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Research Article

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Analyzing the Effectiveness of HIV Prevention and Treatments through a Mathematical Model in Simulated Populations

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Abstract

An epidemiological model for the transmission of HIV/AIDS was developed to analyze the transmission dynamics of HIV in a simulated population. Differential equations derived from the model will be used to show the effectiveness of various treatments and preventative measures used to prevent further spreading of HIV in susceptible populations. Additionally, separate simulations for each of the WHO regions were included to view the spread of HIV on a more focused level rather than on broad global terms to account for regional differences in cases of HIV per capita. HIV data used for the simulations are pulled from WHO's population data and treatment data was taken from various clinical studies. The results of the simulations show that the world basic reproduction number is 3.33, but regional numbers range from 1.14 to 2.98. We found that post exposure prophylaxis was far more effective at preventing the spread of HIV compared to treatment to viral suppress the infection. Also, without the use of quality post exposure prophylaxis, HIV infections could grow rapidly in the coming years.

Introduction

The Human Immunodeficiency Virus (HIV) is a type of lentivirus that, if left untreated, will progress to Acquired Immune Deficiency Syndrome (AIDS) [1]. AIDS was first discovered in 1981, and the discovery of HIV followed soon after. The accepted theory to explain the rise of HIV is the cross species transmission event between humans and chimpanzees infected with the chimpanzee variant of Simian Immunodeficiency Virus (SIVcpz) [1]. Exposure to SIVcpz through contact with infected bodily fluid from the chimpanzee likely lead to the creation of HIV-1 and its four major groups M, O, N, and P [1]. For this model, we will only be analysing the transmission of HIV-1 M as it is the most prevalent strain worldwide [2].

HIV requires direct contact with bodily fluids to spread. Transmission can occur via blood transfusion, organ transplant, gestation, breast feeding, mucosal membrane (i.e. penile, vaginal, and rectal), and/or skin wounds (including needle punctures) [3, 4]. However, the majority of infections occur through sexual contact, especially in homosexual male populations [3].

HIV will take around two weeks for the viral load to build up to detectable levels throughout the body [3]. Initial symptoms start as early as three weeks after infection, listed as "fever, lymph node enlargement, fatigue, malaise, rash with small, only slightly raised lesions and/or gastrointestinal symptoms" [3]. Following the symptomatic stage, the virus goes into a latent phase where a viral load is still present, but causes few if any symptoms [3]. This period can last anywhere from two to twenty-four years [3]. During this time, CD4 immune cell levels continue to lower, allowing HIV to reach its final stage known as AIDS [3].

HIV isn't able to be cured as of yet, however it is able to be treated and prevented. The approach to treating HIV has changed greatly since the development of the first HIV medications. Currently, HIV is treated using a number of drugs at the same time [5]. The highly active antiviral treatment program (HAART) utilizes three HIV medications from two or more of the major HIV treatment groups [5]. These treatment groups include nucleoside-analog reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), integrase inhibitors, protease inhibitors (PI), and entry inhibitors which includes fusion inhibitors and CCR5 antagonists [5]. In short, NRTIs prevent the transcription of HIV-1's viral RNA into viral DNA, and thus, prevents the formation of new human immunodeficiency viruses [5]. This process is achieved by the NRTI binding to the HIV-1's reverse transcriptase protein, with the lack of a hydroxyl group on the NRTI at carbon three, 3'-5' bonds become impossible to form, so the formation of viral DNA is unable to occur [5, 6]. NNRTI's actions also take place within the reverse transcriptase protein [5]. NNRTIs change the shape of the protein near the active site which results in the obstruction of incoming nucleosides, meaning that, like the NRTI interactions, the formation of viral DNA is prevented [5, 7]. Integrase inhibitors prevent work after reverse transcription has already occurred. After reverse transcriptase synthesizes viral DNA, HIV-1 integrase will then try to integrate viral DNA into the host cell's DNA [8]. The integrase inhibitor binds to HIV-1 integrase at the enzyme and viral DNA connection point [5]. With this path-

way blocked, viral DNA is no longer able to integrate itself into the host's DNA, so the host cell will not make HIV-1 proteins that would result in advancing the infection [5, 8]. Protease inhibitors are effective after the formation of viral proteins. The protease enzymes separate these large HIV-1 proteins as the virus reaches maturity and the ability to infect other cells [5, 9]. The inhibitor attaches to its binding site inhibiting the attachment of the protein to the enzyme, thus not allowing cleaving of the large protein, preventing the maturation process from occurring [5]. We have not used any entry inhibitors in our model as the drug combinations did not include any, however, CYP3A4 inhibitors were included. CYP3A4 is an enzyme that metabolizes medications [10]. When certain drugs are used in high concentrations, the enzyme can cause unwanted and severe side effects [11]. In order to continue using a medication at an effective, high concentration, the enzyme needs to be inhibited [11]. So, CYP3A4 inhibitors don't treat HIV-1 directly, but they assist the medications that do treat HIV. Many of the medications used to treat an active HIV infection are also used to prevent an infection through post exposure prophylaxis (PEP) [5, 12]. Unlike HIV treatment, PEP is used within days of exposure to HIV with the goal of stopping the virus before an HIV infection occurs [13, 14].

Derivation of Model Formation

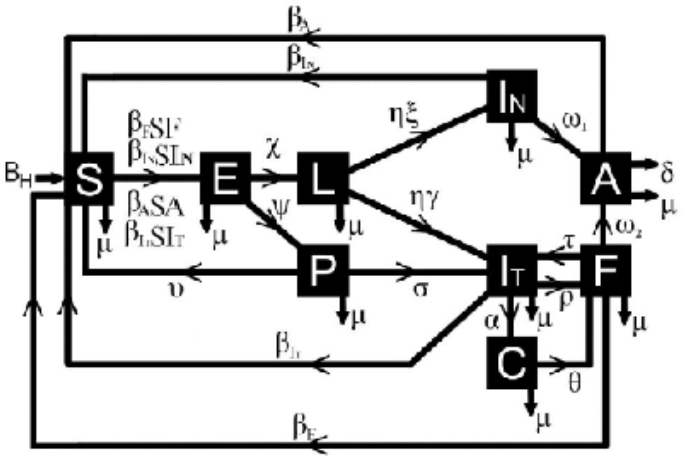


Figure 1: The HIV/AIDS model

Description of the Model Parameters

The HIV/AIDS model contains nine groups. The S group, or susceptible group, contains all humans that haven't been infected, nor exposed to the human immunodeficiency virus. Once exposed to an infectious human in groups *IN, IT, F, or A,* they will proceed to the Exposed group denoted as E. From the exposed group, two things could happen. If the person knew that they were exposed to HIV, then they may receive post exposure prophylaxis (PEP), group P, if the risk of contracting an infection is significant enough to warrant preventative medication [13]. If the treatment is successful, then the person will return to the susceptible class as they are no longer infected, but if the treatment fails, then they will automatically be moved to the treatment group, IT, as it's assumed that they know of their infection and are continuing treatment to prevent the progression to AIDS [12]. Otherwise, if the person didn't know they were exposed to the virus, or simply did not receive the preventative medication, then they will follow the infectious path to the latent group, labeled as L. The L group contains those that have contracted HIV, but not yet at a detectable level, which can take weeks until diagnostic tests can detect HIV antibodies [3]. At L there is also a split. Once HIV passes through its latent stage and begins to show symptoms with detectable antibody levels, then that person will either receive treatment, IT, or won't receive treatment, IN. Those that don't receive treatment will eventually progress to AIDS but, those that do receive treatment have more options [3]. While receiving treatment, the person is still infectious as they have not yet decreased their viral load to safe levels [14]. If the treatment is successful and the viral load drops below the acceptable threshold, then they are moved into the cured class, C, [15-26]. These people are not completely cured as the virus still resides inside of them, but they are no longer infectious [15-26]. Once in the C class, most will continue to stay in that class unless natural death occurs or their treatment is no longer effective due to a mutation in the virus leading to resistance against the treatment medication [15-26]. If the treatment is ineffective prior to or after viral suppression, then those people will move into the failed treatment group, F. For our model, ρ is the parameter that moves the treated population into the failed treatment population. ρ is a combination of the lack of efficacy of the treatment plus the discontinuation of a certain treatment due to severe side effects. The failed treatment group runs the risk of acquiring AIDS if another treatment regimen is not started [3]. The switching of treatment regimens is shown as τ which is moving from the failed group and back into the treatment group. AIDS, A, is the final group in the model and is the final stage of an HIV infection [3]. These people have compromised immune systems and do not receive treatment, which allows opportunistic infections to take over the body with little immune response leading to a higher death rate, δ, compared to the average healthy person. This model does not take into account the use of pre-exposure prophylaxis (PrEP). Description of all classes and parameters are mentioned in Table 1.

Table 1: Description of Parameters

$S(t)$: Susceptible population in time t	$E(t)$: Exposed population in time t
$L(t)$: Latent population in time t	$P(t)$: Post exposure prophylaxis population in time t
$I_N(t)$: Untreated HIV population in time t	$I_T(t)$: Treated HIV population in time t
$C(t)$: Successfully treated population in time t	$F(t)$: Failed treatment population in time t
$A(t)$: Untreated AIDS population in time t	$N_H(t)$: Total human population in time t
β_F : Transmission rate of the HIV from the failed treatment population	β_{IN} : Transmission rate of the HIV from the untreated HIV population
β_A : Transmission rate of the HIV from the untreated AIDS population	β_{IT} : Transmission rate of the HIV from the treated population
χ : Rate of transition from the exposed to the latent group	ψ : Percentage of the population going to receive PEP from the exposed group
υ : Percentage of the PEP population that was successfully treated	σ: Percentage of the PEP population that seroconverted and moved to the treatment group
η: Amount of time for HIV to reach detectable levels, ending the latent stage	ξ: Percentage of those infected with HIV not receiving treatment
γ: Percentage of those infected with HIV receiving treatment	α: Efficacy of the treatment medication leading to viral suppression,\ resulting in the person no longer being contagious
ρ : Percentage of the population that did not respond well to the medication or stopped due to its side effects	θ : Percentage of the successfully treated population that had the infection rebound due to viral resistance
τ : Percentage of the failed treatment population that received another medication	ω_1 : Amount of time until a person infected with HIV is classified as having AIDS
ω_2 : Amount of time until a person infected with HIV is classified as having AIDS after being treated	δ : Death rate of those classified as having AIDS
μ : Natural death rate of humans	B_H : Birth rate of humans

Equations form based on derived models.

$$\begin{aligned}
\frac{dS}{dt} &= B_H N_H + \upsilon P - (\beta_{IN} S I_N + \beta_F S F + \beta_A S A + \beta_{IT} S I_T) - \mu S \\
\frac{dE}{dt} &= \beta_{IN} S I_N + \beta_F S F + \beta_A S A + \beta_{IT} S I_T - (\chi + \psi + \mu) E \\
\frac{dL}{dt} &= \chi E - (\eta\xi + \eta\gamma + \mu) L \\
\frac{dP}{dt} &= \psi E - (\sigma + \upsilon + \mu) P \\
\frac{dI_N}{dt} &= \eta\xi L - (\omega_2 + \mu) I_N \\
\frac{dI_T}{dt} &= \eta\gamma L + \sigma P + \tau F - (\rho + \alpha + \mu) I_T \\
\frac{dC}{dt} &= \alpha I_T - (\mu + \theta) C \\
\frac{dF}{dt} &= \rho I_T + \theta C - (\omega_2 + \tau + \mu) F \\
\frac{dA}{dt} &= \omega_1 I_N + \omega_2 F - A(\delta + \mu)
\end{aligned} \tag{1}$$

$$\text{And } N_H(t) = S(t) + E(t) + L(t) + P(t) + I_N(t) + I_T(t) + C(t) + F(t) + A(t) \tag{2}$$

Stability of the Model

All of our parameters are positive or non-negative, therefore all parameters must remain positive or non-negative for positive initial conditions for $t \geq 0$. From the model's equations, we have:

$$\frac{dN_H}{dt} = B_H - \mu N_H - \delta A \leq B_H - \mu N_H$$

The closed set

$$D\left\{(S,E,L,P,H,I,I_N,I_T,C,F,A)\varepsilon R_+^{11} : N_H \leq \frac{B_H}{\mu}\right\}$$

is a feasible region for the graph.

Theorem 1: The closed set D is bounded and positive invariant.

Proof: Since $\frac{dN_H}{dt} \leq B_H - \mu N_H$, $(0 \leq B_H - \mu N_H; N_H \leq \frac{B_H}{\mu})$, so N_H is bounded by $\frac{B_H}{\mu}$, hence $\frac{dN_H}{dt} < 0$ whenever $N_H(t) > \frac{B_H}{\mu}$.

