

UNIVERSITY OF ZIMBABWE

**MODELLING THE EFFECTS OF
BEHAVIOURAL CHANGE ON THE
TRANSMISSION DYNAMICS OF HERPES
SIMPLEX VIRUS TYPE 2 (HSV-2)**

ADQUATE MHLANGA

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OF HERPES SIMPLEX VIRUS TYPE 2 (HSV-2)**

by

ADQUATE MHLANGA

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requirements for the degree of
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Declaration

I declare that this thesis is my own, unaided work. It is being submitted for the degree of Doctor of Philosophy in the University of Zimbabwe. It has not been submitted before for any degree or examination in any other University.

Dedication

To my beloved parents, John and Alice Mhlanga-Nyambe, for their constant support and unconditional love,

& To **Samara Thandiwe Mhlanga.**

In loving memory of my supervisor, Professor Claver Pedzesai Bhunu.

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Abstract

Herpes simplex virus type 2 (HSV-2) is the most prevalent sexually transmitted disease worldwide, despite the availability of highly effective anti-viral treatment. It is of great concern that as other sexually transmitted infections (STIs) are on the decrease, HSV-2 is on the rise in other parts of the world. HSV-2 is very expensive to control and it is one of the major contributors to the prevalence of HIV. Numerous statistical and mathematical models for investigating the transmission dynamics of HSV-2 have been proposed. This study aims to extend all the experience acquired from these studies in order to assess the effects of behavioural change on the transmission dynamics of HSV-2. Behavioural changes can be implemented to complement the already existing intervention strategies. Deterministic models in the form of non linear differential equations are developed and analysed to study the effects of various behavioural changes on the transmission dynamics of HSV-2. Prior studies have shown that adolescents are the most vulnerable group to HSV-2 due to their risky sexual behaviours. The models developed capture the effects of some risky sexual behaviours among the adolescents and the general population. Two deterministic models for investigating the dynamics of HSV-2 among adolescents have been proposed. The models focus on (i) the spread of HSV-2 within a community with substance abusing adolescents (ii) assess the impact of sexting and peer influence on the spread of HSV-2. Further, two other deterministic models for investigating the dynamics of HSV-2 among the general population have been proposed. The models focus on, (iii) investigating the impact of poor treatment adherence on the prevalence of HSV-2 and (iv) explore the association between gender and poor treatment adherence. In all the constructed models, the effects of prevention and intervention strategies on controlling the spread of HSV-2 have been comprehensively investigated. Analysis of the models suggest that various behavioural changes have an effect on reducing the prevalence and transmission of HSV-2. Results from the study suggest that educational campaigns and condom use are effective on reducing HSV-2 among substance abusing adolescents. The

study also realised that, awareness campaigns and filtering are effective in reducing the prevalence of HSV-2 among the sexting adolescents. Among the general population, monitoring and counselling all the HSV-2 patients under treatment would be vital in reducing HSV-2 prevalence. We further noted that, for us to keep the levels of HSV-2 cases as low as possible it is vital to keep the level of female adherence as high as possible compared to the one for males. Directions for further research studies are also suggested in this thesis.

Contents

1	Introduction	1
1.1.	Background	1
1.2.	HSV-2 infectivity and transmission	3
1.3.	HSV-2 vaccination	5
1.4.	HSV-2 treatment	6
1.5.	HSV-2 and behaviour	8
1.6.	The role of mathematical models in epidemiology	10
1.7.	Review of mathematical models for HSV-2	13
1.8.	Mathematical Preliminaries	17
1.8.1.	Introduction	17
1.8.2.	Equilibria and Linearisation	17
1.8.3.	Stability of Equilibria	18
1.8.4.	Lyapunov stability	19
1.8.5.	Invariance Principle	21
1.8.6.	Perron-Frobenius Theorem	22
1.8.7.	Comparison Theorem	23
1.8.8.	Persistence	24
1.8.9.	Next Generation Operator Matrix and Backward bifurcation .	25
1.8.10.	Pontryagin's Maximum Principle	28
1.9.	Motivation and thesis structure	31
1.10.	Publications	34
2	HSV-2 and substance abuse amongst adolescents: Insights through mathematical modelling	35

2.1. Introduction	35
2.2. Model formulation	37
2.2.1. Positivity and boundedness of solutions	39
2.3. Model Analysis	41
2.3.1. The reproductive number	41
2.3.2. Global stability of the disease free equilibrium	44
2.3.3. Endemic equilibrium and stability analysis	46
2.4. Numerical results	64
2.5. Optimal condom use and educational campaigns	74
2.5.1. Existence of an optimal control	76
2.5.2. Characterisation	77
2.5.3. Numerical Simulations	79
2.6. Concluding remarks	82
3 A computational study of HSV-2 with poor treatment adherence	84
3.1. Introduction	84
3.2. Model Framework	85
3.3. Model Analysis and Results	90
3.3.1. Positivity and boundedness of solutions	90
3.3.2. Equilibrium points and their stability analysis	91
3.4. Optimal control problem	111
3.4.1. Numerical Simulations	114
3.5. Concluding remarks	119
4 Modelling the effects of sexting on the transmission dynamics of HSV-2 amongst adolescents	121
4.1. Introduction	121
4.2. Model formulation	123
4.3. Analytic Results	126
4.3.1. Basic properties of the model	126

4.3.2. Disease-free equilibrium and its stability analysis	129
4.3.3. Persistence	134
4.3.4. Endemic equilibrium	136
4.4. Numerical results	140
4.5. Optimal control problem	145
4.5.1. Existence of the optimal control	146
4.5.2. The characterisation of the optimal control	148
4.5.3. Numerical simulations	151
4.6. Concluding remarks	154
5 Exploring the association between gender and HSV-2 treatment ad-	
herence	156
5.1. Introduction	156
5.2. Model Formulation	157
5.3. Model Analysis	160
5.3.1. Basic properties of the model	160
5.3.2. Disease-free equilibrium and its stability analysis	161
5.3.3. Endemic equilibrium and its stability analysis	165
5.4. Numerical Simulations	173
5.5. Concluding remarks	181
6 Conclusions and future directions	182
6.1. Introduction	182
6.2. Summary and concluding remarks	182
6.3. Future research directions	184

List of Figures

2.1	Structure of the model.	39
2.2	Effects of varying the effective contact rate (β) on the reproduction numbers. $\mathbf{R}$ represents the Reproduction number.	67
2.3	The relationship between the reproduction number (R_{na}), rate of becoming a substance abuser (ρ), and rate of quitting substance abuse (ϕ).	68
2.4	Numerical results of model system (2.3) showing the effect in the change of substance abusing habits. Parameter values used are in Table 2.1 with ϕ and ρ , varying from 0.0 to 1.0.	69
2.5	Partial rank correlation coefficients showing the effect of parameter variations on R_{na} using ranges in Table 2.1. Parameters with positive PRCCs will increase R_{na} when they are increased, whereas parameters with negative PRCCs will decrease R_{na} when they are increased.	70
2.6	Monte Carlo Simulations of 1000 sample values for three illustrative parameters (ρ , θ , and β) chosen via Latin Hypercube Sampling.	72
2.7	Simulations of model system (2.3) showing the effects of an increase on condom use efficacy on the HSV-2 cases ($I_a + I_n$) over a period of 60 years. The rest of the parameters are fixed on their baseline values, with Figure 2.7(a) having $\rho > \phi$ and Figure 2.7(b) having $\phi > \rho$	73
2.8	Simulations of model system (2.3) showing the effects of increasing the proportion of recruited substance abusers (π_1), varying from 0.0 to 1.0 with a step size of 0.25, for the 2 cases where (a) $\rho > \phi$ and (b) $\phi > \rho$	74

