Supplement

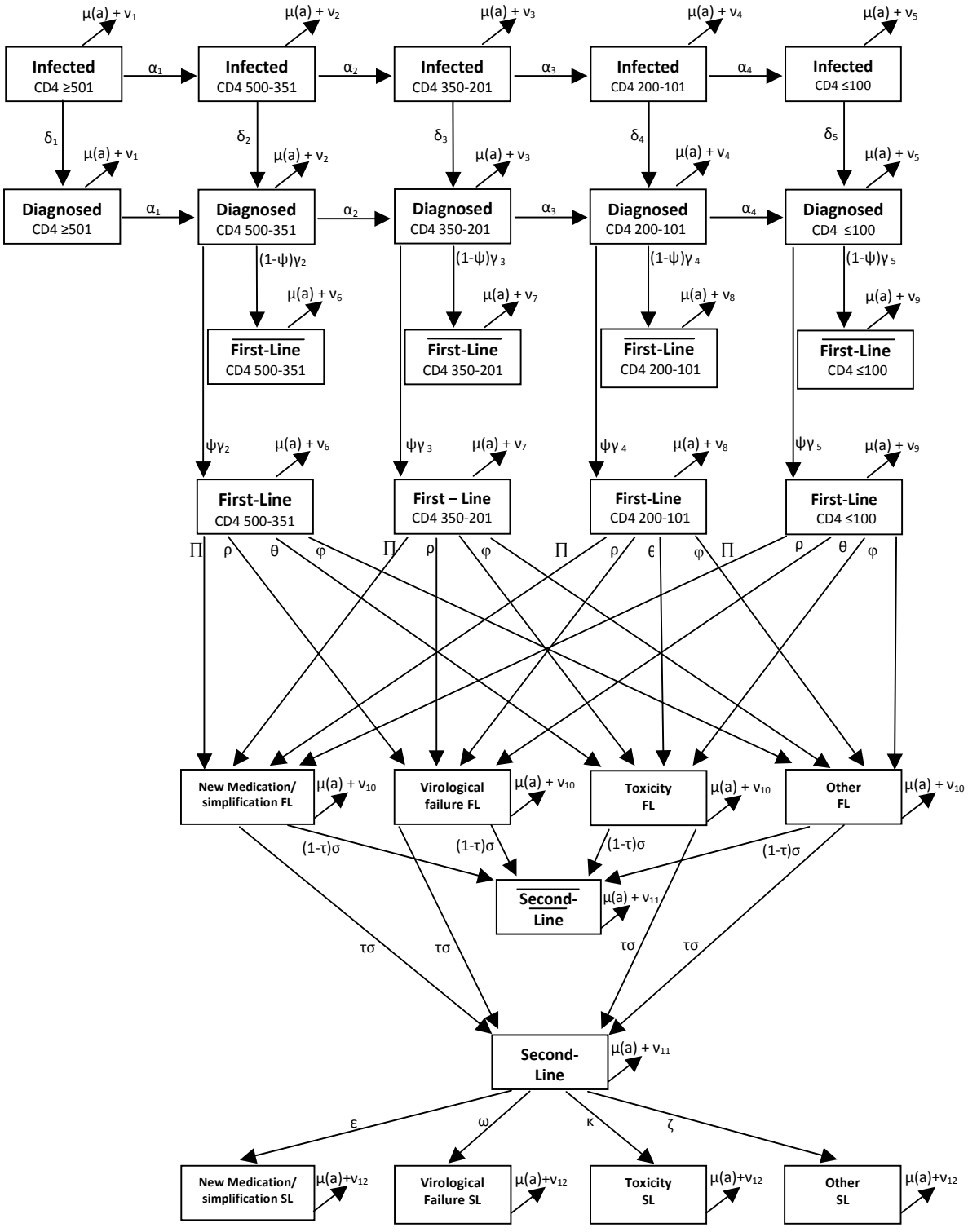
A deterministic model describing HIV infection and treatment in the Netherlands was developed using ATHENA data. The model represents a cohort of hypothetical HIV-infected individuals who were assumed to have been infected with HIV at the same time and age (42 years old in 2005). Individuals transition through different stages representing the natural course of infection and treatment, including first- and second-line cART (Fig.1 Supplement).

Infected individuals progress through five stages of HIV infection, defined by a range of CD4 counts. The rate of moving from $Infected_n$ to $Infected_{n+1}$ is α_n , for stage $n$and time spent at each stage is distributed exponentially. Infected individuals are diagnosed with HIV at a rate δ_n. Diagnosed individuals are put onto first-line treatment at a rate γ, which depends on their CD4 cell count. While on first-line treatment some individuals can experience the need to switch to second-line because of toxicity, virological failure, simplification/new medication becoming available or for other reasons.The same happens for individuals on second-line. At each stage, individuals can die either at a background death rate, μ, dependent on age and based on Dutch national statistics data, or at an HIV-related death rate, v_n, depends on the different infection stages. The model takes into account the fact that not all patients on first- and second-line cART will experience switching. All equations were programmed and solved in Excel 2007.

The same baseline epidemiological, healthcare and demographic inputs are used throughout the analysis, except where otherwise specified as listed in Table 1. Where possible these were calculated using ATHENA. However, assumptions had to be made and a demographic model and literature were used to obtain parameter values not directly available from ATHENA.

The model allows tracking of the same outcomes, including calculating survival time and average time on first- and second-line cART. The model simulates changes in patient's outcomes when prescribed a new drug regimen with different toxicity and virological failure profiles, two potential targets for future drug development.