On simplification we have

$$N_H(t) \leq N_H(0)e^{-\mu t} + \frac{B_H}{\mu}(1 - e^{-\mu t})$$

As $t \to \infty$, $e^{-\mu t} \to 0$ and so $\lim_{t\to\infty} N_H(t) \leq \frac{B_H}{\mu}$.

Thus D is bounded and positively invariant in. R_+^{11}

Basic Reproduction Number

The basic reproduction number is the average number of secondary infections caused by a single infection within a susceptible population.

The basic reproduction number is calculated by $R_o = \rho(FV^{-1})$, where ρ is the spectral radius of the matrix FV^{-1} and F and V are the matrices of new infection terms and remaining transmission terms respectively.

$$F=\begin{bmatrix} 0 & 0 & 0 & \mu_{IN} & \mu_{IT} & \mu_{F} & \beta_{A} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V=\begin{bmatrix} \chi+\psi+\mu & 0 & 0 & 0 & 0 & 0 & 0 \\ -\chi & \eta\xi+\eta\gamma-\mu & 0 & 0 & 0 & 0 & 0 \\ \psi & 0 & \sigma+\upsilon+\mu & 0 & 0 & 0 & 0 \\ 0 & -\eta\xi & 0 & \omega_1+\mu & 0 & 0 & 0 \\ 0 & -\eta\gamma & -\upsilon & 0 & \rho+\alpha-\mu & -\tau & 0 \\ 0 & 0 & 0 & 0 & -\rho & \omega_2+\tau+\mu & 0 \\ 0 & 0 & 0 & \omega_1 & 0 & -\omega_2 & \delta+\mu \end{bmatrix}$$

$$V^{-1}=\begin{bmatrix} \frac{1}{Q} & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\chi}{QR} & \frac{1}{R} & 0 & 0 & 0 & 0 & 0 \\ \frac{\psi}{QT} & \frac{\eta\xi}{RT} & \frac{1}{T} & 0 & 0 & 0 & 0 \\ \frac{\chi\eta\xi}{QRU} & \frac{\eta\xi}{RU} & 0 & \frac{1}{U} & 0 & 0 & 0 \\ \frac{\chi\eta\gamma}{QRM} + \frac{\psi\sigma}{QTM} & \frac{\eta\gamma}{RM} + \frac{\sigma}{TM} & \frac{\sigma}{TM} & 0 & \frac{1}{M} & \frac{\tau}{M(MY-\tau\rho)} & 0 \\ \frac{\chi\eta\gamma\rho}{QRMY} + \frac{\psi\sigma\rho}{QTMY} & \frac{\eta\gamma\rho}{RMY} & 0 & 0 & \frac{\rho}{MY} & \frac{1}{Y} & 0 \\ \frac{\chi\eta\xi\omega_1}{QRUZ} + \frac{\chi\eta\gamma\rho}{QRZ(MY-\tau\rho)} + \frac{\psi\sigma\rho}{QTZ(MY-\tau\rho)} & \frac{\eta\xi\omega_1}{RUZ} + \frac{\eta\gamma\rho}{RZ(MY-\tau\rho)} & \frac{\sigma\rho}{TZ(MY-\tau\rho)} & \frac{\omega_1}{UZ} & \frac{\rho}{MZ} & \frac{\tau}{YZ} & \frac{1}{Z} \end{bmatrix}$$

Where $H=\omega_2, M=(\rho+\alpha+\mu), Q=(\chi+\psi+\mu), R=(\eta\xi+\eta\gamma+\mu), T=(\sigma+\upsilon+\mu),$
$U=(\omega_1+\mu), Y=(\omega_2+\tau+\mu)$, and $Z=(\delta+\mu)$

$$FV^{-1}(1,1)=\frac{\beta_{IN}\chi\eta\xi}{QRU}+\frac{\beta_{IT}}{QM}\left[\frac{\chi\eta\gamma}{R}+\frac{\psi\sigma}{T}\right]+\frac{\tau\beta_{IT}}{QM(MY-\tau\rho)}\left[\frac{\chi\eta\gamma\rho}{R}+\frac{\psi\sigma\rho}{T}\right]+\frac{\beta_{F}}{Q(MY-\tau\rho)}\left[\frac{\chi\eta\gamma\rho}{R}+\frac{\psi\sigma\rho}{T}\right]+\frac{\beta_{A}\chi\eta\xi\omega_1}{QRUZ}+\frac{\beta_{A}H}{QZ(MY-\tau\rho)}\left[\frac{\chi\eta\gamma\rho}{R}+\frac{\psi\sigma\rho}{T}\right]$$

$$FV^{-1}(2,2)=0;\ FV^{-1}(3,3)=0;\ FV^{-1}(4,4)=0;FV^{-1}(5,5)=0;\ FV^{-1}(6,6)=0$$

$$FV^{-1}(7,7)=0$$

R_0 = Tr (Diagonal elements of FV^{-1})

$$R_{\sigma}=\frac{\eta\chi\xi[\beta_{IN}(\delta+\mu)+\beta_{A}\omega_1]}{(\chi+\psi+\mu)(\eta\xi+\eta\gamma+\mu)(\omega_2+\mu)(\delta+\mu)}+\left[\frac{\chi\eta\gamma}{\eta\xi+\eta\gamma+\mu}+\frac{\psi\sigma}{\sigma+\upsilon+\mu}\right]\left[\frac{\beta_{IT}(\omega_2+\mu)(\delta+\mu)+\rho[\beta_{F}(\delta+\mu)+\beta_{A}\omega_2]}{(\chi+\psi+\mu)(\delta+\mu)[(\rho+\alpha+\mu)(\omega_2+\mu)-\tau\rho]}\right]$$. In table 2

we have the calculated basic reproduction number for each region along with the parameter values.

Table 2. Calculation of the basic reproduction number

	World Data	Americas	Africa	South East Asia	West Pacific	European Data	Eastern Medderian		
Parameter	% / amount	% / amount	% / amount	% / amount	% / amount	% / amount	% / amount	Units	Source
βln	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	year^-1	13
βlt	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	year^-1	13
βf	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	year^-1	13
βa	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	0.0046375	year^-1	13
χ	0.04485	0.04485	0.04485	0.04485	0.04485	0.04485	0.04485	year^-1	32,36
ψ	0.66	0.66	0.66	0.66	0.66	0.66	0.66	year^-1	33
υ	0.8745	0.8745	0.8745	0.8745	0.8745	0.8745	0.8745	year^-1	11-13
σ	0.1255	0.1255	0.1255	0.1255	0.1255	0.1255	0.1255	year^-1	11-13
θ	0.01297	0.01297	0.01297	0.01297	0.01297	0.01297	0.01297	year^-1	14-25
η	0.76712	0.76712	0.76712	0.76712	0.76712	0.76712	0.76712	year^-1	34
ξ	0.38	0.033	0.36	0.47	0.41	0.45	0.79	year^-1	35
γ	0.62	0.67	0.64	0.53	0.59	0.55	0.21	year^-1	35
α	0.7875	0.7875	0.7875	0.7875	0.7875	0.7875	0.7875	year^-1	14-25
ρ	0.1928	0.1928	0.1928	0.1928	0.1928	0.1928	0.1928	year^-1	14-25
ω (1 and 2)	0.15385	0.15385	0.15385	0.15385	0.15385	0.15385	0.15385	year^-1	34
δ	0.0176	0.014	0.01828793774	0.03947368421	0.02526315789	0.0152	0.0375	year^-1	36,37
μ	0.000754678211	0.006749389745	0.009918825852	0.006544728176	0.006371402781	0.009541311709	0.005351456894	year^-1	38
Bh	0.01822	0.01528173312	0.04150769694	0.01809112708	0.01635438535	0.01177043773	0.02219134875	year^-1	38
r	0.975	0.975	0.975	0.975	0.975	0.975	0.975	year^-1	39
Ro	3.337596173	1.14595674	2.246435656	1.936842831	2.28210388	2.895560172	2.97690758	year^-1	

Qualitative Analysis

Stability analysis, Disease-free-equilibrium, Global stability, and endemic equilibrium of the model has been established and given in Appendix A.

Numerical Simulation

Numerical Parameter Values

The population values of table 3 are only for the overall population and the parameters in table 2 contain the averages of all HIV treatments and PEP. We grouped all of those infected with HIV into the latent stage as they would not be able to receive PEP and it would allow the model to divide the population into the subsequent groups, rather than our own calculations with the given data. Any group that isn't listed in table 3 has a population of 0.

Unless otherwise stated, these are the values that have been used in the simulations.

Table 3. Regional population values used in the MATLAB simulations.

Parameter	World Data	Americas	Africa	South East Asia	West Pacific	European Data	Eastern Medderian
S(t)	7700.1	979.7	1103.97	1899.564	1861.484	978.6	665.4
L(t)	37.9	3.5	25.7	3.8	1.9	2.5	0.4
N(t)	7738	983.2	1129.67	1903.364	1863.384	981.1	665.8

Table 4 contains all of the treatment values. The efficacy of the treatment (α), discontinuations, and resistance percentages (θ) were pulled directly from sources [15-26]. The discontinuation percentage is a measure of the amount of people that stopped using the treatment due to severe side effects. ρ (rho) was calculated by the equation *Discontinuation (1 − Efficacy)*. The reason this was done was to show that even though some medications may have a high efficacy, and thus would have a better percentage of successful viral suppression, the inclusion of severe side effects would result in more people stopping that medication. That way the best working medications may not actually be the ones with the highest numbers of successful treatments.

Table 4: Numerical values of treatment parameters used in the MATLAB simulations.

Drug names	Shorten Version	Efficacy	Discontinued	Rho	Resistance	Source
atazanavir/cobicistat/tenofovir disoproxil fumarate/Emtricitabine	ATV/c/TDF/TCF	85.20%	7.30%	0.2210	0.04285714286	15
atazanavir/ritonavir/tenofovir disoproxil fumarate/Emtricitabine	ATV/r/TDF/TCF	87.40%	7.20%	0.1980	0.06896551724	15
darunavir/cobicistat/tenofovir disoproxil fumarate/Emtricitabine	DRV/c/TDF/TCF	83%	4.79%	0.2179	0.006389776358	15
darunavir/ritonavir	DRV/r	84%	3.50%	0.1950	0.002915451895	16
lopinavir and ritonavir	LPV/r	78%	6.94%	0.2894	0.008670520231	16
abacavir/lamivudine/zidovudine	ABC/3TC/AZT	75.00%	6.60%	0.3160	n/a	17
abacavir/lamivudine	ABC/3TC	59%	12.80%	0.5380	0	18
Emtricitabine/tenofovir disoproxil fumarate	TCF/TDF	93%	2.10%	0.0910	n/a	19
Emtricitabine/tenofovir alafenamide	TCF/TAF	94%	0.009%	0.0601	n/a	19
Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate	DOR/3TC/TDF	84.30%	2.74%	0.1844	0.01648351648	20
Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate	EFV/TCF/TDF	80.80%	6.32%	0.2552	0.03021978022	20
rilpivirine/emtricitabine/tenofovir disoproxil fumarate	RPV/TCF/TDF	85.8%	8.70%	0.2290	n/a	21
elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate	EVG/c/TCF/TAF	97.00%	3.08%	0.0608	0.006928406467	22
elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate	EVG/c/TCF/TDF	93.00%	1.67%	0.0867	0.005767012687	22
darunavir/cobicistat/emtricitabine/tenofovir alafenamide	DRV/c/TCF/TAF	91.4%	1.93%	0.1053	0.002762430939	23
dolutegravir/abacavir/lamivudine	DTG/ABC/3TC	88.00%	3.14%	0.1514	0	24
bictegravir/emtricitabine/tenofovir alafenamide	BIC/TCF/TAF	89.00%	1.56%	0.1256	0	24
dolutegravir/emtricitabine/tenofovir alafenamide	DTG/TCF/TAF	93.0%	0.307%	0.0731	0	25
dolutegravir/rilpivirine	DTG/RPV	95.0%	3.31%	0.0831	n/a	26

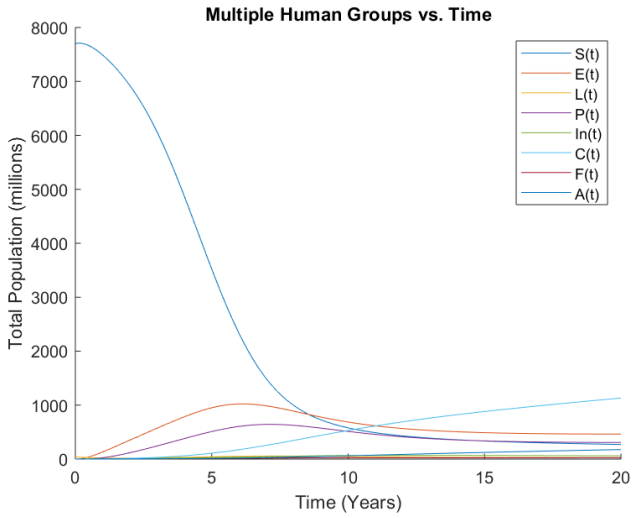
Efficacy (υ) for HIV PEP was calculated by subtracting the seroconversion percent by 1. Unfortunately, due to this being a study on primates, we could not get a discontinuation percentage as we did in table 4, so the failure rate of PEP is purely based on is seroconversion percentage (σ) [12].