2.9	Time series plots showing the effects of optimal control on the susceptible non-substance abusing adolescents S_n , susceptible substance abusing adolescents S_a , infectious non-substance abusing adolescents I_n and the infectious substance abusing I_a , over a period of 20 years	80
2.10	The optimal control graphs for the two controls, namely, condom use (u_1) and educational campaigns (u_2).	82
3.1	Structure of the model.	87
3.2	Effect of varying the effective contact rate β on the reproduction numbers. Where R represents the reproduction number(s).	106
3.3	Simulations of model system (3.2) showing the contour plots of R_{ac} as a function of the effective contact rate for HSV-2 infection (β), and the proportion of individuals who are adhering to the HSV-2 anti-viral treatment (θ).	109
3.4	Simulations of model system (3.2) showing the effects of varying the treatment rate of acute HSV-2 and the proportion of individuals who are adhering to the HSV-2 anti-viral treatment (θ).	110
3.5	Simulations of model system (3.2) showing the contour plots of R_{ac} as a function of the modification parameter (η) and the proportion of individuals who are adhering to the HSV-2 anti-viral treatment (θ).	111
3.6	Graphs of the numerical solutions of the optimality system, showing propagation of, (a) susceptibles S , (b) infected with acute HSV-2 and also under anti-viral treatment A_a , (c) infected with latent HSV-2 after undergoing successful anti-viral treatment L_a , (d) infected with acute HSV-2 and not under anti-viral treatment after quitting before completion A_u , (e) and the infected with latent HSV-2 after undergoing natural healing L_u , over a period of 50 months.	116
3.7	Graphs of the numerical solutions to the behaviour of the control constrain, (a) with the weight constant $z = 0.4$, (b) with the weight constant z being varied.	118

3.8	Graph of the numerical solutions to the behaviour of the control constrain, with the weight and cost factor ϑ being varied.	119
4.1	Model flow diagram.	125
4.2	Effects of varying the effective contact rate for HSV-2 infection (β_h), on the reproduction numbers. $\mathbf{R}$ represents the reproduction number	131
4.3	Figure 4.3 shows the influence of β_p on cumulative HSV-2 cases over a pe- riod of 60 years, with β_p varying from 0 to 1 with a step size of 0.2 and the rest of the parameters being fixed on their baseline values from Table 4.2. The direction of the arrow shows an increase of β_p	141
4.4	Figure 4.4 shows the effects of the effective contact rate for HSV-2 infection β_h , and the sexting quitting rate ϕ , on $\mathcal{R}_{HP}$	142
4.5	Partial rank correlation coefficients showing the effects of parameter varia- tion on $\mathcal{R}_{HP}$ using ranges from Table 4.2. Parameters with positive PRCCs will increase $\mathcal{R}_{HP}$ when they are increased, whereas parameters with neg- ative PRCCs will decrease $\mathcal{R}_{HP}$ when they are increased.	143
4.6	Latin Hypercube Sampling for varying of (a) peer influence effective contact rate and (b) the rate of quitting sexting.	144
4.7	Dynamics of model system (4.41) showing the impact of filtering and aware- ness campaigns on HSV-2 dynamics and sexting.	152
4.8	Control profiles for control functions (a) $u_1(t)$ and (b) $u_2(t)$	154
5.1	Structure of the model.	159
5.2	Figure 3(a) shows the effects of varying the male and female treatment adherence on the reproduction number R_{mf}	178
5.3	Figure 5.3(a) shows the effects of varying the proportion of males adherence (θ_m) and 5.3(b) shows the effects of varying the proportion of female adher- ence (θ_f) both on the female population, while all other parameters are at their baseline values.	179

5.4	Figure 5.4(a) shows the effects of varying the proportion of males adherence (θ_m) and 5.4(b) shows the effects of varying the proportion of female adherence (θ_f) both on the female population, while all other parameters are at their baseline values.	180
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List of Tables

2.1	Model parameters and their interpretations (B^* represents the Base-line values.)	66
2.2	The linear dependence of the reproduction number R_j on the constant rate β , for $j = 0, a, c, na$	67
3.1	Model parameters and their baseline values. The time unit is in months	89
3.2	The linear dependence of the reproduction number R_j on the constant rate β , for $j = 0, a, ac$	106
3.3	Sensitivity indices of model parameters to R_{ac}	107
4.1	The linear dependence of the reproduction number R_i on the constant rate β_h , for $i = 0P, H0, HP$	132
4.2	Model parameters and their interpretations (B^* represents the Base-line Values).	141
5.1	Model parameters and their baseline values. The time unit is in months	175
5.2	Sensitivity indices of model parameters to R_{mf}	177

Glossary

Abbreviation	Meaning
CDC	Centres for Disease Control and Prevention
DFE	Disease-free equilibrium
DNA	Deoxyribonucleic acid
GDP	Gross domestic product
FSW	Female sex worker
GAS	Globally-asymptotically stable
HIV	Human immunodeficiency virus
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simplex virus type 2
LAS	Locally-asymptotically stable
ODE	Ordinary differential equation
PRCC	Partial rank correlation coefficient
SAMHSA	Substance Abuse and Mental Health Services Administration
TEDS	Treatment Episode Data Set

Chapter 1

Introduction

1.1. Background

Herpes simplex virus-2 (HSV-2) is a highly prevalent sexually transmitted infection (STI) that causes severe public health burden globally, with the highest prevalence in the Sub-Saharan Africa and some Asian countries (Weiss, 2004). Humans are the only natural hosts of the HSV-2 (Dordevic, 2006). There are 1.5 million HSV-2 infections among 15-19 year old females in Sub-Saharan Africa every year (Looker et al., 2008) and an estimated 1.6 million new infections annually in the United States of America (USA) (Glass et al., 2005). In 2003, for instance, up to 536 million people aged 15-49 years were living with HSV-2 globally and 23.6 million new infections were recorded in that year (Looker et al., 2008). Although HSV-2 is the leading cause of genital ulcer disease worldwide (Mertz et al., 1998; Paz-Bailey et al., 2005), most people are not aware of the infection (Xu et al., 2002). In contrast to other STIs such as chlamydia, gonorrhea, syphilis and trichomoniasis, infection with HSV-2 is lifelong, and once established, there is currently no treatment to eliminate it (Geretti et al., 2006; Gupta et al., 2007). HSV-2 is currently the STI most widely advocated for use in evaluating the impact of interventions to reduce

sexual risk behaviours, and for use as a marker to validate self-reports of sexual behaviour (Owusu-Edusei Jr. et al, 2013). During the period of adolescence, many individuals begin to engage in risky sexual behaviours, hence making them the age group at greatest risk for nearly all STIs, including HSV-2 (Hill and Biro, 2009).

In the United States of America (USA), annual health costs for STIs has reached US\$ 17 Billion, with HSV-2 chewing up US\$ 541 million, making it the third most costly STI after HIV-1 and human papillomavirus (HPV) (CDC, 1999). Nearly 1500 neonatal HSV-2 infections are noted every year in the USA at an estimated cost of up to US\$ 225 000 per disseminated infection with central nervous system involvement (Kimberlin, 2001; Gardella, 2008). Thus, it represents a worldwide public health problem with significant attendant economic burden (Cunningham and Mikloska, 2001). Vaccines to prevent disease or reduce recurrent disease and viral shedding in those already infected would be a significant achievement in helping control HSV-2 (Veselenak, 2012). HIV-1 epidemic is known to be fueled by HSV-2 among other factors, consequently leading to an increased focus on HSV-2 transmission and prevention (Wald, 2004; Reynolds and Quinn, 2005).

Herpesviridae is a large family of deoxyribonucleic acid (DNA) viruses that cause diseases in animals, including humans, and its members are known as herpesviruses (Ryan and Ray, 2004; Mettenleiter, 2008). There are over 130 herpesviruses, of which 8 are known to infect humans (Brown, 2011). These are; Herpes simplex virus-1 (HSV-1), Herpes simplex virus-2 (HSV-2), Varicella Zoster virus (VSV), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Herpes lymphotropic virus (HHV-6), Human herpes virus-7 (HHV-7) and Kaposi sarcoma associated herpes virus (KSHV) (Carter and Saunders, 2012). There are two types of herpes simplex virus (HSV), HSV type 1 (HSV-1) and type 2 (HSV-2). HSV-1 in many cases causes oral infection while HSV-2 commonly causes genital infections. HSV-2 is a double-stranded DNA virus, and it infects almost any human cell (Ryan and Ray, 2004). The virus binds onto the surface of the host cell using its glycoprotein (Patrick et al., 2005). After contact with abraded skin or mucosal skin surfaces, the virus repli-

cates and initiates infection in the epidermal cells of the target area. Following this initial infection, the virus travels in a retrograde fashion within axons of sensory nerves to the dorsal nerve root ganglion where it continues to replicate to establish lifelong latency (Mark, 2010). Although some HSV-2 infected patients may not experience symptomatic recurrences, virtually all will have repeated episodes of asymptomatic viral shedding from their genital secretions (Parks, 2013).

