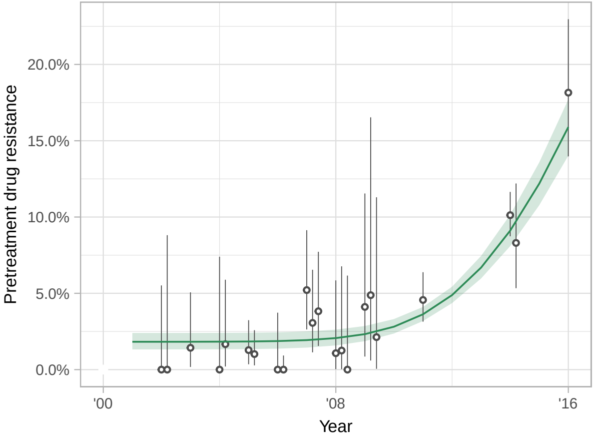

Figure 11: Fit of model 4 to $\mathbb{E}$ (in RSA)

Model 4M

We now extend model 4 to the 9 countries of the region:

- independence for the parameters related to the local dynamics of HIV

$$\{\beta_k, \tau_k, \nu_k, \xi_k, \eta_k, \delta_k, \sigma_{a,\ldots,d,k}\}$$

- hierarchical structure for the parameters related to resistance

$$\omega_k \sim \text{lognormal}(\mu_\omega, \sigma_\omega)$$

$$\log \frac{\iota_j}{1-\iota_j} \sim \mathcal{N}(\mu_\iota, \sigma_\iota)$$

Model 4M

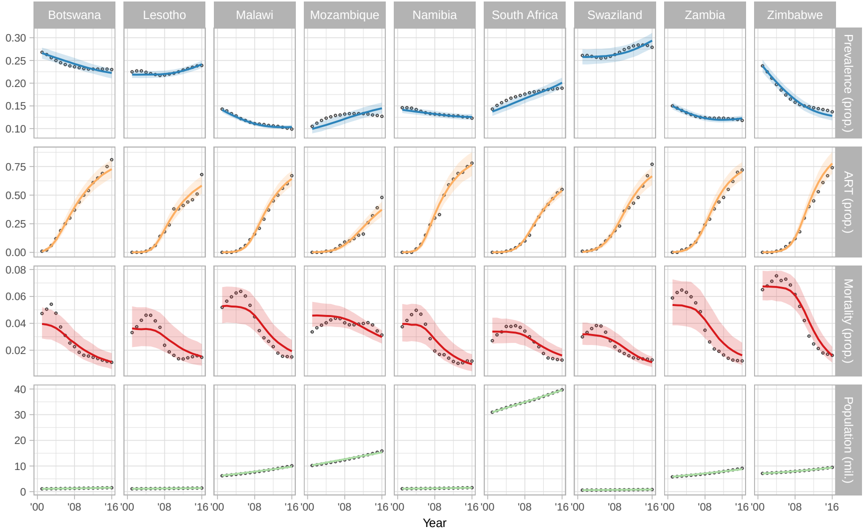

Figure 12: Fit of model 4M to $\mathbb{A}$, $\mathbb{B}$, $\mathbb{C}$ and $\mathbb{D}$ (in all countries)

Model 4M

Posterior estimates of ι, the initial proportion of resistance (in 2000):

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
mu_iota	0.019	0.000	0.003	0.013	0.017	0.019	0.021	0.026	2367	1.000
sigma_iota	0.346	0.004	0.129	0.145	0.255	0.330	0.418	0.639	1322	1.001
iota[1]	0.013	0.000	0.004	0.006	0.010	0.013	0.015	0.021	2399	1.000
iota[2]	0.020	0.000	0.007	0.008	0.015	0.019	0.023	0.036	4088	1.000
iota[3]	0.020	0.000	0.005	0.011	0.016	0.019	0.023	0.029	5197	1.000
iota[4]	0.019	0.000	0.004	0.012	0.016	0.019	0.021	0.027	5666	1.000
iota[5]	0.018	0.000	0.007	0.007	0.014	0.018	0.022	0.033	3862	1.000
iota[6]	0.019	0.000	0.003	0.014	0.017	0.019	0.021	0.024	5600	1.000
iota[7]	0.016	0.000	0.006	0.006	0.012	0.016	0.020	0.029	3079	1.000
iota[8]	0.024	0.000	0.006	0.014	0.020	0.023	0.027	0.036	6238	0.999
iota[9]	0.034	0.000	0.004	0.025	0.031	0.034	0.037	0.042	3434	0.999

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Posterior estimates of ι, the initial proportion of resistance (in 2000):