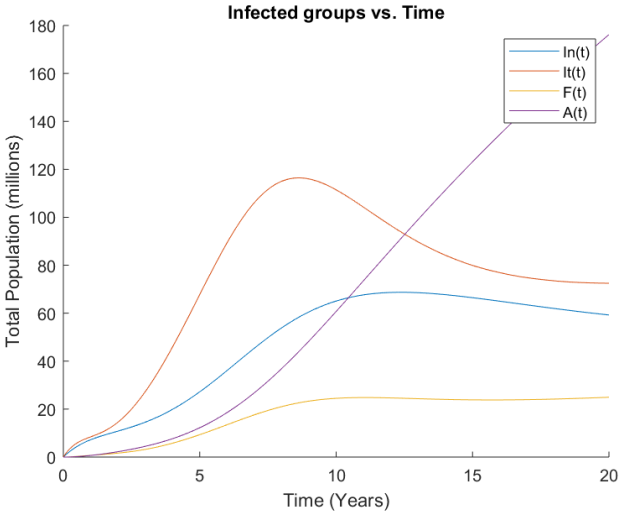
Table 5: Numerical values of PEP parameters used in the MATLAB simulations for the overall population.

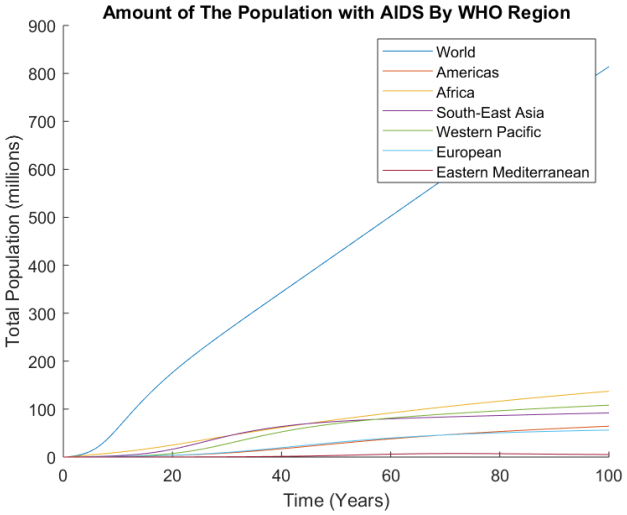
Drug names	Seroconversion percent	Efficacy	Source
azidothymidine	43.00%	57.00%	11
stavudine	7.00%	93.00%	11
2',3'-Dideoxy-3'-hydroxymethyl cytidine (BEA005)	6%	94%	11
GW420867	7%	93%	11
tenofovir	9.00%	91.00%	11
tenofovir disoproxyl fumarate	10.00%	90.00%	11
azidothymidine/lamivudine/ indinavir	10%	90%	11
tenofovir disoproxyl fumarate/emtricitabine	12%	88%	11
MIV-150/zinc acetate/carrageenan gel	12.00%	88.00%	11
raltegravir	11.00%	89.00%	11
azidothymidine/lamivudine	11%	89%	11

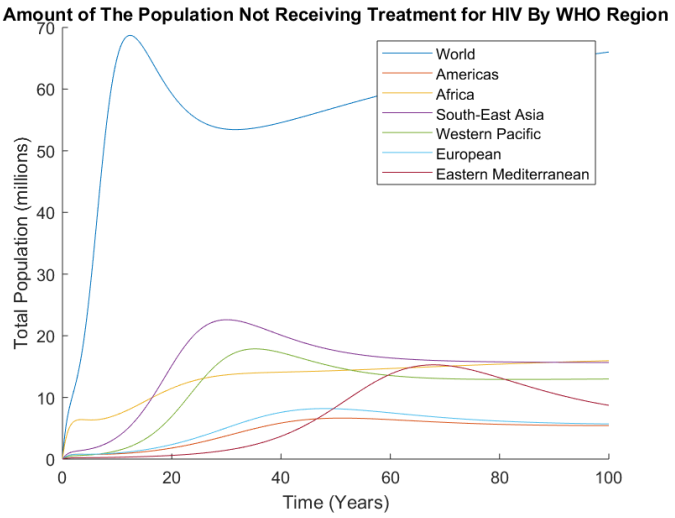
Table 6 : Effect of Treatments on Class C listed from highest to lowest Population (NoResistance)

World	Americas	Africa	South-East Asia	Western Pacific	Europe	E.mediterranean
RPV/TCF/TDF	ATV/r/TDF/TCF	RPV/TCF/TDF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	RPV/TCF/TDF
ATV/r/TDF/TCF	RPV/TCF/TDF	ATV/r/TDF/TCF	RPV/TCF/TDF	RPV/TCF/TDF	RPV/TCF/TDF	ATV/c/TDF/TCF
ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/r/TDF/TCF
EFV/TCF/TDF	DTG/ABC/3TC	DRV/c/TDF/TCF	DTG/ABC/3TC	DTG/ABC/3TC	DRV/c/TDF/TCF	EFV/TCF/TDF
DRV/c/TDF/TCF	DRV/r	DRV/r	DRV/r	DRV/r	DRV/r	DRV/c/TDF/TCF
LPV/r	DOR/3TC/TDF	EFV/TCF/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DTG/ABC/3TC	DRV/r
DRV/r	DRV/c/TDF/TCF	DOR/3TC/TDF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	DOR/3TC/TDF	LPV/r
DOR/3TC/TDF	BIC/TCF/TAF	DTG/ABC/3TC	BIC/TCF/TAF	BIC/TCF/TAF	EFV/TCF/TDF	DOR/3TC/TDF
DTG/ABC/3TC	EFV/TCF/TDF	LPV/r	DRV/c/TCF/TAF	EFV/TCF/TDF	BIC/TCF/TAF	DTG/ABC/3TC
ABC/3TC/AZT	DRV/c/TCF/TAF	BIC/TCF/TAF	DTG/RPV	DRV/c/TDF/TAF	LPV/r	ABC/3TC/AZT
BIC/TCF/TAF	TCF/TDF	DRV/c/TCF/TAF	TCF/TDF	DTG/RPV	DRV/c/TCF/TAF	BIC/TCF/TAF
DRV/c/TCF/TAF	DTG/RPV	ABC/3TC/AZT	EFV/TCF/TDF	TCF/TDF	TCF/TDF	DRV/c/TCF/TAF
DTG/RPV	EVG/c/TCF/TDF	TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF	DTG/RPV	TCF/TDF
TCF/TDF	LPV/r	DTG/RPV	EVG/c/TCF/TAF	LPV/r	EVG/c/TCF/TDF	EVG/c/TCF/TDF
EVG/c/TCF/TDF	DTG/TCF/TAF	EVG/c/TCF/TDF	DTG/TCF/TAF	EVG/c/TCF/TAF	ABC/3TC/AZT	DTG/RPV
EVG/c/TCF/TAF	EVG/c/TCF/TAF	RPV/TCF/TDF	LPV/r	DTG/TCF/TAF	DTG/TCF/TAF	DTG/TCF/TAF
DTG/TCF/TAF	ABC/3TC/AZT	EVG/c/TCF/TAF	TCF/TAF	ABC/3TC/AZT	EVG/c/TCF/TAF	EVG/c/TCF/TAF
TCF/TAF	TCF/TAF	TCF/TAF	ABC/3TC/AZT	TCF/TAF	TCF/TAF	TCF/TAF
ABC/3TC	Ideal	Ideal	Ideal	Ideal	Ideal	ABC/3TC
Ideal	ABC/3TC	ABC/3TC	ABC/3TC	ABC/3TC	ABC/3TC	Ideal





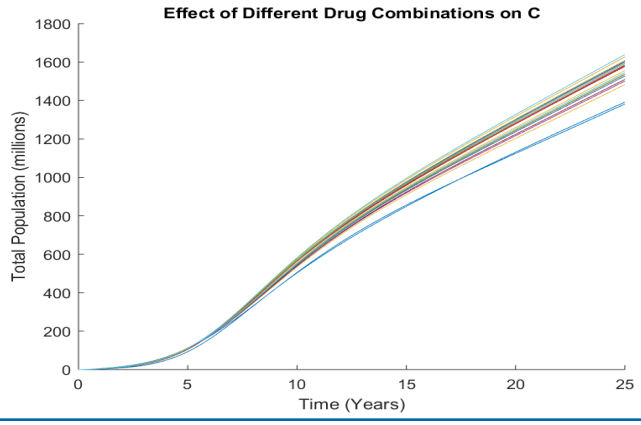


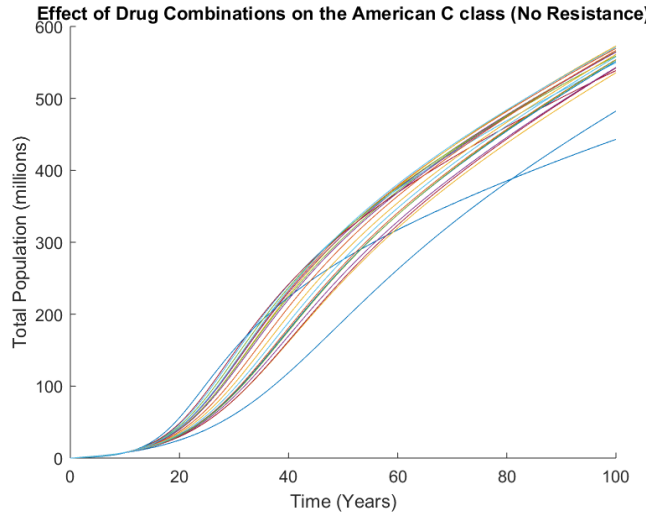


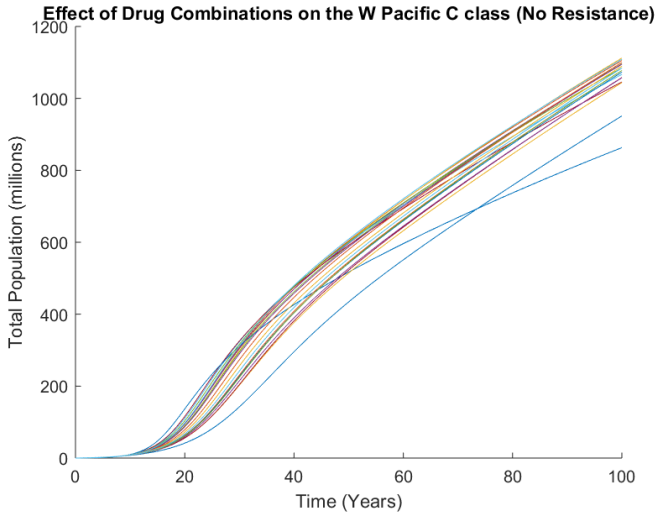
Discussion of Results

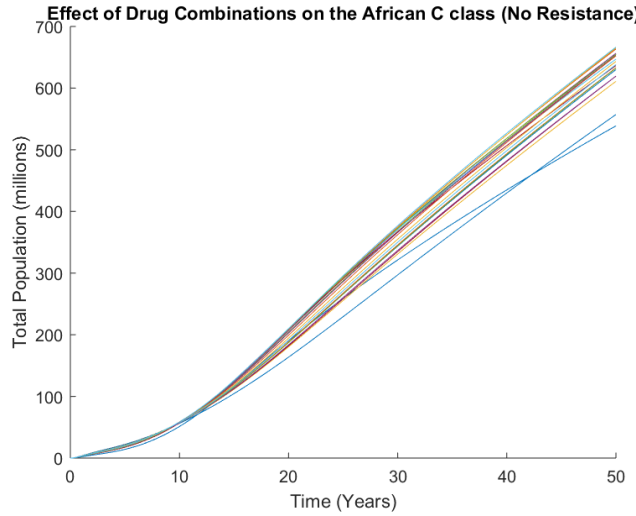
Figure 1(a), and 1(b) depict the dynamics of each group. There are significant time delays before the successfully treated population (C) and AIDS population begins to increase due to HIV's indistinct initial symptoms, and the fact that latent stage that lasts years before the onset of AIDS. Figure 1b excludes the susceptible group in order to get a closer look at the other groups. Figure 2(a) shows that AIDS will continue to grow well into the future if nothing changes as seen by the world line. However, in the Eastern Mediterranean (EM) region, it seems that the AIDS population has nearly died out by the hundredth year. It is the only region that has its AIDS population shrinking rather than growing, despite it having the highest basic reproduction number out of all the regions. It's possible that it's due to the EM having such a low population and high death rate due to AIDS that the AIDS patients are dying at a faster rate than they can be replaced, which would explain the shrinking population.