1.2. HSV-2 infectivity and transmission

HSV-2 is a highly contagious infection and transmission occurs primarily through genital to genital skin contact with an infected partner (Parks, 2013). HSV-2 can be contracted through male to male, male to female and female to female intercourse or outercourse (Blower et al. 1998; Konda et al., 2005; Raddad et al., 2008; Bastien et al., 2012). Despite HSV-2 infections being more of skin to skin contacts, they can also result from exposure to infected saliva, semen, vaginal secretions or fluid from active herpetic lesions (Parks, 2013). HSV-2 transmission is believed to be negligible through exposure to fomites since drying up and room temperature quickly inactivate the virus, meaning HSV-2 uncommonly causes infection by non-sexual means, although possible (Chen et al., 2004; Pickering et al., 2005; Nahmias et al., 1990; Stanberry et al., 2000; Wald et al., 2002). In some rare instances, HSV-2 may be transmitted vertically during birth. Vertical transmission of HSV-2 in pregnancy either in utero or intrapartum may be life threatening to babies who acquire the virus (Sacks et al., 2004). Transmission of infections from mother to baby usually occurs during vaginal delivery (85 % of transmissions) and is independent of the prevalence of genital viral shedding at the time of delivery (Smith et al., 2009). Without treatment, 80% of the infants with disseminated disease die, and those who survive are often brain damaged (Brown, 2004).

HSV-2 can be transmitted by an infected partner who is shedding the virus symptomatically or asymptotically (Freeman et al., 2006), and most of the infection transmitted by the asymptomatic individuals (Bastien et al., 2012; Tronstein et

al., 2011). Asymptomatic shedding of HSV-2 transmissibility is greater from men to women than women to men. There are differences between the genders in terms of frequency of active herpes recurrences, with more recurrence among men as compared with women making more men infectious (Kamali et al., 1999; Freeman et al., 2006). Asymptomatic shedding is also more easily detected in women, mainly from the cervix and vulva (Brugah et al., 1997).

There are three types of HSV-2 infections; which are primary infection, non-primary infection and recurrent infection. A primary infection with HSV-2 is the one that occurs in a patient without prior exposure to HSV (HSV-1 or HSV-2), that is, for patients who have no antibodies to HSV-2. 2 to 14 days after exposure, lesions begin to appear and without antiviral treatment may last up to 20 days (Glass et al., 2005; Chentoufi et al., 2010; Parks, 2013). About 75% of individuals with primary HSV-2 infection are asymptomatic and viral shedding lasts for about 12 days and ceases before complete resolution of lesions, if present (Glass et al., 2005). Antibody response occurs 2 to 12 weeks after the infection and unlike protective anti-bodies to other viruses, antibodies to HSV-2 do not prevent local recurrences (Glass et al., 2005). These lesions begin as tender vesicles that may rupture and ulcerate with additional symptoms associated with primary HSV-2 that include malaise, nausea, headache, fever, intense pain, lymphadenopathy and women may also experience vaginal discharge (Glass et al., 2005; Chentoufi et al., 2010; Parks, 2013). An initial, non-primary infection is defined as a first HSV infection with one HSV type in a patient who is already infected with another type of HSV family (e.g. a new HSV-2 infection in a patient with prior HSV-1 infection). The most common type of HSV-2 infection is the non-primary infection (Parks, 2013). Due to the partial protection of the pre-existing antibodies, symptoms may be fewer and of shorter duration. The duration of lesions in a non-primary first episode averages 15 days, and shedding lasts for about 7 days. The clinical presentation of a primary infection cannot be reliably distinguished from a non-primary first episode infection (Parks, 2013).

Recurrent infections are outbreaks owing to re-activation of a previously acquired

HSV-2 infection (not a re-infection) (Parks, 2013). Recurrent infections may be symptomatic or asymptomatic, and since HSV-2 is a chronic infection, the frequency of symptomatic reactivation decreases over time in a majority of individuals (Benedetti et al., 1999). Recurrent infections have similar symptoms like those of primary infections although lesions from recurrent infections are present approximately for 7 days with viral shedding for 4 days (Glass et al., 2005; Parks, 2013). A person does not need sexual contact in any part of that area to have outbreaks there, for example, an individual does not need to have anal sex to have an outbreak around the anus (Warren, 2014). Sometimes outbreaks occur in the same place every time they appear, but sometimes they move to a different location. When outbreaks show up in a new location in the boxer shorts area, it is not because the infected person has spread the virus themselves, but because the virus has chosen to travel along a different nerve to get to the surface of the skin (Warren, 2014). The ability by the HSV-2 virus to successfully avoid clearance by the immune system by entering a non-replicating phase known as latency leads to life-long infection, although whether latency always accompanies infection is unclear (Stanberry et al., 2000; Berger and Houff, 2010).

1.3. HSV-2 vaccination

The most economic and effective way to overcome HSV-2 is to develop a vaccine (Johnston et al., 2011; Johnston et al., 2013) and various vaccine candidates have been developed, with the first ones in the 1920s, however none has been successful to date (Chentoufi, 2012). A prophylactic vaccine would be valuable from both the patient and public health standpoint, if it were able to meet or exceed the efficacy of currently available preventive therapies (Johnston et al., 2011). Efficacy trials for prophylactic HSV-2 vaccines are expensive and take many years to complete (Whitley and Roizman, 2002). Several platforms have been tested for prophylactic vaccines, and they have been reviewed (Johnston et al., 2011). The most promising and advanced has been the recombinant glycoprotein vaccines, with more than 20 000 human volunteers studied in the clinical trials (Johnston et al., 2013). End-

points of interest in a prophylactic vaccine study include both acquisition of HSV-2 infection, to measure the ability of the vaccine to induce sterilising immunity and frequency of viral shedding (Johnston et al., 2011).

Therapeutic vaccines are being developed with the aim of preventing viral shedding recurrences (or at least minimising their frequency, duration and severity), and reducing the probability of transmission (Hosken, 2005; Koelle, 2006). Several of the therapeutic HSV-2 vaccine clinical trials (1920's-1930's) initially showed great therapeutic effects, however, they lacked placebo controlled groups, and when later tested against control groups showed little to no difference from the placebo group (Stanberry, 2004; Jones, 2014). Vaccines are still being tried and tested, but to no avail (Johnston et al., 2011; Johnston et al., 2013).

1.4. HSV-2 treatment

HSV-2 can be difficult to diagnose since some of the infected persons have no classical symptoms (Fatahzadeh and Schwartz, 2007). Viral culture is the major diagnosis for HSV-2 and it may take 3 to 7 days to process with a sensitivity of 50% and a specificity of around 100%. Although these procedures produce highly sensitive and specific diagnoses, their high costs and time constraints discourage their regular use in clinical practice (Fatahzadeh and Schwartz, 2007). HSV-2 treatment usually involves general-purpose antiviral drugs that interfere with viral replication, reduce the physical severity of outbreak-associated lesions and lower the chance of transmission to others. Antiviral treatment of HSV-2 infection with nucleoside analogues (acyclovir, valacyclovir and famciclovir) has been the mainstay of therapy for genital herpes (Strick et al., 2006).

Acyclovir is a purine nucleoside analog that is a competitive inhibitor of viral DNA chain elongation and was the first drug approved by the Centres for Disease Control and Prevention (CDC) (CDC, 2002) for the treatment of HSV-2. If given on time in the initial stage of HSV-2 infection, acyclovir reduces the duration of symp-

toms by an average of 2 days, healing time of ulcers by 4 days and 7 days for viral shedding as compared to the placebo (Parks, 2013). Valacyclovir is a prodrug of acyclovir that is converted to acyclovir in the liver, its disadvantage being high cost and unavailability of nonoral formulations (Parks, 2013). The major advantage of valacyclovir over acyclovir being its twice daily tablets, as compared to thrice daily for acyclovir. Famciclovir is the oral form of penciclovir, a nucleoside analog with properties similar to acyclovir with an improved bioavailability (Diaz-Mitoma et al., 1998), but being more expensive than acyclovir. The major advantage of oral acyclovir therapy over other oral agents is its lower cost, smaller tablets and the availability of a liquid formulation (Parks, 2013). Clinical trials indicate that acyclovir, famciclovir and valacyclovir are equally effective in the episodic treatment of HSV-2, although famciclovir is slightly less effective in reducing viral shedding (Wald et al., 2006). Valacyclovir has been proven to reduce both the frequency of asymptomatic shedding and the risk of transmission (Corey et al., 2004; Moretlwe and Celum, 2004). Without any significant complications by many individuals having used either valacyclovir or acyclovir (Trying, 2002), and since treatment cannot fully protect against transmission of HSV-2, the use of condoms and adoption of safe sex practices should be encouraged to complement treatment.