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
mu_iota	0.019	0.000	0.003	0.013	0.017	0.019	0.021	0.026	2367	1.000
sigma_iota	0.346	0.004	0.129	0.145	0.255	0.330	0.418	0.639	1322	1.001
iota[1]	0.013	0.000	0.004	0.006	0.010	0.013	0.015	0.021	2399	1.000
iota[2]	0.020	0.000	0.007	0.008	0.015	0.019	0.023	0.036	4088	1.000
iota[3]	0.020	0.000	0.005	0.011	0.016	0.019	0.023	0.029	5197	1.000
iota[4]	0.019	0.000	0.004	0.012	0.016	0.019	0.021	0.027	5666	1.000
iota[5]	0.018	0.000	0.007	0.007	0.014	0.018	0.022	0.033	3862	1.000
iota[6]	0.019	0.000	0.003	0.014	0.017	0.019	0.021	0.024	5600	1.000
iota[7]	0.016	0.000	0.006	0.006	0.012	0.016	0.020	0.029	3079	1.000
iota[8]	0.024	0.000	0.006	0.014	0.020	0.023	0.027	0.036	6238	0.999
iota[9]	0.034	0.000	0.004	0.025	0.031	0.034	0.037	0.042	3434	0.999

Model 4M

Posterior estimates of ω, the rate of occurrence of NNRTI resistance:

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
mu_omega	0.26	0.00	0.08	0.12	0.20	0.25	0.31	0.44	2221	1
sigma_omega	0.51	0.00	0.17	0.25	0.39	0.48	0.60	0.89	5707	1
omega[1]	0.05	0.00	0.03	0.01	0.03	0.04	0.06	0.13	2459	1
omega[2]	0.96	0.02	0.86	0.33	0.56	0.76	1.09	2.90	2985	1
omega[3]	3.71	0.09	5.28	0.84	1.71	2.62	4.21	12.18	3370	1
omega[4]	0.03	0.00	0.03	0.00	0.01	0.02	0.04	0.10	3783	1
omega[5]	0.07	0.00	0.02	0.04	0.06	0.07	0.08	0.11	4310	1
omega[6]	0.20	0.00	0.03	0.15	0.18	0.20	0.22	0.27	4470	1
omega[7]	1.77	0.03	2.00	0.42	0.84	1.29	2.06	5.90	3300	1
omega[8]	3.65	0.07	4.37	0.85	1.76	2.60	4.19	12.39	3674	1
omega[9]	0.25	0.01	0.32	0.07	0.13	0.19	0.27	0.71	1510	1

Model 4M

Posterior estimates of ω, the rate of occurrence of NNRTI resistance:

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
mu_omega	0.26	0.00	0.08	0.12	0.20	0.25	0.31	0.44	2221	1
sigma_omega	0.51	0.00	0.17	0.25	0.39	0.48	0.60	0.89	5707	1
omega[1]	0.05	0.00	0.03	0.01	0.03	0.04	0.06	0.13	2459	1
omega[2]	0.96	0.02	0.86	0.33	0.56	0.76	1.09	2.90	2985	1
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omega[5]	0.07	0.00	0.02	0.04	0.06	0.07	0.08	0.11	4310	1
omega[6]	0.20	0.00	0.03	0.15	0.18	0.20	0.22	0.27	4470	1
omega[7]	1.77	0.03	2.00	0.42	0.84	1.29	2.06	5.90	3300	1
omega[8]	3.65	0.07	4.37	0.85	1.76	2.60	4.19	12.39	3674	1
omega[9]	0.25	0.01	0.32	0.07	0.13	0.19	0.27	0.71	1510	1

Model 4M

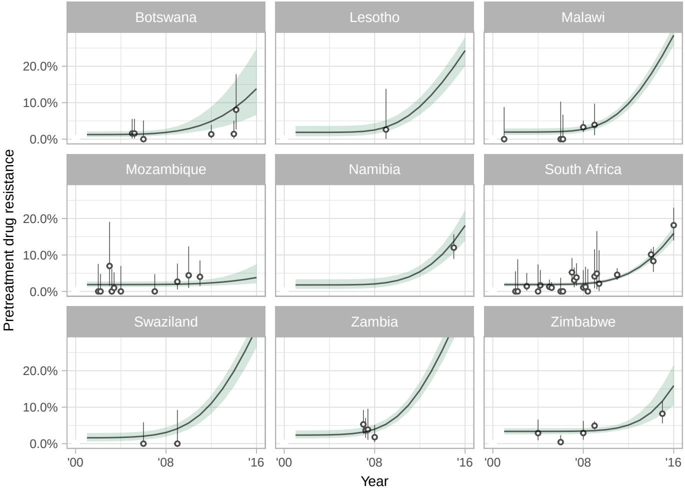

Figure 13: Fit of model 4M to $\mathbb{E}$ (in all countries)

Conclusions

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Very large heterogeneity between countries regarding the rate of occurrence of NNRTI resistance during ART ω_k:

- already visible from PDR data
- persists after accounting for the local HIV dynamics

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Very large heterogeneity between countries regarding the rate of occurrence of NNRTI resistance during ART ω_k:

- already visible from PDR data
- persists after accounting for the local HIV dynamics

Going forward:

- improve estimates (study-specific measurement error)
- assess model uncertainty
- identify country-level drivers of NNRTI resistance

Acknowledgments

- Christian Althaus, Matthias Egger
- Silvia Bertagnolio (WHO), John Gregson (LSHTM), Ravindra Gupta (UCL) for granting us access to the original data