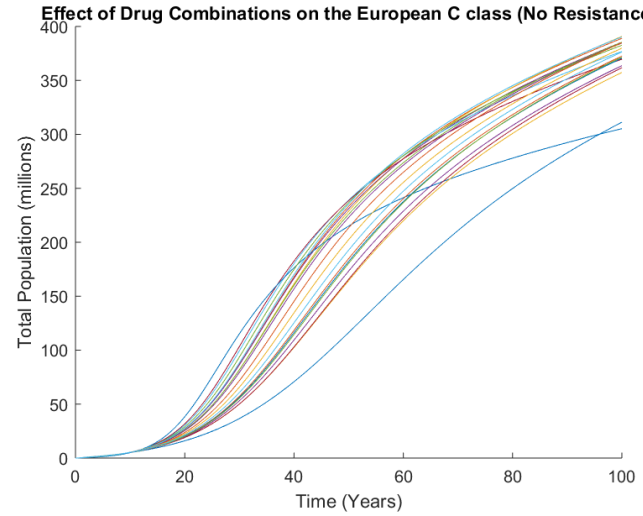
Figure 2b clearly shows that the amount of untreated people in all WHO defined regions (except EM) are decreasing between 30 to 40 years, indicating that either the populations are either progressing towards AIDS or are being treated faster than the rate of incoming infectious people. In EM, the HIV untreated population slowly is increasing from 0 to 60 years. The reason again can be contributed to the explanation of the EM's strange trajectory in figure 2a.

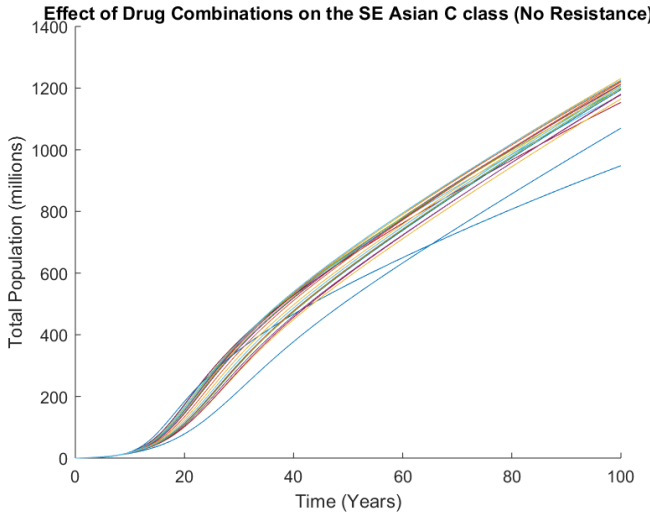


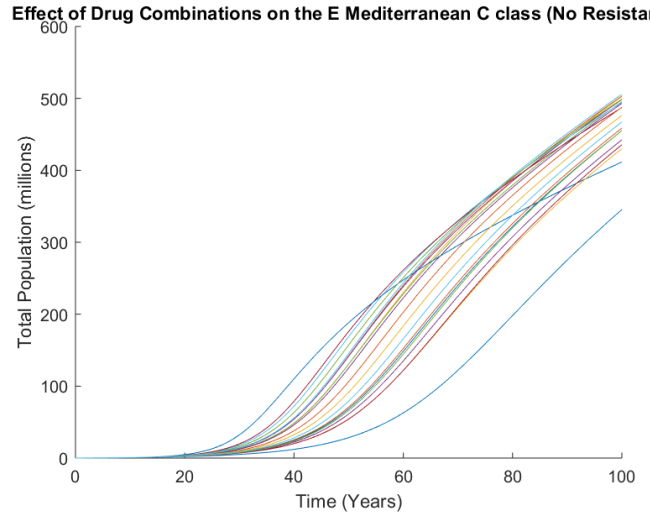

Effect of Drug Combinations on the American C class (No Resistance)
Total Population (millions)
Time (Years)
0
100
200
300
400
500
600
0
20
40
60
80
100


Effect of Drug Combinations on the W Pacific C class (No Resistance)
Total Population (millions)
Time (Years)
0
200
400
600
800
1000
1200
0
20
40
60
80
100


Effect of Drug Combinations on the African C class (No Resistance)
Total Population (millions)
Time (Years)
0
100
200
300
400
500
600
700
0
10
20
30
40
50


Effect of Drug Combinations on the European C class (No Resistance)
Total Population (millions)
Time (Years)
0
50
100
150
200
250
300
350
400
0
20
40
60
80
100


Effect of Drug Combinations on the SE Asian C class (No Resistance)
Total Population (millions)
Time (Years)
0
200
400
600
800
1000
1200
1400
0
20
40
60
80
100

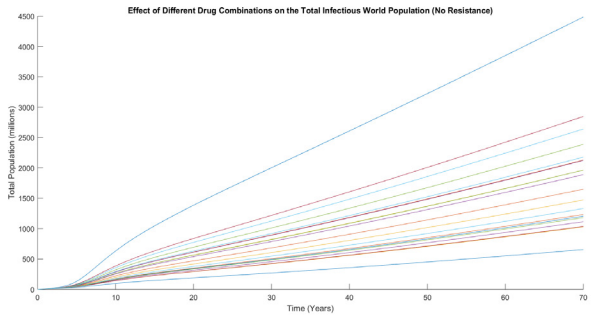

Effect of Drug Combinations on the E Mediterranean C class (No Resistance)
Total Population (millions)
Time (Years)
0
100
200
300
400
500
600
0
20
40
60
80
100

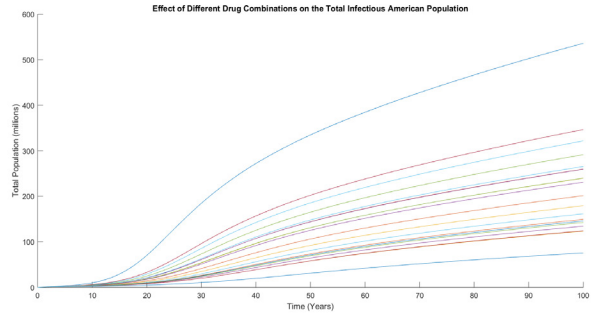
Effect of treatments on C listed from highest to lowest population (no resistance)						
World	**Americas**	**Africa**	**South-East Asia**	**Western Pacific**	**Europe**	**E. mediterranean**
RPV/TCF/TDF	ATV/r/TDF/TCF	RPV/TCF/TDF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	RPV/TCF/TDF
ATV/r/TDF/TCF	RPV/TCF/TDF	ATV/r/TDF/TCF	RPV/TCF/TDF	RPV/TCF/TDF	RPV/TCF/TDF	ATV/c/TDF/TCF
ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/r/TDF/TCF
EFV/TCF/TDF	DTG/ABC/3TC	DRV/c/TDF/TCF	DTG/ABC/3TC	DTG/ABC/3TC	DRV/c/TDF/TCF	EFV/TCF/TDF
DRV/c/TDF/TCF	DRV/r	DRV/r	DRV/r	DRV/r	DRV/r	DRV/c/TDF/TCF
LPV/r	DOR/3TC/TDF	EFV/TCF/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DTG/ABC/3TC	DRV/r
DRV/r	DRV/c/TDF/TCF	DOR/3TC/TDF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	DOR/3TC/TDF	LPV/r
DOR/3TC/TDF	BIC/TCF/TAF	DTG/ABC/3TC	BIC/TCF/TAF	BIC/TCF/TAF	EFV/TCF/TDF	DOR/3TC/TDF
DTG/ABC/3TC	EFV/TCF/TDF	LPV/r	DRV/c/TCF/TAF	EFV/TCF/TDF	BIC/TCF/TAF	DTG/ABC/3TC
ABC/3TC/AZT	DRV/c/TCF/TAF	BIC/TCF/TAF	DTG/RPV	DRV/c/TDF/TAF	LPV/r	ABC/3TC/AZT
BIC/TCF/TAF	TCF/TDF	DRV/c/TCF/TAF	TCF/TDF	DTG/RPV	DRV/c/TCF/TAF	BIC/TCF/TAF
DRV/c/TCF/TAF	DTG/RPV	ABC/3TC/AZT	EFV/TCF/TDF	TCF/TDF	TCF/TDF	DRV/c/TCF/TAF
DTG/RPV	EVG/c/TCF/TDF	TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF	DTG/RPV	TCF/TDF
TCF/TDF	LPV/r	DTG/RPV	EVG/c/TCF/TAF	LPV/r	EVG/c/TCF/TDF	EVG/c/TCF/TDF
EVG/c/TCF/TDF	DTG/TCF/TAF	EVG/c/TCF/TDF	DTG/TCF/TAF	EVG/c/TCF/TAF	ABC/3TC/AZT	DTG/RPV
EVG/c/TCF/TAF	EVG/c/TCF/TAF	RPV/TCF/TDF	LPV/r	DTG/TCF/TAF	DTG/TCF/TAF	DTG/TCF/TAF
DTG/TCF/TAF	ABC/3TC/AZT	EVG/c/TCF/TAF	TCF/TAF	ABC/3TC/AZT	EVG/c/TCF/TAF	EVG/c/TCF/TAF
TCF/TAF	TCF/TAF	TCF/TAF	ABC/3TC/AZT	TCF/TAF	TCF/TAF	TCF/TAF
ABC/3TC	Ideal	Ideal	Ideal	Ideal	Ideal	ABC/3TC
Ideal	ABC/3TC	ABC/3TC	ABC/3TC	ABC/3TC	ABC/3TC	Ideal

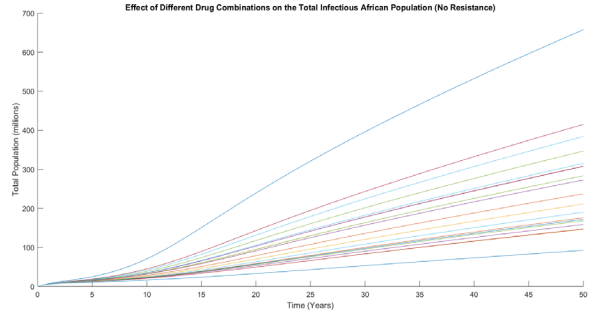
Figure 3a-3g and **Table 6** (inserted in above figure): Simulations of those successfully treated for HIV disregarding viral resistance for each WHO region.

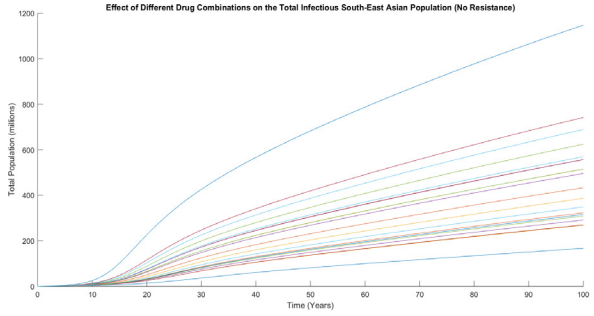
This simulation uses the regional differences in table 2 and 3, and the treatment information seen in table 4.

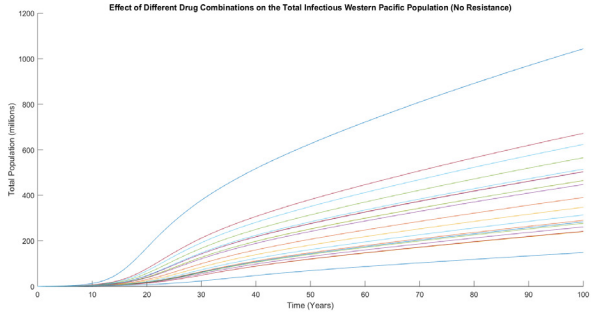
The model in this simulation is not isolated to the treatment loop (It, C, and F), instead the entire model was run to see the effect of the treatments on a changing population. They have a similar shape and the lines are very concentrated throughout with slight separation being seen towards the end of the century. However, each region does not have the same order of best medications. We see that the ideal medication with 100% success only has the lowest population in the world graph (figure 3a) and none of the others. The ideal medication is on the bottom for the Eastern Mediterranean (figure 3g), but judging by the graph, it will soon follow the other regions as the ideal medication's population grows where the ABC/3TC population begins to stagnate. But this doesn't mean that ABC/3TC is the best medication since it has the lowest population, it actually means the opposite. Where the ideal medication is low due to its high efficacy which is preventing people from transferring to the failed class, resulting in less viral transmission; ABC/3TC is low because it works so poorly that the majority of the people receiving that treatment end up failing it, which doesn't show up on this graph. Another treatment of interest is LPV/r. In the world population it has a relatively high population when compared to the other treatments, however in most of the other regions, LPV/r has a relatively low population.