There are two possible treatment strategies for HSV-2, that is, episodic therapy and suppressive therapy. Episodic treatment strategy is aimed at providing relief to symptomatic episodes of HSV-2, but has no effect on recurrence rates (CDC, 2015; Moretlwe and Celum, 2004). Treatment is usually given for 5 days and reduces pain, decreases time of ulcer healing by one or two days, and reduces HSV-2 shedding by one to two days. Suppressive therapy is continuous daily therapy to prevent frequent recurrences of genital herpes, and it has been shown to reduce HSV-2 asymptomatic shedding and transmission by approximately 50% (Moretlwe and Celum, 2004). In 2004, Patrick et al. found that 17% of patients in the study that were being treated for genital herpes reported using alternative therapy, such as herbal or dietary supplements. In general, there is sufficient empirical evidence on the efficacy and safety of herbal and dietary supplements for the treatment of

HSV-2 (Gaby, 2006; Mishra et al., 2007).

1.5. HSV-2 and behaviour

Behaviour is the response of the system or organism to various stimuli or inputs, whether internal or external, conscious or subconscious, overt or covert, and voluntary or involuntary (Elizabeth et al., 2014). Behaviour change is a central objective in public health interventions (WHO, 2002) with an increased focus on prevention prior to onset of disease (CDC, 2015). This is particularly important in low and middle income countries, where efficiency of health spending, costs and benefits of health interventions has come under increased scrutiny in recent decades (Jamison, 2006). Many health conditions are caused by risk behaviours, such as problem drinking, substance abuse, smoking, reckless driving, poor treatment adherence, or unprotected sexual intercourse (Johnson et al., 2008; Llyod-Jones, 2010; Stenbacka et al., 2010; Wu et al., 2010), with adolescents being the individuals involved in most of them (Leigh and Stall, 1993; CDC, 2010).

Adolescents are the range of people who are 10-19 years old (WHO, 1998), making up approximately 20% of the worlds population, with about 85% living in developing countries (Denhe and Riender, 2005). These are the individuals who mostly engage in risky sexual behaviours (Hill and Biro, 2009). Adolescents are more vulnerable to STIs because of lack of education, (in some schools sex education begins late, when adolescents have already been initiated into sexual intercourse (Chinsembu et al., 2009)). Many adolescents experiment with substances. Parents, teachers, and policy makers want to know the consequences of adolescent substance abuse. Since the abuse of substances affects their thinking capacity, most of them who are substance abusers have higher rates of HSV-2 infection (Cook et al., 2002; Buchacz et al., 2000). Sexting (sex-texting) was also found to be associated with risky sexual behaviour and higher rates of STIs amongst adolescents (Benotsch et al., 2013). Sexting is a playword on the words “sex-texting”, which involves sending, posting or forwarding nude, semi-nude, sexually suggestive or

vulgar text, pictures or messages via an electronic device (Siegle, 2010).

One study in Zimbabwe among adolescent females aged 15-19 years, in which they were tested for HSV-2, reported that 12% of them tested positive for HSV-2 (Birdthistle et al., 2008). Those adolescents who are infected with HSV-2 infection may be at greater risk for transmission and acquisition of human immunodeficiency virus (HIV) (Corey et al., 2004). Interventions to control HSV-2 infection could prevent as many as 50% to 60% of new HIV infections (Freeman et al., 2009). Furthermore, pregnant adolescents infected with HSV-2 (particularly those with a primary infection) can transmit infection to the neonate, which can lead to serious complications for the neonate, such as neurologic problems and even death (Nahmias et al., 1971 and Whitley, 1999). Misuse of alcohol and other substances can contribute to treatment non-adherence across a range of medical and mental health service settings (Eggleston et al., 2010).

Despite advances in health care, all too often the benefits of these treatments are not fully realised because of patient non adherence (Bosworth, 2010). Adherence has been defined as the extent to which a person behaves while taking medication, following a diet, and/or executing lifestyle changes, in agreement with recommendations from a health-care provider (Bosworth, 2010). Almost all medical and behavioural health treatments require at least some degree of adherence to treatment (e.g., coming to appointments, picking up medications, agreeing to have procedures performed, use of contraception, obtaining immunisations, attending follow-up appointments), and many treatments require significant behaviour change (e.g., following long-term demanding and complex medication regimens, improving diet and physical activity, reducing alcohol consumption, and cigarette smoking) (Bosworth, 2010). Adherence is significantly a bit higher among patients taking medication with a once-daily dosing schedule compared to three or more frequent dosing, signifying that HSV-2 patients who also need to take their medication twice or three times a day are susceptible to non adherence (Senst et al., 2001). It is worth noting that poor treatment adherence have serious adverse effects on

the (Gross Domestic Product) GDP of a nation, for instance, a study in USA estimated the total costs associated with poor treatment adherence to be in the range \$100-\$300 billion each year, including both direct and indirect costs (Senst et al., 2011). Given the clear relationships between health behaviours and outcomes, the lack of focus on treatment adherence is a shame (Bosworth, 2010).

1.6. The role of mathematical models in epidemiology

Epidemiology is defined as the study of the distribution and determinants of health-related events in specified populations, and the application of this study to control health problems (Anderson and May, 1991; Brauer and Castillo-Chavez, 2001). Infectious diseases are disorders caused by organisms such as bacteria, viruses, fungi or parasites and most of the organisms live in and on our bodies (Ryan, et al, 2014; CDC, 2015; CDC, 2015; Longo et al, 2015; Razonable, 2011; Group B Strep, 2015). They are normally harmless or even helpful, but under certain conditions, some organisms may cause disease (Ryan, et al, 2014; CDC, 2015; CDC, 2015; Longo et al, 2015; Razonable, 2011; Group B Strep, 2015). We have two types of transmissions, namely, direct and indirect transmissions. Direct transmission is characterised by the transfer of an infectious agent from the infected individual directly to the host, like biting, sexual intercourse, touching, etcetera. Indirect transmission being the transfer of an infectious agent by contaminated inanimate. In many developing countries, infectious diseases are still the major causes of mortality (WHO, 2002). The emerging and re-emerging diseases have lead to a revived interest in infectious disease modelling (Hethcote, 2000). The effectiveness of improved sanitation, antibiotics and vaccination programs created a confidence in the 1960s that infectious diseases would soon be eliminated (Hethcote, 2000).

Mathematical representation and analysis of infectious diseases has been central to infectious disease epidemiology since its inception as a discipline more than a

century ago (Dietz and Heesterbeek 2002; Heesterbeek, 2005). The history of the use of mathematical modelling in disease transmission dates back to the pioneering works of the likes of Daniel Bernoulli, Sir Ronald Ross, Kermack and McKendrick (see, Bernoulli, 1776; Ross, 1911; Kermack and McKendrick, 1927; Anderson and May, 1982; Anderson and May, 1991; ; Hethcote, 2000;). In 1760, Daniel Bernoulli formulated and solved a model for smallpox in order to evaluate the effectiveness of variolation of healthy people with smallpox (Bernoulli, 1760). In 1906, Hamer first applied the mass action principle for a deterministic epidemic model in discrete time (Anderson and May, 1991; Hamer, 1906). Starting in 1926, Kermack and McKendrick published papers on epidemic models and obtained the epidemic threshold result that the density of susceptibles must exceed a critical value in order for an epidemic outbreak to occur (Bailey, 1975; Kermack and McKendrick, 1927). The model formulation process clarifies assumptions, variables, and parameters, moreover, models provide conceptual results such as thresholds, basic reproduction numbers, contact numbers, and replacement numbers (Hethcote, 2000). Mathematical models and computer simulations are useful experimental tools for building and testing theories, assessing quantitative conjectures, answering specific questions, determining sensitivities to changes in parameter values, and estimating key parameters from data (Hethcote, 2000). Mathematical models are used in comparing, planning, implementing, evaluating and optimising various detection, prevention, therapy and control programs (Hethcote, 2000).