Fig.1 Flow diagram of HIV infection and treatment model



Model equations

The state variables are given by X_n , where X stands for the compartment and n denoted the CD4 range of the infected individuals (≥501, 500-351, 350-201, 200-101 and ≤100). Initial condition are $I_1(0)$= 100,000 and X(0)=0, where X stands for all compartments other than I_1.

Infected Individuals:

$$\frac{dI(t)_1}{dt} = -(\alpha_1 + \delta_1 + \mu(a) + v_1)I_1$$

$$\frac{dI(t)_n}{dt} = \alpha_{n-1}I_{n-1} - (\alpha_n + \delta_n + \mu(a) + v_i)I_n \quad \text{for } n = 2,3,4,5$$

Diagnosed Individuals:

$$\frac{dD(t)_1}{dt} = \delta_1 I_1 - (\alpha_1 + \mu(a) + v_1) D_1$$

$$\frac{dD(t)_n}{dt} = \delta_n I_n + \alpha_{n-1} D_{n-1} - (\alpha_n + \gamma_n + \mu(a) + v_i)D_n \quad \text{for } n = 2,3,4,5$$

Individuals on first-line cART

$$\frac{d\overline{FL}(t)_n}{dt} = (1-\psi)\gamma_n D_n - (\mu(a) + v_i)FL_n \quad \text{for } n = 2,3,4,5$$

$$\frac{dFL(t)_n}{dt} = \psi\gamma_n D_n - (\varphi + \rho + \theta + \square + \mu(a) + v_i)FL_n \quad \text{for } n = 2,3,4,5$$

Individuals stopping first-line cART

$$\frac{dNMSFL(t)}{dt} = \varphi FL_2 + \varphi FL_3 + \varphi FL_4 + \varphi FL_5 - (\sigma + \mu(a) + v_{10})NMSFL$$

$$\frac{dRFL(t)}{dt} = \rho FL_2 + \rho FL_3 + \rho FL_4 + \rho FL_5 - (\sigma + \mu(a) + v_{10})VFFL$$

$$\frac{dTFL(t)}{dt} = \theta FL_2 + \theta FL_3 + \theta FL_4 + \theta FL_5 - (\sigma + \mu(a) + v_{10})TFL$$

$$\frac{dOFL(t)}{dt} = \imath FL_2 + \imath FL_3 + \imath FL_4 + \imath FL_5 - (\sigma + \mu(a) + v_{10})OFL$$

Individuals on second-line

$$\frac{d\overline{SL}(t)}{dt} = (1 - \tau)\sigma NMSFL + (1 - \tau)\sigma VFFL + (1 - \tau)\sigma TFL + (1 - \tau)\sigma OFL - (\mu(a) + v_{11})SL$$

$$\frac{dSL(t)}{dt} = \tau\sigma NMSFL + \tau\sigma VFFL + \tau\sigma TFL + \tau\sigma OFL - (\varepsilon + \omega + \kappa + \zeta + \mu(a) + v_{11})SL$$

Individuals stopping second-line cART

$$\frac{dNMSSL(t)}{dt} = \varepsilon SL - (\mu(a) + v_{12})NMSSL$$

$$\frac{dVLSL(t)}{dt} = \omega SL - (\mu(a) + v_{12})RSL$$

$$\frac{dTSL(t)}{dt} = \kappa SL - (\mu(a) + v_{12})TSL$$

$$\frac{dOSL(t)}{dt} = \zeta SL - (\mu(a) + v_{12})OSL$$

Compartment and parameter definition:

I_n: HIV-infected undiagnosed patients in stage n

D_n: Diagnosed patients in stage n

FL_n: Patients receiving first-line cART in stage n who are at risk of stopping first-line

$\overline{FL}_n$: Patients receiving first-line cART in stage n who are not at risk of stopping first-line

$NMSFL$: Patients stopping first-line cART due to new medication or simplification

$VFFL$: Patients stopping first-line cART due to virological failure

TFL : Patients stopping first-line cART due to toxicity

OFL: Patients stopping first-line cART due to other reasons

SL : Individuals receiving second-line cART who are at risk of stopping second-line

$\overline{SL}$: Individuals receiving second-line cART who are not at risk of stopping second-line

$NMSSL$: Patients stopping second-line cART due to new medication or simplification

$VFSL$: Patients stopping second-line cART due to virological failure

TSL : Patients stopping second-line cART due to toxicity

OSL : Patients stopping second-line cART due to other reasons

Parameter Definitions:

α_n: Rate of disease progression from Infected in stage *n* to *n+1*

v_i: HIV-related death rate for different stage of infection *i*

$\mu(a)$: Age-specific background death rate

δ_n: Rate of testing and diagnosis when in stage *n*

γ_n: Rate of cART initiation for diagnosed patients in stage *n*

ψ_n: Proportion on first-line cART at risk of stopping first-line in stage *n*

φ: Rate of stopping first-line cART due to new medication becoming available or simplification

ρ: Rate of virological failure on first-line cART

θ: Rate of discontinuing first-line cART due to toxicity

ι: Rate of stopping first-line cART due to other reasons

σ: Rate of switching to second-line cART after stopping first-line cART

τ: Proportion on second-line at risk of stopping second-line

ε: Rate of stopping second-line cART due to new medication or simplification

ω: Rate of virological failure on second-line cART

κ: Rate of discontinuing second-line cART due to toxicity

ζ: Rate of stopping second-line cART due to other reasons

where stage X_n:

X_1: CD4 cell count ≥501

X_2: CD4 cell count 500-351

X_3: CD4 cell count 350-201

X_4: CD4 cell count 200-101

X_5: CD4 cell count ≤100