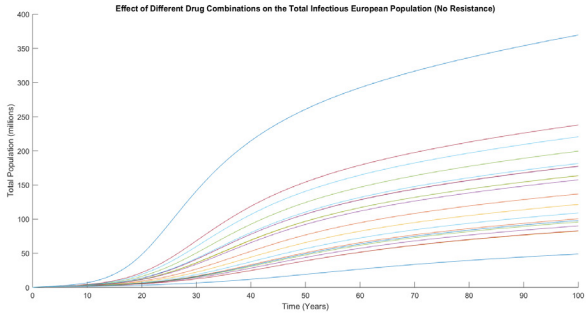


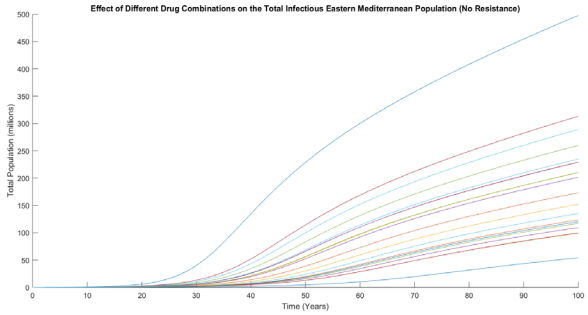








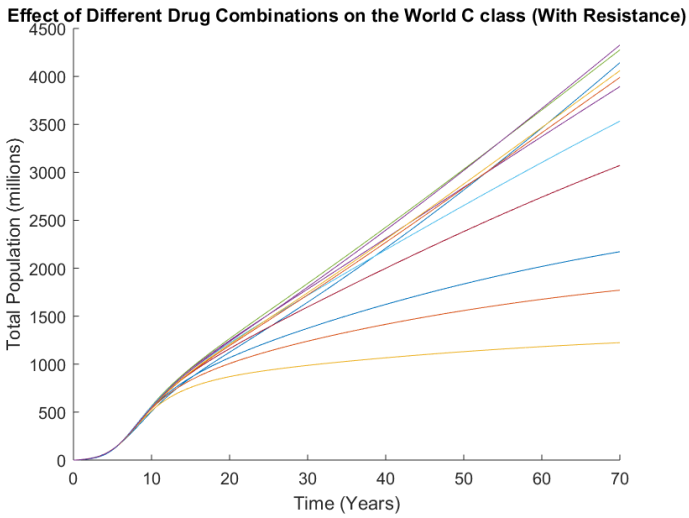


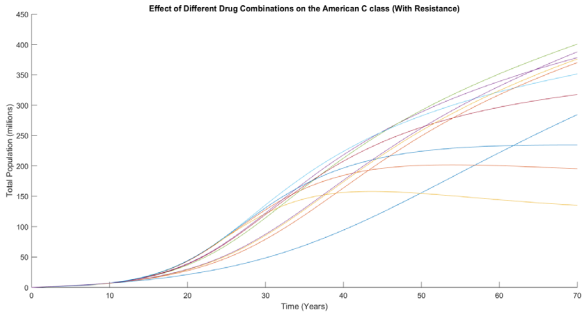


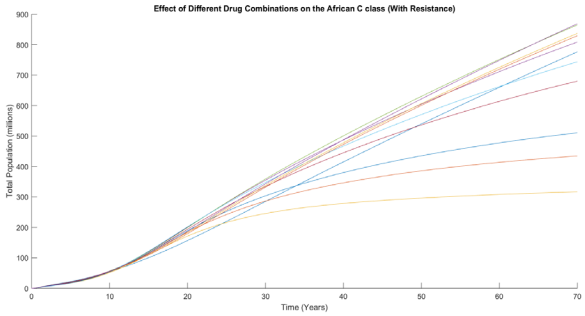
Effect of treatments on the total infectious population listed from highest to lowest population (no resistance)

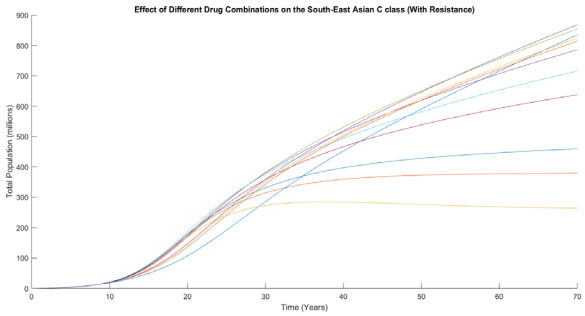
World	Americas	Africa	South-East Asia	Western Pacific	Europe	E. mediterranean
ABC/3TC	ABC/3TC	ABC/3TC	ABC/3TC	ABC/3TC	ABC/3TC	ABC/3TC
ABC/3TC/AZT	ABC/3TC/AZT	ABC/3TC/AZT	ABC/3TC/AZT	ABC/3TC/AZT	ABC/3TC/AZT	ABC/3TC/AZT
LPV/r	LPV/r	LPV/r	LPV/r	LPV/r	LPV/r	LPV/r
EFV/TCF/TDF	EFV/TCF/TDF	RPV/TCF/TDF	EFV/TCF/TDF	EFV/TCF/TDF	EFV/TCF/TDF	EFV/TCF/TDF
RPV/TCF/TDF	RPV/TCF/TDF	EFV/TCF/TDF	RPV/TCF/TDF	RPV/TCF/TDF	RPV/TCF/TDF	RPV/TCF/TDF
ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF
DRV/c/TDF/TCF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	DRV/c/TDF/TCF
ATV/r/TDF/TCF	DRV/r	DRV/r	DRV/r	DRV/r	DRV/r	DRV/r
DRV/r	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF
DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF
DTG/ABC/3TC	DTG/ABC/3TC	DRV/c/TCF/TAF	DTG/ABC/3TC	DTG/ABC/3TC	DTG/ABC/3TC	DTG/ABC/3TC
BIC/TCF/TAF	BIC/TCF/TAF	DTG/ABC/3TC	BIC/TCF/TAF	BIC/TCF/TAF	BIC/TCF/TAF	BIC/TCF/TAF
DRV/c/TCF/TAF	DRV/c/TCF/TAF	BIC/TCF/TAF	DRV/c/TCF/TAF	DRV/c/TCF/TAF	DRV/c/TCF/TAF	DRV/c/TCF/TAF
TCF/TDF	TCF/TDF	TCF/TDF	TCF/TDF	TCF/TDF	TCF/TDF	TCF/TDF
EVG/c/TCF/TDF	EVG/c/TCF/TDF	DTG/RPV	EVG/c/TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF
DTG/RPV	DTG/RPV	EVG/c/TCF/TDF	DTG/RPV	DTG/RPV	DTG/RPV	DTG/RPV
DTG/TCF/TAF	DTG/TCF/TAF	DTG/TCF/TAF	DTG/TCF/TAF	DTG/TCF/TAF	DTG/TCF/TAF	DTG/TCF/TAF
EVG/c/TCF/TAF	EVG/c/TCF/TAF	EVG/c/TCF/TAF	EVG/c/TCF/TAF	EVG/c/TCF/TAF	EVG/c/TCF/TAF	EVG/c/TCF/TAF
TCF/TAF	TCF/TAF	TCF/TAF	TCF/TAF	TCF/TAF	TCF/TAF	TCF/TAF
Ideal	Ideal	Ideal	Ideal	Ideal	Ideal	Ideal

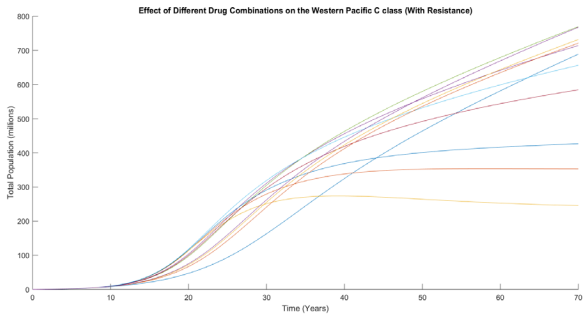
This simulation also uses tables 2, 3, and 4's parameter values. Unlike figures 3, figures 4a-4g are far more predictable. For the most part all of the graphs follow the same pattern with some minor switches in the world, African, and American regions. The trend is mostly in terms of efficacy with the poorly performing medications seen at the top of the graph. Where it was difficult to see what was going on outside of the successfully treated group in figures 3, figures 4 clearly shows the impact of the medications on the actual HIV population. In the world population (figure 4a), we see that it could drop the infectious HIV population over eight times when compared to ABC/3TC.

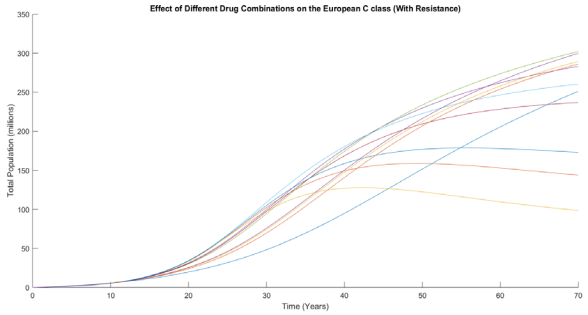


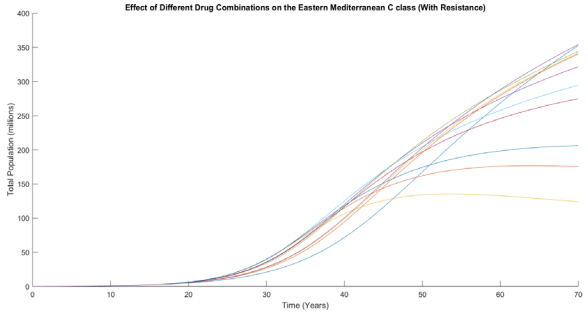










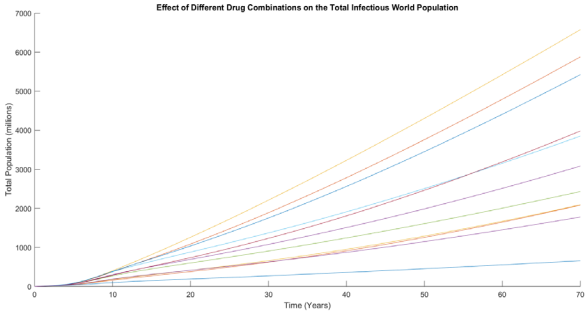


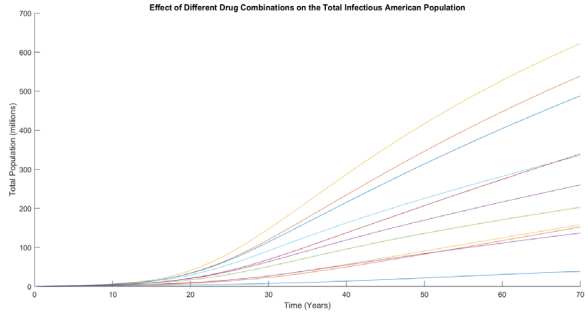
Effect of treatments on C listed from highest to lowest population

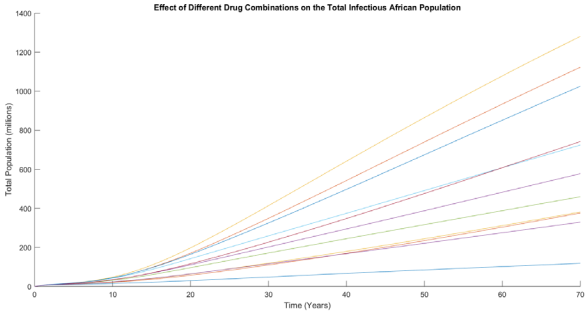
World	Americas	Africa	South-East Asia	Western Pacific	Europe	E. mediterranean
DRV/c/TCF/TAF	DRV/r	DRV/c/TCF/TAF	DRV/c/TCF/TAF	DRV/r	DRV/r	DRV/c/TCF/TAF
DRV/r	DRV/c/TCF/TAF	DRV/r	DRV/r	DRV/c/TCF/TAF	DRV/c/TCF/TAF	Ideal
Ideal	DRV/c/TDF/TCF	EVG/c/TCF/TDF	Ideal	EVG/c/TCF/TAF	EVG/c/TCF/TAF	DRV/r
EVG/c/TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TAF	EVG/c/TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF
EVG/c/TCF/TAF	EVG/c/TCF/TAF	DRV/c/TDF/TCF	EVG/c/TCF/TAF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	EVG/c/TCF/TAF
DRV/c/TDF/TCF	LPV/r	Ideal	DRV/c/TDF/TCF	Ideal	LPV/r	DRV/c/TDF/TCF
LPV/r	DOR/3TC/TDF	LPV/r	LPV/r	LPV/r	Ideal	LPV/r
DOR/3TC/TDF	Ideal	DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF
EFV/TCF/TDF	EVF/TCF/TDF	EFV/TCF/TAF	EFV/TCF/TAF	EFV/TCF/TAF	EFV/TCF/TAF	EFV/TCF/TAF
ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF
ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF

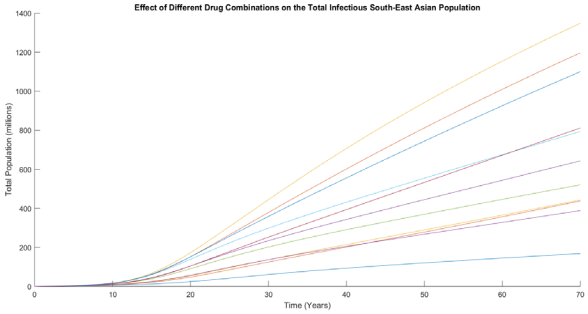
Figure 5a-5g uses **tables 2, 3, and 4 with the resistance factor.**

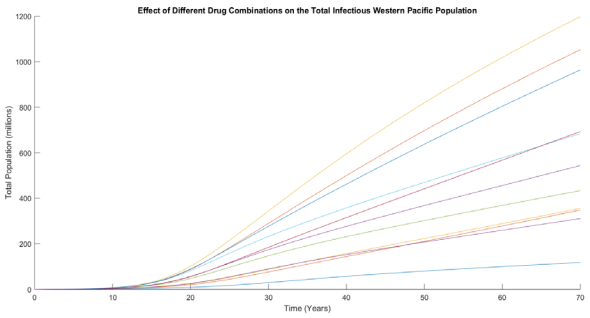
Figure 5a-5g uses tables 2, 3, and 4 with the resistance factor. Not all medications will be as effective as the day they were administered to a patient. As time goes on, HIV will begin to fight back against the treatment through viral resistance [27-33]. Viral resistance to medication occurs when the virus mutates, resulting in a change that makes it less susceptible to the ways that the treatment medications try to hinder its replication [33]. Unlike figures 3, figures 5a-5g have people leaving the successfully treated group, and moving to the failed treatment group. So, where the ideal was once the lowest population, it now ranks much higher due to the fact that no one is leaving that group. With the inclusion of resistance, we see that many medications drop below the ideal, not because they perform so well that infection is prevented, but because the efficacy of the medication is being overshadowed by the resistance factor, eventually resulting in an even flow in and out of the successfully treated class that performs far below the ideal.

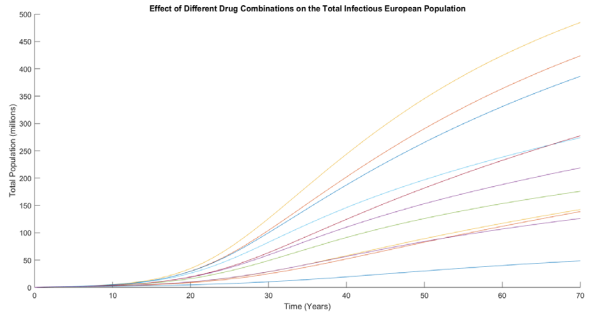


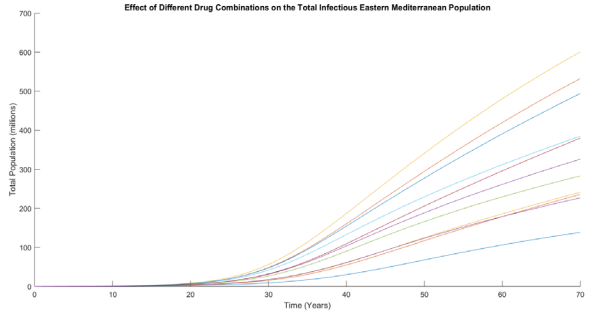








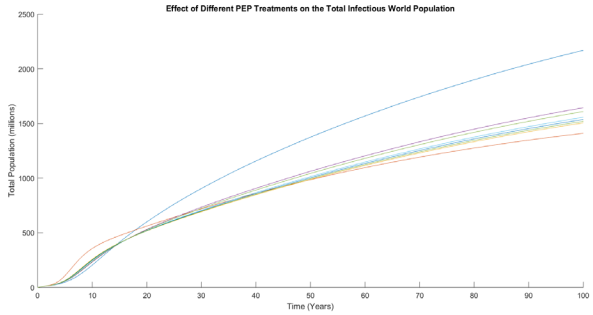


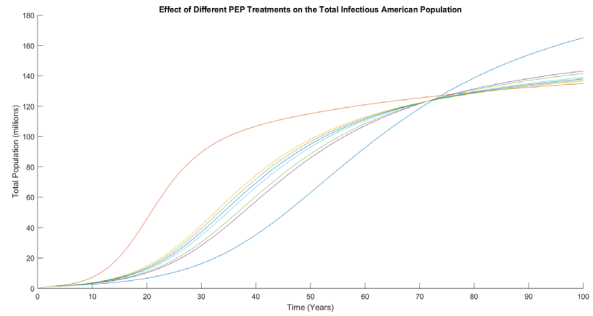


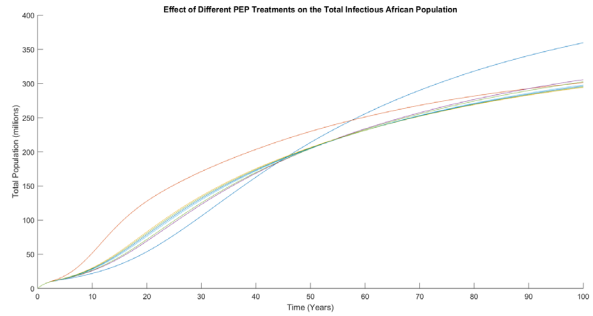
Effect of treatments on the total infectious population listed from highest to lowest population (with viral resistence)

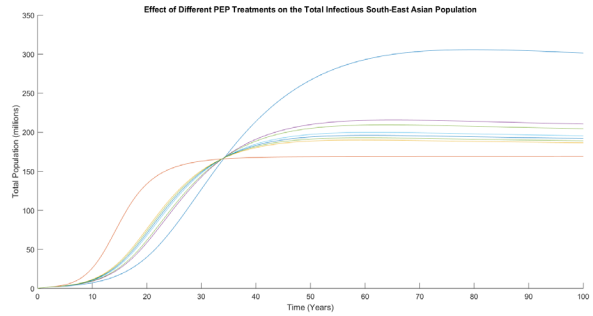
World	Americas	Africa	South-East Asia	Western Pacific	Europe	E. mediterranean
ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF	ATV/r/TDF/TCF
ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF	ATV/c/TDF/TCF
EFV/TCF/TDF	EFV/TCF/TDF	EFV/TCF/TDF	EFV/TCF/TDF	EFV/TCF/TDF	EFV/TCF/TDF	EFV/TCF/TDF
DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF	DOR/3TC/TDF	LPV/r
LPV/r	LPV/r	LPV/r	LPV/r	LPV/r	LPV/r	DOR/3TC/TDF
DRV/c/TDF/TCF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	DRV/c/TDF/TCF	DRV/c/TDF/TCF
DRV/r	DRV/r	DRV/r	DRV/r	DRV/r	DRV/r	DRV/r
EVG/c/TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF	EVG/c/TCF/TDF
EVG/c/TCF/TAF	EVG/c/TCF/TAF	EVG/c/TCF/TAF	EVG/c/TCF/TAF	EVG/c/TCF/TAF	EVG/c/TCF/TAF	EVG/c/TCF/TAF
DRV/c/TCF/TAF	DRV/c/TCF/TAF	DRV/c/TCF/TAF	DRV/c/TCF/TAF	DRV/c/TCF/TAF	DRV/c/TCF/TAF	DRV/c/TCF/TAF
Ideal	Ideal	Ideal	Ideal	Ideal	Ideal	Ideal

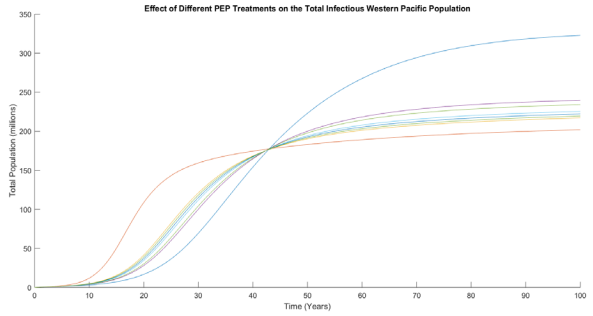
Figure 6 uses the same parameter values as figures 5.
Like figures 4, in figures 6a-6g, we are exploring the effect of the medications on all infectious HIV patients, except we included the resistance factor as seen in figures 5. We excluded the medications whose studies did not include resistance and ones that had no resistance detected. Again we see that the ideal medication has the lowest infectious population. These graphs are even more consistent than figures 4, and given some more time, all regions would have the same list. Looking at the lowest performing medication (ATF/r/TDF/TCF) at 25 years in figure 6a we have around 1.5 billion people infectious, but if we remove the resistance factor as seen in figure 4a, the infectious population is only around 600 million people, giving us a 2.5 times increase in infectious people once resistance was introduced. So, we see that resistance does have a significant effect on the spread of HIV.

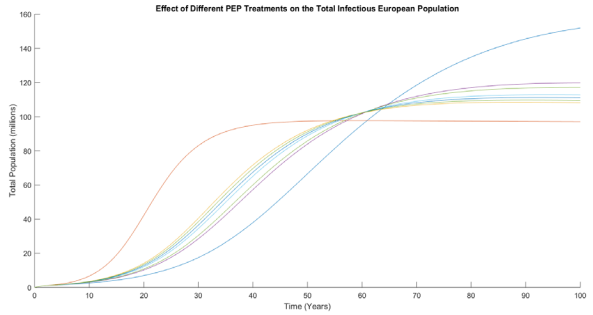


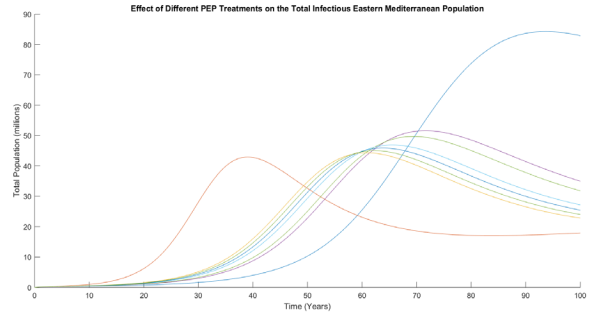












Effect of PEP treatments on the total infectious population listed from highest to lowest population

World	Americas	Africa	South-East Asia	Western Pacific	Europe	E. mediterranean
Ideal	Ideal	Ideal	Ideal	Ideal	Ideal	Ideal
2',3'-Dideoxy-3'-hydroxymethyl cytidine (BEA005)	2',3'-Dideoxy-3'-hydroxymethyl cytidine (BEA005)	2',3'-Dideoxy-3'-hydroxymethyl cytidine (BEA005)	2',3'-Dideoxy-3'-hydroxymethyl cytidine (BEA005)	2',3'-Dideoxy-3'-hydroxymethyl cytidine (BEA005)	2',3'-Dideoxy-3'-hydroxymethyl cytidine (BEA005)	2',3'-Dideoxy-3'-hydroxymethyl cytidine (BEA005)
stavudine and GW420861	stavudine and GW420862	stavudine and GW420863	stavudine and GW420864	stavudine and GW420865	stavudine and GW420866	stavudine and GW420867
tenofovir	tenofovir	azidothymidine	tenofovir	tenofovir	tenofovir	tenofovir
TDF and azidothymidine/3TC/indinavir	TDF and azidothymidine/3TC/indinavir	tenofovir	TDF and azidothymidine/3TC/indinavir	TDF and azidothymidine/3TC/indinavir	TDF and azidothymidine/3TC/indinavir	TDF and azidothymidine/3TC/indinavir
raltegravir and azidothymidine/3TC	raltegravir and azidothymidine/3TC	TDF and azidothymidine/3TC/indinavir	raltegravir and azidothymidine/3TC	raltegravir and azidothymidine/3TC	raltegravir and azidothymidine/3TC	raltegravir and azidothymidine/3TC
TDF/TCF and MIV-150/zinc acetate/carrageenan gel	TDF/TCF and MIV-150/zinc acetate/carrageenan gel	raltegravir and azidothymidine/3TC	TDF/TCF and MIV-150/zinc acetate/carrageenan gel	TDF/TCF and MIV-150/zinc acetate/carrageenan gel	TDF/TCF and MIV-150/zinc acetate/carrageenan gel	TDF/TCF and MIV-150/zinc acetate/carrageenan gel
azidothymidine	azidothymidine	TDF/TCF and MIV-150/zinc acetate/carrageenan gel	azidothymidine	azidothymidine	azidothymidine	azidothymidine

Figures 7a-7g uses the data in tables 2, 3, and 5.
In this final set of graphs, the post exposure prophylaxis set of variables are changed, and we run the treatment circle with the average parameters. Unlike the treatment graphs, the ideal PEP is actually the one with the highest infectious population at about 15 years into the simulation in figure 7a. This is likely due to everyone returning to the susceptible class when receiving the ideal PEP treatment, with no need to go to the treatment group. Therefore, there is a higher chance that more people are ending up in the untreated infectious group due to the way that the model is built. Also, more people would be at risk for being infected again since they are all returned to the susceptible group. That being said, we see a dramatic drop in the infectious population in all PEP treatments. Most PEP treatments result in somewhere between 1.25 and 1.5 billion infectious people in figure 7a, when compared with figure 6a, the infectious populations range from 1.5 billion to 5 billion people. Figures 7a-7g proves that the best way to combat HIV is through post exposure prophylaxis in order to stop the infection before it gets a foothold in the body. By stopping the infection early, then there is no need to take long term treatments that may fail or become too expensive to afford to continue taking regularly, both of which will result in an infection that is no longer being suppressed, leading to a higher viral load resulting in an infectious person that was once viral suppressed [34-40].