The prototype of almost all models is the one by Kermack and McKendrick. They subdivided the population N into three separate distinct populations: Susceptibles (represent the number of individuals not yet infected with the disease at time t , or those susceptible to the disease), the infected (the individuals who have been infected with the disease and are capable of spreading the disease to those in the susceptible category) and the removed (is the individuals who have been infected and then removed from the disease, either due to immunisation or due to death (Müller and Kuttler, 2015). Those in this category are not able to be infected again or to transmit the infection to others). The individuals schematically go through

the states given by $S \rightarrow I \rightarrow R$. This type of model is referred to as the SIR model and it is described by a set of 3 equations with the independent variable being time, t . Over the years, the Kermack and McKendrick model has been extended to incorporate other important epidemiological concepts such as seasonality, vaccination, antiviral treatment, treatment adherence, isolation, etc. Other mathematical models such as the SI, SIS, SEIRS, SEI, SEIS, and MSEIRS (Hethcote, 2000) have also been developed with the objective of understanding epidemics. It is worth noting that acronyms for epidemiological models are often based on the flow patterns between the compartments, such as the SIR explained above. Reviews of the literature (see, for instance, Dietz, 1967; Becker, 1978; Dietz, 1988; Chavez, 1989; Hethcote and Levin, 1989; Hethcote, 1994) show the rapid growth of epidemiology modelling.

There are two common and useful types of models that are used in the study of the infectious diseases at a population scale, and these are deterministic and stochastic models. Deterministic models, also known as compartmental models, are the ones in which every set of variables is uniquely defined by parameters in the model and by sets of previous states of these variables. They well fit large populations and contain no element of chance or uncertainty. Stochastic models rely on chance, variation in risks of exposure to disease and other factors. In a stochastic model, randomness is there, and variable states are not described by unique values but rather by probability distributions. In this thesis we are interested in large populations and thus we shall use deterministic approach in trying to understand HSV-2 dynamics. We use data from published work and reasonable estimates. Differential equations are preferred because a lot is known about their behaviour. For instance, given a set of parameters and a particular set of differential equations, one can often predict the behaviour of the system and tell the range of the parameter values for which the system makes biological sense and bifurcate from one state to the other.

1.7. Review of mathematical models for HSV-2

HSV-2 being an ancient disease, it could not escape the treatment of mathematical models to understand its dynamics. The models developed, and the subsequent modifications made to the existing models, are motivated by the continued improvement in understanding the dynamics of the disease. Basically, there are eight different basic HSV-2 models that have been developed (Foss et al., 2009), (see, for instance, Gershengorn and Blower, 2000; Newton and Kuder, 2000; Blower et al., 1998; White and Garnett, 1999; Schinazi, 1999; Fisman et al., 2002; Garnett et al., 2004; Ghani and Aral, 2005).

White and Garnett, (1999), developed a simple mathematical model of HSV-2 transmission dynamics, which was meant to explore the influence of the natural history of HSV and the impact of antiviral therapy. A sex and sexual activity stratified deterministic differential equation model of the natural history of HSV-2 was developed and analysed by Garnett et al. in 2004. Schinazi (1999) introduced and discussed a basic spatial stochastic model to discuss strategies to control the epidemic. Fisman et al. (2002) constructed a mathematical model to project future increases in HSV-2 seroprevalence in the USA with the probability of heterosexual transmission of HSV-2 estimated from cross-sectional estimates of infection prevalence reported by the National Health and Examination Survey (NHANES). Blower et al. (1998), developed and analysed a mathematical model used as a health policy tool to predict the levels of antiviral drug resistance that would emerge, if treatment rates were increased and to identify the key factors in determining the emergence of drug resistance. Ghani and Aral (2005) developed an individual based simulation model to explore how variation in number of client contacts per sex worker, and the relative sizes of the sex worker and client population influence the endemic prevalence of gonorrhea and HSV-2 infection. Newton and Kuder (2000) devised a mathematical model to examine the parameter sensitivity and assess control strategies such as behaviour change. The model consisted of a population made up of individuals in their late teens to mid twenties. In 2000, Gershengorn

and Blower managed to assess the impact of antivirals and emergence of drug resistance.

Of all the basic models for HSV-2, the most followed, adapted and revised model is the one by Gershengorn and Blower (2000). Gershengorn and Blower developed a basic mathematical model to predict the impact of increasing antiviral usage on HSV-2 prevalence. The model consisted of three differential equations

$$\begin{aligned}\frac{dX}{dt} &= \pi - X(c\lambda + \mu), \\ \frac{dH}{dt} &= c\lambda X + rQ - H(\mu + q), \\ \frac{dQ}{dt} &= qH - (r + \mu)Q.\end{aligned}\tag{1.1}$$

The force of infection is given by $\lambda = \beta H/N$, where N represents the size of the sexually active population, $N = X + H + Q$. The second equation in (1.1) specifies the rate of change in the number of individuals shedding infectious virus (H) over time t . The group H includes the symptomatic and the asymptomatic individuals. Gershengorn and Blower in their model included the quiescent individuals into their calculation of the force of infection, even though they do not shed the virus as shown by the absence of the force of infection. Gershengorn and Blower model yields that the increased use of antivirals was always beneficial and the potential detrimental effects due to the emergence of drug-resistant strains would be minimal. In our thesis, we shall also derive some of our models based on the one developed by Gershengorn and Blower (2000).

As efforts are currently underway to develop therapeutic vaccines for HSV-2, several authors have used mathematical modelling to predict the potential public health impact of imperfect therapeutic and prophylactic vaccines (see, Schwartz and Blower, 2005; Schwartz et al., 2007; William et al., 2007; Podder and Gumel,

2009; Al Sallaq et al., 2010; Lou et al., 2012). In 2005 Schwartz et al. developed a model which was based on the basic model developed by Gershengorn and Blower (2000). They modelled the future impact of pre-exposure vaccines with both prophylactic and therapeutic properties. Schwartz and Blower, (2007), developed another model based on Gershengorn and Blower (2000), which was meant to predict the potential public health impact of imperfect therapeutic vaccines. In 2009 Podder and Gumel extended the model by Schwartz and Blower (2005), by including the exposed compartment and also assuming that the quiescent individuals are infectious. In their model, Podder and Gumel qualitatively analysed the effects of an imperfect HSV-2 vaccine. William et al., (2007), designed a mathematical model to understand the potential impact of suppressive valacyclovir therapy on the transmission of HSV-2 within a population. Al Sallaq et al. (2010), applied mathematical modelling to derive 3 summary measures for the population effect of imperfect HSV-2 vaccines as a function of their efficacies in reducing susceptibility, genital shedding and infectivity. In 2012 Lou et al. developed a mathematical model to describe the epidemiology of vaccination targeting young females against HSV-2 with the population delineated with respect to group, sexual activity and infection status.

The risk of HIV-1 acquisition is 3-times higher among HSV-2 seropositive persons in populations with 80% seropositive, nearly 50% of HIV infections are attributable to prevalent HSV-2 (Wald and Link, 2002; Johnston et al., 2011). This has motivated various authors to model HIV and HSV-2 co-infections, (see Feng et al., 2013; Alvey et al., 2015; Foss et al., 2011; Freeman et al., 2006; Kapitanov et al., 2015). In 2015 Alvey et al. constructed a mathematical model that described and incorporated the joint dynamics of HSV-2 and HIV. The model was meant to gain more insights into the transmission dynamics of HIV and HSV-2 in a population that constituted both heterosexuals and homosexuals. The basic HSV-2 model used by Alvey et al. (2015) was the one proposed by Gershengorn and Blower (2000). Applying the model proposed by Gershengorn and Blower in 2000, Feng et al. (2013) proposed and analysed a model to understand the synergy between HIV and HSV-2

and the potential impact of HSV-2 therapy. In the model, Feng et al. (2013), incorporated the aspects of gender and heterogeneous mixing between activity groups. Foss et al., (2011) developed a mathematical model, parameterised and fitted it to Mysore data. They used the model to estimate the contribution of HSV-2 to HIV transmission from clients to female sex workers (FSW) in a Southern Indian setting and the maximum potential impact of perfect HSV-2 suppression therapy on HIV incidence. In 2009 Freeman et al. explored the impact of the potential impact of a prophylactic HSV-2 vaccination on HIV incidence in Africa using STD-SIM an individual-based model. In 2015, Kapitanov et al. constructed a model of the co-infection dynamics between the two diseases by incorporating a time-since-infection variable to track the alternating periods of infectiousness of HSV-2. The model considered only heterosexual and distinguishes three population groups males, general population females and female sex workers.

Within HSV-2 modelling, the development of HSV-2 models with an emphasis on behaviour have received less attention, even though some authors have looked into the effects of vaccines against individuals with risky behaviours (see, Garnett et al., 2004; White et al., 2008; Blower and Ma, 2004; Lou et al., 2012; Newman and Kuder, 2000). Most researchers discussed behaviour change in general without looking at the specific behaviours, such as early sexual debut, substance abuse, poor treatment adherence, sexting, etcetra, and the population level effects in relation to the behaviours. Newton and Kuder in 2000, assessed the impact of efforts to control the epidemic and the focus on vaccine development and prevention of transmission during both symptomatic and asymptomatic phases, in the absence of behaviour change. Lou et al. in 2012 developed a mathematical model to describe the epidemiology of vaccination targeting young females against HSV-2. The model population was delineated with respect to age group, sexual activity and infection status. Newman and Kuder in 2000 and Lou et al. in 2012 managed to discuss about the relationship between HSV-2, behaviour and young individuals (including adolescents), without specifying the specific behaviours. In this thesis, we shall look at various specific in the adolescents and in the general population.

1.8. Mathematical Preliminaries

1.8.1. Introduction

This section summarises some of the mathematical theories and methodologies relevant to the thesis. In this section, *autonomous* system of ordinary differential equations would be considered. Autonomous ODEs are the ones which do not explicitly depend on the independent variable, time (t)

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \quad (1.2)$$

as compared to *non-autonomous* ODEs, which are ODEs that explicitly depend on time (t). Here, the dot represents differentiation with respect to t .

$$\dot{x} = f(x, t), \quad x \in \mathbb{R}^n. \quad (1.3)$$

1.8.2. Equilibria and Linearisation

The following are standard theorems and definitions necessary for analysing stabilities for equilibrium points of an autonomous system.

Definition 1.1. A point $\bar{x} \in \mathbb{R}^n$ is called an *equilibrium point* (also *steady state*, *critical point*, etc.) of (1.2), if $f(\bar{x}) = 0$. Further, an equilibrium point $\bar{x}$ is called a *hyperbolic equilibrium point* of (1.2) if none of the eigenvalues of the matrix $Df(\bar{x})$ have zero real part.

Definition 1.2. The *Jacobian matrix* of f at the equilibrium $\bar{x}$, denoted by $Df(\bar{x})$, is the matrix

$$J(\bar{x}) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(\bar{x}) & \dots & \frac{\partial f_1}{\partial x_n}(\bar{x}) \\ \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot \\ \frac{\partial f_n}{\partial x_1}(\bar{x}) & \dots & \frac{\partial f_n}{\partial x_n}(\bar{x}) \end{pmatrix}$$

of partial derivatives of f evaluated at $\bar{x}$.

Theorem 1.1. (*Fundamental Existence-Uniqueness Theorem (Perko, 2000)*).

Let E be an open subset of $\mathbb{R}^n$ containing x_0 and assume that $f \in C^1(E)$. Then, there exists an $a > 0$ such that the initial value problem (IVP):

$$\dot{x} = f(x), \quad x(0) = x_0,$$

has a unique solution $x(t)$ on the interval $[-a, a]$.

Consider the linear system

$$\dot{x} = Ax, \tag{1.4}$$

with the matrix $A = Df(\bar{x})$. The linear function $Ax = Df(\bar{x})x$ is called the linear part of f at $\bar{x}$.

Definition 1.3. The linear system (1.4) with the matrix $Ax = Df(\bar{x})x$ is called the linearisation of (1.4) at $\bar{x}$.

Definition 1.4. An equilibrium point of (1.4) is called a sink if all of the eigenvalues of the matrix $Df(\bar{x})$ have negative real part; it is called a source if all the eigenvalues of $Df(\bar{x})$ have positive real part; and it is called a saddle if it is a hyperbolic equilibrium point and $Df(\bar{x})$ has at least one eigenvalue with a positive real part and at least one negative real part.

1.8.3. Stability of Equilibria

The idea of stability of an equilibrium point is of considerable theoretical and practical importance, and it has been widely discussed in the literature, for example,

books on the dynamical systems: theory (Guckenheimer and Holmes, 2002; Lakshmikantham et al., 1989; LaSalle, 1976; Perko, 2000) and application (Murray, 2002, 2003; Brauer and Castillo Chavez, 2001; Anderson and May, 1991).

An equilibrium point $\bar{x}$ is said to be stable if all solutions sufficiently close to $\bar{x}$ stay nearby for all $t \geq 0$. It is asymptotically stable if nearby solutions actually converge to $\bar{x}$ as $t \rightarrow \infty$. Thus, the formal definitions are;

Theorem 1.2. *Suppose all the eigenvalues of $Df(\bar{x})$ have negative real parts. Then the equilibrium point $\bar{x}$ of the system (1.2) is locally asymptotically stable, and unstable if at least one of the eigenvalues has positive real part.*

Definition 1.5. *(Lyapunov stability).*

An equilibrium point $\bar{x}$ of (1.2) is said to be stable if given $\epsilon > 0$, there exists a $\delta(\epsilon) > 0$, such that, for any x_0 for which $|\bar{x} - x_0| < \delta(\epsilon)$, the solution $y(t, x_0)$ of (1.2) through x_0 at 0 satisfies $|y(t, x_0) - \bar{x}| < \epsilon$ for all $t \geq 0$.

Definition 1.6. *An equilibrium point $\bar{x}$ is said to be unstable if it is not stable.*

Definition 1.7. *(Asymptomatic Stability).*

An equilibrium point $\bar{x}$ of (1.2) is said to be asymptotically stable if it is stable and, in addition, there exists a constant $c > 0$ such that if $|\bar{x} - x_0| < c$ then $|y(t, x_0) - \bar{x}| \rightarrow 0$ as $t \rightarrow \infty$.

Definition 1.8. *An equilibrium point $\bar{x}$ is said to be globally asymptotically stable if it is asymptotically stable and the domain of asymptotic stability $D_{\bar{x}} = \{x_0 \in \mathbb{R}^n : \lim_{t \rightarrow \infty} |y(t, x_0) - \bar{x}| = 0\} = \mathbb{R}^n$ (i.e., every solution $y(t, x_0)$ of (1.2) possesses the property $|y(t, x_0) - \bar{x}| \rightarrow 0$ as $t \rightarrow \infty$).*

1.8.4. Lyapunov stability

Lyapunov function can be thought of as modified energy function. There is no general method to construct or find a Lyapunov function which proves the stability of

an equilibrium.

Definition 1.9. *Let $\mathcal{W}$ be a neighbourhood of $\bar{x}$. A function $V : \mathcal{W} \rightarrow \mathbb{R}$ is said to be a positive definite function if*

- (i) $V(x) > 0$ for all $x \neq 0$,
- (ii) $V(x) = 0$ if and only if $x = 0$,
- (iii) $V(x) \rightarrow \infty$ as $x \rightarrow \infty$.

Theorem 1.3. *If there exists a positive definite function V such that $\dot{V} < 0$ outside M and $\dot{V} \leq 0$ on M , where M is a set which contains no entire trajectories apart from the point 0 , then the equilibrium point 0 is asymptotically stable.*

Theorem 1.4. *Let $\bar{x}$ be an equilibrium point of (1.2) and let $V : \mathcal{W} \rightarrow \mathbb{R}$ be a C^1 function defined on some neighbourhood $\mathcal{W}$ of $\bar{x}$ such that*

- (i) $V(\bar{x}) = 0$ and $V(x) > 0$ if $x \neq \bar{x}$.
- (ii) $\dot{V}(x) \leq 0$ in $\mathcal{W} - \{\bar{x}\}$.

Then $\bar{x}$ is stable. Moreover, if

- (iii) $\dot{V}(x) < 0$ in $\mathcal{W} - \{\bar{x}\}$,

then $\bar{x}$ is asymptotically stable.

Furthermore, if $\mathcal{W}$ can be chosen to be all of $\mathbb{R}^n$, then $\bar{x}$ is said to be *globally asymptotically stable* (GAS), if (i) and (iii) are satisfied. The notion is that if V is a Lyapunov function then V decreases along trajectories, and hence (since V is strictly positive except at zero) trajectories tend to zero, which is a minimum value of V . Thus, any function V that satisfies the condition in Theorem 1.4 is called a Lyapunov function (Barbashin, 1970; Wiggins, 2003).