Conclusion

Our research focused on the global and regional HIV/AIDS epidemics. In our model we found that HIV was most common in the African region, and least common in the Eastern Mediterranean and European regions. Also, despite the Eastern Mediterranean region having an uncharacteristically high ratio of untreated HIV infections to total infections, it also had the lowest level of AIDS that also seemed to be shrinking, and despite the African region having a high level of successfully treated patients, it continued to have increased and growing levels of HIV/AIDS across the board.

The second part of our research focused on lowering the level of HIV through both treatment and prevention. Treatment wise, there was very little change in the successfully treated population and it continued to grow at a constant rate without regard to the treatments' efficacy. However, adding a viral resistance factor caused a dramatic effect on the successfully treated population as time went on, with some treatment plans performing worse over the course of 70 years compared to 25 years despite the rising levels of HIV and HIV treatment. While looking at the total infectious populations we saw that the medications were more consistent between regions, although they still varied slightly. The initial graphs without introducing the resistance factor showed that HIV would be growing slowly into the future, whereas the introduction of resistance gave the graphs a more curved shape showing that HIV may begin to grow rapidly into the future.

On the other hand, the prevention of HIV through PEP had a huge positive change on the population of people receiving treatment. Where HIV continued to grow in both of the treatment graphs, the PEP graphs showed that HIV would begin to level out and possibly even plateau. Also, the PEP graphs only had a maximum of around 1.5 billion infectious people where treatments with the possibility of viral resistance could reach over 4 billion infectious people in a shorter amount of time that would only continue to grow.

So, on the basis of our model and simulations, if post exposure pro-

phylaxis is not taken advantage of before infection sets in by the majority of people exposed to HIV, then the global epidemic will not only continue, but worsen. The regular treatments are shown to help, but PEP is simply more effective. We did not include pre exposure prophylaxis (PrEP) in this model, however, judging by how effective PEP was, PrEP would also likely have a significant impact on the battle against HIV/AIDS.

Appendix A
Disease-free-equilibrium.

For a system of differential equations, an equilibrium point (also called critical point or equilibrium solution) may be defined as follows:

Definition 2 (equilibrium point). For a system of differential equations, dt/dx Ax, a substitution of zero on the right hand side gives points that corresponds to constant solutions (that do not change with time), and are called equilibrium points [27].

$$\begin{vmatrix} -\mu & 0 & 0 & \upsilon & 0 & 0 & 0 & 0 & 0 \\ 0 & -(\chi+\psi+\mu) & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \chi & -(\eta\xi+\eta\gamma+\mu) & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \psi & 0 & -(\sigma+\upsilon+\mu) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \eta\xi & 0 & -(\omega_1+\mu) & 0 & 0 & 0 & 0 \\ 0 & 0 & \eta\gamma & \sigma & 0 & -(\rho+\alpha+\mu) & 0 & \tau & 0 \\ 0 & 0 & 0 & 0 & 0 & \alpha & -(\mu+\theta) & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \rho & \theta & -(\omega_2+\tau+\mu) & 0 \\ 0 & 0 & 0 & 0 & \omega_1 & 0 & 0 & \omega_2 & -(\delta+\mu) \end{vmatrix}$$

Theorem 1: The system of equations (1) is locally asymptotically stable for the disease free equilibrium when Ro < 1.

Proof: the diagonals of the block matrix of the jacobian of system of equations (1) are

$$A_1 = \begin{vmatrix} -\mu & 0 \\ 0 & -(\chi+\psi+\mu) \end{vmatrix}$$

$$A_2 = \begin{vmatrix} -(\eta\xi+\eta\gamma+\mu) & 0 \\ 0 & -(\sigma+\upsilon+\mu) \end{vmatrix}$$

$$A_3 = \begin{vmatrix} -(\omega_1+\mu) & 0 \\ 0 & -(\rho+\alpha+\mu) \end{vmatrix}$$

$$A_4 = \begin{vmatrix} -(\mu+\theta) & 0 \end{vmatrix}$$

$\Delta A_1(t) = t^2 + (\mu + \chi + \psi + \mu)t + \mu(\chi + \psi + \mu) = (t + \mu)(t + \chi + \psi + \mu)$,

$\Delta A_2(t) = t^2 + (\eta\xi + \eta\gamma + \mu + \sigma + \upsilon + \mu)t + (\eta\xi + \eta\gamma + \mu)(\sigma + \upsilon + \mu) = (t + \eta\xi + \eta\gamma + \mu)(t + \sigma + \upsilon + \mu)$,

$\Delta A_3(t) = t^2 + (\omega_1 + \mu + \rho + \alpha + \mu)t + (\omega_1 + \mu)(\rho + \alpha + \mu) = (t + \omega 1 + \mu)(t + \rho + \alpha + \mu)$,

$\Delta A_4(t) = t^2 + (\mu + \theta + \omega_2 + \tau + \mu)t + (\omega_1 + \mu)(\rho + \alpha + \mu) = (t + \mu + \theta)(t + \omega_2 + \tau + \mu)$,

$$\Delta A_5(t) = (t + \delta + \mu),$$

and for the full jacobian

$\Delta A(t) = \Delta A_1(t) * \Delta A_2(t) * \Delta A_3(t) * \Delta A_4(t) * \Delta A_5(t) = (t + \mu)(t + \chi + \psi + \mu)(t + \eta\xi + \eta\gamma + \mu)$

$(t + \sigma + \upsilon + \mu)(t + \omega_1 + \mu)(t + \rho + \alpha + \mu)(t + \mu + \theta)(t + \omega_2 + \tau + \mu)(t + \delta + \mu)$.

The eigenvalues are:

$\lambda_1 = -\mu$, $\lambda_2 = -(\chi + \psi + \mu)$, $\lambda_3 = -(\eta\xi + \eta\gamma + \mu)$, $\lambda_4 = -(\sigma + \upsilon + \mu)$, $\lambda_5 = -(\omega_1 + \mu)$, $\lambda 6 = -(\rho + \alpha + \mu)$, $\lambda 7 = -(\mu + \theta)$, $\lambda 8 = -(\omega_2 + \tau + \mu)$, and $\lambda_9 = -(\delta + \mu)$.

Hence all eigenvalues λ_1 , λ_2 , λ_3 , λ_4 , λ_5 , λ_6 , λ_7 , λ_8 , and λ_9 are negative when $R_o < 1$. This proves that our system is locally asymptotically stable when Ro < 1 .

Global Stability of Diseases-free Equilibrium

We show the global stability of the model using the method given by Kamgang and Sallet [28]. In this method, to show global stability, the model has to satisfy the five hypotheses, which has been summarized briefly in the appendix of Kamgang and Sallet's paper [28].

Theorem 2 states that the system (1) is globally stable for disease-free equilibrium when $R_0 \leq 1$.

Proof: We have shown above that $D = \{(S, E, L, P, IN, IT, C, F, A) \varepsilon R^9 + : N_H \leq B_H/\mu_H\}$ is bounded and positively invariant in R^9_+ , where the hypothesis H_1 and H_2 are satisfied.

$x_1 = (S, P, C)$
$x_2 = (E, L, I_N , I_T , F, A)$
$x = (x_1, x_2)$

The matrix $A_2(x)$ is given by

$$\begin{vmatrix} -(\chi+\psi+\mu) & 0 & \beta_{IN}S & \beta_{IT}S & \beta_F S & \beta_A S \\ \chi & -(\eta\xi+\eta\gamma+\mu) & 0 & 0 & 0 & 0 \\ 0 & \eta\xi & -(\omega_1+\mu) & 0 & 0 & 0 \\ 0 & \eta\gamma & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho & \tau & 0 \\ 0 & 0 & 0 & 0 & -(\omega_2+\tau+\mu) & 0 \\ 0 & 0 & \omega_1 & 0 & \omega_2 & -(\delta+\mu) \end{vmatrix}$$

As requested by hypothesis H3 , for any x ϵR^9 , the matrix is irreducible.

Now for hypothesis H_4 , there is a maximum and uniquely realized in R^9_+ if at DFE. The

+ S = 1

maximum matrix J_2 , the block of Jacobian at DFE, corresponding to the matrix $A_2(x)$ is given by

$$J_2 = \begin{bmatrix} -(\chi+\psi+\mu) & 0 & \beta_{IN}S & \beta_{IT}S & \beta_F S & \beta_A S \\ \chi & -(\eta\xi+\eta\gamma+\mu) & 0 & 0 & 0 & 0 \\ 0 & \eta\xi & -(\omega_1+\mu) & 0 & 0 & 0 \\ 0 & \eta\gamma & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho & \tau & 0 \\ 0 & 0 & 0 & 0 & -(\omega_2+\tau+\mu) & 0 \\ 0 & 0 & \omega_1 & 0 & \omega_2 & -(\delta+\mu) \end{bmatrix}$$

We are in the situation of corollary 4.4, where the maximum is attained at the DFE [28].

Moreover, in the case of BVDV the maximum is uniquely attained. The hypothesis H_5 requires that $\alpha(J_2) \le 0$, writing J_2 as a block matrix.

$$J_2 = \begin{vmatrix} U & V \\ W & Y \end{vmatrix}$$

constituted of block 3x3 matrices. Since U is already a Metzler stable matrix, the condition
$\alpha(J2) \le 0$ is equivalent to the condition $\alpha(Y - WU^{-1}V) \le 0$, and this last condition is equivalent to T_o condition.

$$U^{-1} = \begin{bmatrix} \frac{G_3G_4}{G_1} & \frac{\beta_{IT}\eta\xi}{G_1} & \frac{\beta_{IN}G_4}{G_1} \\ \frac{\chi G_3}{G_1} & \frac{G_2G_3}{G_1} & \frac{\beta_{IN}\chi}{G_1} \\ \frac{\chi\eta\xi}{G_1} & \frac{\eta\xi G_2}{G_1} & \frac{G_2G_4}{G_1} \end{bmatrix}$$