1.8.5. Invariance Principle

All parameters and state variables for our epidemiological models are assumed to be non-negative for biological relevance. Thus, epidemiological models should be considered in (feasible) regions where such property (non-negative) is preserved.

Definition 1.10. A point $x_0 \in \mathbb{R}^n$ is called an ω - limit point of $x \in \mathbb{R}^n$, denoted by $\omega(x)$, if there exists a sequence $\{t_i\}$, $t_i \rightarrow \infty$, such that

$$\phi(t_i, x) \rightarrow x_0.$$

Definition 1.11. A point $x_0 \in \mathbb{R}^n$ is called an α - limit point of $x \in \mathbb{R}^n$, denoted by $\alpha(x)$, if there exists a sequence $\{t_i\}$, $t_i \rightarrow -\infty$, such that

$$\phi(t_i, x) \rightarrow x_0.$$

Definition 1.12. The set of all ω - limit points of a flow is called the ω - limit set and the set of all α -limit points of a flow is called the α -limit set.

Definition 1.13. A set $\mathcal{H}$ is invariant if and only if for all $x \in \mathcal{H}$, $\phi(x, t) \in \mathcal{H}$ for all t . A set is positively invariant if for all $x \in \mathcal{H}$, $\phi(x, t) \in \mathcal{H}$ for all $t > 0$ and negatively invariant if for all $x \in \mathcal{H}$, $\phi(x, t) \in \mathcal{H}$ for all $t < 0$ (Barbashin, 1970).

Theorem 1.5. (LaSalle Invariance Principle (LaSalle, 1968)).

Suppose that the equilibrium point of system (1.2) at $\bar{x} = 0$ and V is a Lyapunov function on some neighbourhood $\mathcal{W}$ of $\bar{x} = 0$. If $x_0 \in \mathcal{W}$ has its forward trajectory bounded with limit points in $\mathcal{W}$ and $\mathcal{H}$ is the largest invariant set of

$$E = \{\bar{x} \in \mathcal{W} : \dot{V}(\bar{x}) = 0\},$$

then $\phi(x_0, t) \rightarrow \mathcal{H}$ as $t \rightarrow \infty$.

1.8.6. Perron-Frobenius Theorem

The mathematical theory of positive systems is usually based on the theory of non-negative matrices founded by Perron and Frobenius. In this Thesis, we make use of the Perron-Frobenius theorem, in analysing the stability and persistence of our model systems.

Definition 1.14. *The spectral radius of a square matrix is the supremum among the absolute values of the elements in its spectrum, which is sometimes denoted by $\rho(\cdot)$.*

Definition 1.15. *A non-negative square matrix A is called primitive if there is a k such that all the entries of A^k are positive and it is called irreducible if for any i, j there is a $k = k(i, j)$ such that $(A^k)_{i,j} > 0$.*

Theorem 1.6. *(Perron Theorem (Perron, 1907))*

Suppose A is a primitive matrix, with spectral radius λ . Then λ is a simple root of the characteristic polynomial which is strictly greater than the modulus of any other root, and λ has strictly positive eigenvectors.

Theorem 1.7. *(Perron-Frobenius Theorem (Graham, 1987)) Let A be an irreducible matrix of period ρ .*

- (i) A has a non-negative right eigenvector r . This eigenvector is strictly positive, its eigenvalue λ is the spectral radius of A , and any non-negative eigenvector of A is a scalar multiple of r .*
- (ii) The roots of the characteristic polynomial of A of modulus λ are all simple roots, and these roots are precisely the ρ numbers $\lambda, \xi\lambda, \dots, \xi^{-1}\lambda$ where ξ is a primitive ρ th root of unity.*
- (iii) The non-zero spectrum of A is invariant under multiplication by ξ .*

1.8.7. Comparison Theorem

The use of comparison theorem offers an alternative approach for establishing the global asymptomatic stability of equilibria. The methodology entails comparing the solutions of the system of differential equations.

Theorem 1.8. (*Theorem 2.2.2, Comparison Theorem (Pachpatte, 1998)*). Let $f(t, x)$ be continuous in an open set U containing a point (τ_0, x_0) , and suppose that the initial value problem

$$z'(t) = f(t, z(t)), \quad z(\tau_0) = x_0,$$

has a maximal solution $z = z(t)$ with domain $\tau_0 \leq t \leq \tau_1$. If x is any differentiable function on $[\tau_0, \tau_1]$ such that $(t, x(t)) \in U$ for $t \in [\tau_0, \tau_1]$ and

$$x'(t) \leq f(t, x(t)), \quad \tau_0 \leq t \leq \tau_1, \quad x(\tau_0) \leq x_0, \quad (1.5)$$

then

$$x(t) \leq z(t), \quad \tau_0 \leq t \leq \tau_1. \quad (1.6)$$

Moreover, the result remains valid if 'maximal' is replaced by 'minimal' and $< \text{by} >$ in both (1.5) and (1.6).

The Gronwall Lemma is used, among other things to show that a given dynamical system is continuous with respect to the associated initial data.

Lemma 1.1. (*Gronwall Lemma (Gronwall, 1919)*)

Let $z(t)$ satisfy

$$z_t = az + b, \quad z(0) = z_0$$

for constants a, b . Then for $t \geq 0$

$$z(t) \leq e^{at} z_0 + \frac{b}{a} (e^{at} - 1), \quad a \neq 0$$

and

$$z(t) \leq z_0 + bt, \quad a = 0.$$

1.8.8. Persistence

We present the following results which are essential in the proofs of disease persistence in this thesis.

Assumption 1.1. *Compactness assumption (Hale and Waltman, 1989):*

There exists a $\delta > 0$ and a subset B of X with the following

- (i) *If $x \in X$ and $d(x, X_2) < \delta$, then $d(\phi_t(x), B) \rightarrow 0$, $t \rightarrow \infty$.*
- (ii) *The intersection $B \cap B_\delta(X_2)$ of B with the δ -neighbourhood of X_2 , $B_\delta(X_2) = \{x \in X; d(x, X_2) < \delta\}$*

has compact closure.

Theorem 1.9. *(Theorem 3.1 (Thieme, 1993))*

Let X be a locally compact metric space with metric d . Let X be the disjoint union of two sets X_1 and X_2 such that X_2 is compact. Let Φ be a continuous semiflow on X_1 .

Then X_2 is a uniform strong repeller for X_1 , whenever it is a uniform weak repeller for X_1 .

Theorem 1.10. *(Theorem 4.6 (Thieme, 1993))*

Let X_1 be open in X and forward invariant under Φ . Further, let the compactness assumption hold. Assume that Ω_Φ ,

$$\Omega_\Phi = \bigcup_{y \in Y_2} \omega(y), \quad Y_2 = \{x \in X_2; \phi_t(x) \in X_2 \forall t > 0\},$$

has an acyclic isolated covering $M = \bigcup_{k=1}^m M_k$ such that each part M_k of M is a weak repeller of X_1 . Then X_2 is a uniform strong repeller for X_1 .

Theorem 1.11. *(Theorem A12, (Smith and Waltman, 1995))*

Let A have non-negative off diagonal elements and be irreducible. Then

- (i) *if $s(A) < 0$ then $-A^{-1} > 0$; and*
- (ii) *if $s(A) > 0$ and $r > 0$, then $Ax + r = 0$ has no solution x satisfying $x > 0$.*

1.8.9. Next Generation Operator Matrix and Backward bifurcation

Next Generation Operator

The *next generator operator* method (Diekmann et al., 1990; van den Driessche and Watmough, 2002) is popularly used to calculate the associated reproduction number, and also to establish the local asymptotically stability of the associated disease-free equilibrium, of disease transmission models. The formulation in (van den Driessche and Watmough, 2002) is reproduced below.

Suppose that there are n compartments of which m are infected. We define the vector $x = x_i$, $i = 1, \dots, n$, where x_i denotes the number of individuals in the i th compartment. Let $\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment i (it only includes new infections and not terms which describe the transfer of infectious individuals from one infected compartment to another) and let $\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$, where $\mathcal{V}_i^+$ is the rate of transfer of individuals into compartment i by all other means and $\mathcal{V}_i^-$ is the rate of transfer of individuals out of the i th compartment.

$$\dot{x}_i = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x). \quad (1.7)$$

Assuming that $\mathcal{F}_i$ and $\mathcal{V}_i$ satisfy the following axioms outlined by Diekmann et al. (1990) and van den Driessche and Watmough (2002). Let $X_s = \{x \geq 0 | x_i = 0, i = 1, \dots, m\}$ be the disease-free states (non-infected state variables) of the model, where $x = (x_1, \dots, x_m)$, $x \geq 0$.