Where $G_2 = \chi + \psi + \mu$

$G_3 = \omega_1 + \mu$

$G_4 = \eta\xi + \eta\gamma + \mu$

And $G_1 = [\beta_{IN}\chi\eta\xi - (\omega_1+\mu)(\chi+\psi+\mu)(\eta\xi+\eta\gamma+\mu)]$ *or* $G_1 = [\beta_{IN}\chi\eta\xi - G_2G_3G_4]$

$$V = \begin{bmatrix} \beta_{IT} & \beta_F & \beta_A \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$W = \begin{bmatrix} 0 & \eta\gamma & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \omega_1 \end{bmatrix}$$

$$Y = \begin{bmatrix} 0 & \tau & 0 \\ \rho & -(\omega_2+\tau+\mu) & 0 \\ 0 & \omega_2 & -(\delta+\mu) \end{bmatrix}$$

$$WU^{-1}V = \begin{bmatrix} 0 & \eta\gamma & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \omega_1 \end{bmatrix} * \begin{bmatrix} \frac{G_3G_4}{G_1} & \frac{\beta_{IT}\eta\xi}{G_1} & \frac{\beta_{IN}G_4}{G_1} \\ \frac{\chi G_3}{G_1} & \frac{G_2G_3}{G_1} & \frac{\beta_{IN}\chi}{G_1} \\ \frac{\chi\eta\xi}{G_1} & \frac{\eta\xi G_2}{G_1} & \frac{G_2G_4}{G_1} \end{bmatrix} * \begin{bmatrix} \beta_{IT} & \beta_F & \beta_A \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$= \begin{bmatrix} \frac{\beta_{IT}\eta\gamma\chi\eta\xi}{G_1} & \frac{\beta_F\eta\gamma G_3G_4}{G_1} & \frac{\beta_A\beta_{IN}\chi\eta\gamma}{G_1} \\ 0 & 0 & 0 \\ \frac{\beta_{IT}\omega_1\chi\eta\xi}{G_1} & \frac{\beta_F\omega_1\eta\xi G_4}{G_1} & \frac{\beta_A\omega_1 G_2G_3}{G_1} \end{bmatrix}$$

$$V - WU^{-1}V = \begin{bmatrix} \beta_{IT} - \frac{\beta_{IT}\eta\gamma\chi\eta\xi}{G_1} & \tau - \frac{\beta_F\eta\gamma G_3G_4}{G_1} & -\frac{\beta_A\beta_{IN}\chi\eta\gamma}{G_1} \\ \rho & -(\omega_2+\tau+\mu) & 0 \\ -\frac{\beta_{IT}\omega_1\chi\eta\xi}{G_1} & \omega_2 - \frac{\beta_F\omega_1\eta\xi G_4}{G_1} & -(\delta+\mu) - \frac{\beta_A\omega_1 G_2G_3}{G_1} \end{bmatrix}$$

$$\alpha(Y - WU^{-1}V) \le 0$$

$$\frac{-\beta_{IT}\chi\eta\gamma G_3}{G_1}(\omega_2+\tau+\mu)\left[\frac{G_1(\delta+\mu)+\beta_A\chi\eta\xi\omega_1}{G_1}\right] - \rho\left[\frac{-[\tau G_1-\beta_F G_2G_3\eta\gamma]}{G_1}\frac{[G_1(\delta+\mu)+\beta_A\chi\eta\xi\omega_1]}{G_1} + \frac{\beta_A\beta_{IN}\chi\eta\gamma}{G_1} + \left[\frac{\omega_2G_1-\beta_F\chi\eta\xi\omega_1}{G_1}\right]\right] - \frac{\beta_{IT}\chi\eta\xi\omega_1}{G_1}\left[\frac{-\beta_A\beta_{IN}\chi\eta\gamma(\omega_2+\tau+\mu)}{G_1}\right] \le 0$$

$$\beta_{IT}\beta_A\beta_{IN}\chi\eta\xi\gamma\omega_1(\omega_1+\tau+\mu) \le \left\{\frac{[G_1(\delta+\mu)+\beta_A\chi\eta\xi\omega_1][\beta_{IT}\gamma G_3(\omega_2+\tau+\mu)-\rho(\tau G_1-\beta_F\eta\gamma G_2G_3)]+\rho\beta_A\beta_{IN}\eta\gamma\chi(\omega_2G_1-\beta_F\eta\gamma\xi\omega_1)}{\eta\chi}\right\}$$

$$\frac{\beta_{IT}\beta_A\beta_{IN}\chi^2\eta^2\xi\gamma\omega_1(\omega_1+\tau+\mu)}{\{[G_1(\delta+\mu)+\beta_A\chi\eta\xi\omega_1][\beta_{IT}\gamma G_3(\omega_2+\tau+\mu)-\rho(\tau G_1-\beta_F\eta\gamma G_2G_3)]+\rho\beta_A\beta_{IN}\eta\gamma\chi(\omega_2G_1-\beta_F\eta\gamma\xi\omega_1)\}} \le 1$$

So, $T_o = \dfrac{\beta_{IT}\beta_A\beta_{IN}\chi^2\eta^2\xi\gamma\omega_1(\omega_1+\tau+\mu)}{\{[G_1(\delta+\mu)+\beta_A\chi\eta\xi\omega_1][\beta_{IT}\gamma G_3(\omega_2+\tau+\mu)-\rho(\tau G_1-\beta_F\eta\gamma G_2G_3)]+\rho\beta_A\beta_{IN}\eta\gamma\chi(\omega_2G_1-\beta_F\eta\gamma\xi\omega_1)\}} \le 1$.

We have computed T_o and we have seen that the hypothesis H_1, H_2, H_3, H_4, and H_5 are satisfied. Then we have proven that the DFE for global asymptotic stability if $T_o \leq 1$ and it is cleary inspection of Ro computed in section 2.4 (Basic Reproduction Number) is equivalued to R_o and thus $T_o \leq 1$, $R_o \leq 1$. This proves that the model is globally asymptotically stable for disease-free-equilibrium when $R_o \leq 1$. [Note: The basic reproduction number can also be computed by $WU^{-1}VY^{-1}$].

Endemic Equilibrium.

Besides the disease-free equilibrium point, we shall show that the formulated model (1) has an endemic equilibrium point. The endemic equilibrium point is a positive equilibrium solution where the disease persists in the population. Solving the system of equations (1) at endemic equilibrium resulted in

$Q^* = (S^*, E^*, L^*, I_N^*, I_T^*, F^*, A^*)$, $S^* > 0$, $E^* > 0$, $L^* > 0$, $I_N > 0$, $I_T > 0$, $F^* > 0$, $A^* > 0$

Theorem 3: The unique boundary equilibrium of the model equation (1) is globally asymptotically stable in (1) whenever Ro > 1.

Proof: Considering the model equation (1), and $R_o > 1$, so that the associated unique endemic equilibrium Q^* of the model exists. We consider the following non-linear Lyapunov function of Gohn Volterra type:

$$Z_i = \sum_{i=1}^{n} c_i(x_i - x_i^* - x_i^* ln\frac{x_i}{x_i^*})$$

Where x is the variable and c_i are constants. This criterion has been used in establishing the stability of many epidemiological models and is also present in [29-31].

Let $S > S^*$, $E > E^*$, $L > L^*$, $I_N > I_N^*$, $I_T > I_T^*$, $F > F^*$, and $A > A^*$

$$Z_1 = S - S^* - S^* ln\frac{S}{S^*}$$

$$Z_1' = -(\frac{S^*-S}{S})[B_H N_H + \upsilon P - (\beta_{IN} SI_N + \beta_F SF + \beta_A SA + \beta_{IT} SI_T) - \mu S$$

$$B_H N_H = (\beta_{IN} SI_N^* + \beta_F SF^* + \beta_A SA^* + \beta_{IT} SI_T^*) + \mu S^* - \upsilon P$$

$$Z_1' = -(\frac{S^*-S}{S})[(\beta_{IN} SI_N^* + \beta_F SF^* + \beta_A SA^* + \beta_{IT} SI_T^*) + \mu S^* - \upsilon P + \upsilon P - (\beta_{IN} SI_N + \beta_F SF + \beta_A SA + \beta_{IT} SI_T) - \mu S$$

Let $\beta_{IN} I_N^* + \beta_F F^* + \beta_A A^* + \beta_{IT} I_T^* = d_1$ and $\beta_{IN} I_N + \beta_F F + \beta_A A + \beta_{IT} I_T = d_2$

$$Z_1' = -(\frac{S^*-S}{S})[d_1 S^* + \mu(S^* - S) - d_2 S]$$

$$Z_1' = -(\frac{S^*-S}{S})[(d_1 S^* - d_2 S) + \mu(S^* - S)] \text{ and } d_1 S^* - d_2 S \leq 0, \text{ as } S > S^* \quad S^* - S \leq 0$$

So, $Z_1' < 0$

$$Z_2 = E - E^* - E^* ln\frac{E}{E^*}$$

$$Z_2' = -(\frac{E^*-E}{E})[\beta_{IN} SI_N + \beta_F SF + \beta_A SA + \beta_{IT} SI_T - (\chi + \psi + \mu)E]$$

Where, $(\beta_{IN} I_N^* + \beta_F F^* + \beta_A A^* + \beta_{IT} I_T^*)\frac{S^*}{E^*} = (\chi + \psi + \mu)$

$$Z_2' = -(E^* - E)[\frac{(\beta_{IN} I_N + \beta_F F + \beta_A A + \beta_{IT} I_T)S}{E} - (\chi + \psi + \mu)]$$

$$Z_2' \leq -(E^* - E)[\frac{(\beta_{IN} I_N^* + \beta_F F^* + \beta_A A^* + \beta_{IT} I_T^*)S^*}{E^*} - (\chi + \psi + \mu)]$$

$$Z_2' \leq -(E^* - E)[(\chi + \psi + \mu) - (\chi + \psi + \mu)]$$

$$Z_2' \leq 0$$

$$Z_3 = L - L^* - L^* ln\frac{L}{L^*}$$

$$Z_3' = -(\frac{L^*-L}{L})[\chi E - (\eta\xi + \eta\gamma + \mu)]$$

$$Z_3' \leq -(L^* - L)[\frac{\chi E^*}{L^*} - (\eta\xi + \eta\gamma + \mu)]; \qquad \chi E^* - (\eta\xi + \eta\gamma + \mu)L^* = 0$$

$$Z_3' \leq -(L^* - L)[(\eta\xi + \eta\gamma + \mu) - (\eta\xi + \eta\gamma + \mu)]$$

$$Z_3' \leq 0$$

$$Z_4 = I_N - I_N^* - I_N^* ln\frac{I_N}{I_N^*}$$

$$Z_4' = -(\frac{I_N^* - I_N}{I_N})[\eta\xi L - (\omega_1 + \mu)I_N]$$

$$Z_4' \leq -(I_N^* - I_N)[\frac{\eta\xi L^*}{I_N^*} - (\omega_1 + \mu)]; \quad \eta\xi L^* - (\omega_1 + \mu)I_N^* = 0$$

$$Z_4' \leq -(I_N^* - I_N)[\omega_1 + \mu - (\omega_1 + \mu)]$$

$$Z_4' \leq 0$$

$$Z_5 = I_T - I_T^* - I_T^* ln\frac{I_T}{I_T^*}$$

$$Z_5' = -(\frac{I_T^* - I_T}{I_T})[\eta\gamma L + \sigma P + \tau F - (\rho + \alpha + \mu)I_T]$$

$$Z_5' \leq -(I_T^* - I_T)[\frac{\eta\gamma L^* + \sigma P^* + \tau F^*}{I_T^*} - (\rho + \alpha + \mu)]; \quad \frac{\eta\gamma L^* + \sigma P^* + \tau F^*}{I_T^*} = \rho + \alpha + \mu$$

$$Z_5' \leq -(I_T^* - I_T)[\rho + \alpha + \mu - (\rho + \alpha + \mu)]$$

$$Z_5' \leq 0$$

$$Z_6 = F - F^* - F^* ln\frac{F}{F^*}$$

$$Z_6' = -(\frac{F^* - F}{F})[\rho I_T + \theta C - (\omega_2 + \tau + \mu)F]$$

$$Z_6' = -(F^* - F)[\frac{\rho I_T + \theta C}{F} - (\omega_2 + \tau + \mu)]$$

$$Z_6' \leq -(F^* - F)[\frac{\rho I_T^* + \theta C^*}{F^*} - (\omega_2 + \tau + \mu)]; \quad \frac{\rho I_T^* + \theta C^*}{F^*} = \omega_2 + \tau + \mu$$

$$Z_6' \leq -(F^* - F)[\omega_2 + \tau + \mu - (\omega_2 + \tau + \mu)]$$

$$Z_6' \leq 0$$

$$Z_7 = A - A - A^* ln\frac{A}{A^*}$$

$$Z_7' = -(\frac{A^* - A}{A})[\omega_1 I_T + \omega_2 F - (\delta + \mu)A]$$

$$Z_7' = -(A^* - A)[\frac{\omega_1 I_T + \omega_2 F}{A} - (\delta + \mu)]$$

$$Z_7' \leq -(A^* - A)[\frac{\omega_1 I_T^* + \omega_2 F^*}{A^*} - (\delta + \mu)]; \quad \omega_1 I_T^* + \omega_2 F^* - (\delta + \mu)A^* = 0$$

$$Z_7' \leq -(A^* - A)[\delta + \mu - (\delta + \mu)]$$

$$Z_7' \leq 0$$

Therefore Z defines

$$Z = \sum_{i=1}^{7} Z_i = \sum_{i=1}^{7} c_i(x_i - x_i^* - x_i^* ln\frac{x_i}{x_i^*})$$

Thus $Z' = \sum_{i=1}^{7} Z_1' + Z_2' + Z_3' + Z_4' + Z_5' + Z_6' + Z_7'$

So, $Z' = \sum_{i=1}^{7} Z_i'$ and $Z' \leq 0$ for $R_0 > 1$.

is a lyapunov function for the system of equations (1). Arbitrary constants ci can be chosen from R_+ and any linear combination of Z would be a lyapunov function for the system in D and it follows by lesalle's Invariance Principle [31]. That every solution to the equations of the model (1) approaches the associated unique endemic equilibrium *(Q*)*, of the model as t → ∞ for $R_0 > 1$.

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