(A1) if $x \geq 0$, then $\mathcal{F}_i, \mathcal{V}_i^+, \mathcal{V}_i^- \geq 0$ for $i = 1, \dots, m$.

(A2) if $x = 0$, then $\mathcal{V}_i^- = 0$. In particular, if $x \in X_s$ then $\mathcal{V}_i^- = 0$ for $i = 1, \dots, m$.

(A3) $\mathcal{F}_i = 0$ if $i > m$.

(A4) if $x \in X_s$, then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, \dots, m$.

(A5) if $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts, where $Df(x_0)$ is the Jacobian matrix evaluated at the disease free equilibrium (DFE) x_0 .

Definition 1.16. (*M-Matrix*)

An $n \times n$ matrix A is an M -matrix if and only if every off-diagonal entry of A is non-positive and the diagonal entries are all positive.

Lemma 1.2. If x_0 is a DFE of (1.7) and $f_i(x)$ satisfies (A1)–(A5), then the derivatives $D\mathcal{F}(x_0)$ and $D\mathcal{V}(x_0)$ are partitioned as

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \quad D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are the $m \times m$ matrices defined by

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0) \right], \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0) \right], \quad \text{with } 1 \leq i, j \leq m.$$

Further, F is non-negative, V is a non-singular M -matrix and J_3, J_4 are matrices associated with the transition terms of the model, and all eigenvalues of J_4 have positive real parts.

Following Diekmann et al. (1990), FV^{-1} is called the next generation matrix for the model (1.7) and set

$$\mathcal{R}_0 = \rho(FV^{-1}), \tag{1.8}$$

where ρ is the spectral radius (dominant eigenvalue) of the matrix FV^{-1} .

Theorem 1.12. Consider the disease transmission model given by (1.7) with $f(x)$ satisfying conditions (A1) – (A5). If x_0 is a DFE of the model, then x_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$, where $\mathcal{R}_0$ is defined by (1.8).

The above mentioned formulation has been extended for use to establish the local stability of the disease-free solution of non-autonomous models for disease transmission (van den Driessche and Watmough, 2002).

Backward bifurcation

Although the $\mathcal{R}_0$ condition tells us that the disease dies out if $\mathcal{R}_0 < 1$ and grows if $\mathcal{R}_0 > 1$, some models admit subcritical endemic equilibria for $\mathcal{R}_0 < 1$ and a bistability arises whereby a stable endemic equilibrium co-exists with the stable disease-free equilibrium. This is because of a backward bifurcation (Castillo-Chavez, 2004; Strogaz, 2000; van den Driessche and Watmough, 2000; van den Driessche and Watmough, 2002) at the critical value $\mathcal{R}_0 = 1$. It is important to find a subcritical value, denoted $\mathcal{R}_0^*$, below which the stable disease-free equilibrium exists alone in its neighbourhood. We do this using the centre manifold theory of bifurcation analysis found in (Castillo-Chavez, 2004; Pachpatte, 1998; van den Driessche and Watmough, 2000) and several other sources.

Choosing a bifurcation parameter, say c , whose critical value c^1 satisfies $\mathcal{R}_0 = 1$. The Jacobian $J(x_0)$ computed at the disease-free equilibrium is recomputed with $c = c^1$ giving $J(x_0, c^1)$ whose eigenvalues have negative real parts except for a simple zero eigenvalue. Let $u = (u_1, u_2, \dots, u_n)$ and $v = (v_1, v_2, \dots, v_n)$ be the left and right eigenvectors respectively corresponding to the simple zero eigenvalue. The eigenvectors satisfy

$$uJ(x_0, c^1) = J(x_0, c^1)v = 0. \quad (1.9)$$

The direction of the bifurcation at $\mathcal{R}_0 = 1$ is determined by the signs of the bifurcation coefficients a_B and b_B computed as follows:

$$\begin{aligned} a_B &= \sum_{k,i,j=1}^n u_k v_i v_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(x_0, c^1), \\ b_B &= \sum_{k,i=1}^n u_k v_i \frac{\partial^2 f_k}{\partial x_i \partial c}(x_0, c^1). \end{aligned} \quad (1.10)$$

If $a_B > 0$ and $b_B > 0$, then the model (1.7) exhibits a subcritical bifurcation at $\mathcal{R}_0 = 1$. The direction of the bifurcation at $\mathcal{R}_0 = 1$ is backward, hence backward bifurcation. The curve a_B corresponds to $\mathcal{R}_0 - \mathcal{R}_0^* = 0$, giving the stricter threshold below which the stable disease free equilibrium exists alone in its neighbourhood. At $\mathcal{R}_0 = \mathcal{R}_0^*$, the bifurcation is forward.

1.8.10. Pontryagin's Maximum Principle

Pontryagin's Maximum Principle (PMP) is a classical result from optimal control theory that provides a necessary condition that must be satisfied by an optimal solution (Pontryagin et al., 1964). There are various versions of PMP for problem statements of varying generality, here we present a generalised one, that is also suitable for problems discussed in this thesis.

Let $[t_0, T] \subset \mathbb{R}$, U be a bounded subset of $\mathbb{R}^m$ and $u : [t_0, T] \rightarrow U$ be a measurable function. Let $f = (f^1, \dots, f^n)$ for $i \in \{1, \dots, n\} : \mathbb{R}^n \times U \rightarrow \mathbb{R}^n$ be continuous on U and continuously differentiable on $\mathbb{R}^n$. For a fixed u and constant $x_0 \in \mathbb{R}^n$ let $x : [t_0, T] \rightarrow \mathbb{R}^n$ be a function described by $x(t_0) = x_0$ and

$$\dot{x}^i(t) = f^i(x(t), u(t)) \quad \text{a.e. on } [t_0, T], \quad i \in \{1, \dots, n\}. \quad (1.11)$$

We denote $u(t)$ the control applied at time t and $x : [t_0, T] \rightarrow \mathbb{R}^n$ the system trajectory corresponding to control u and initial condition x_0 . Notice that in order to define a system trajectory a corresponding control and initial condition must be specified. We will call $x(t)$ the system at time t .

Given a continuous function $g : \mathbb{R}^n \rightarrow \mathbb{R}$ and a function $f^0 : \mathbb{R}^n \times U \rightarrow \mathbb{R}$ that is continuous on U and continuously differentiable on $\mathbb{R}^n$ define the cost function

$$J(x, u) = \int_{t_0}^T f^0(x(t), u(t)) dt + g(x(T)). \quad (1.12)$$

The goal is to find a control $u : [t_0, T] \rightarrow U$ and corresponding trajectory $x : [t_0, T] \rightarrow \mathbb{R}^n$ that minimises J . There are different variations of this problem depending on

the specific constraints placed on $t_0, T, x(t_0)$ and $x(T)$. We now review some terminology before giving a formal statement.

Definition 1.17. Let $I_0, I_f \subset \mathbb{R}$ denote the sets of possible values for the initial time t_0 and the final time T , respectively. Let $S_0, S_f \subset \mathbb{R}^n$ denote the sets of possible values for the initial and final state values, respectively. Then the set of allowable boundary values for a trajectory is defined by $\mathcal{B} = \{(t_0, x_0, T, x_f) \mid t_0 \in I_0, x_0 \in S_0, T \in I_f \text{ and } x_f \in S_f\}$

Assumption 1.2. Assuming that there exists functions $\zeta_0, \zeta_f \in C^1(\mathbb{R}^n, \mathbb{R})$ such that $S_0 = \zeta_0^{-1}(0)$ and $S_f = \zeta_f^{-1}(0)$ and $D\zeta_0(z)$ and $D\zeta_f(y)$ are surjective for all $z \in S_0$ and $y \in S_f$, where $D\zeta_i$ denotes the Jacobian of ζ_i .

Definition 1.18. Denoting $U \subset \mathbb{R}^m$ the bounded set of all allowable values for the control. Then an admissible control is a measurable function $u : [t_0, T] \rightarrow U$ that satisfies

- (i) there exists an absolutely continuous function $x : [t_0, T] \rightarrow \mathbb{R}^n$,
- (ii) $\dot{x}(t) = f(x(t), u(t))$ a.e. on $[t_0, T]$,
- (iii) $t \rightarrow f^0(x(t), u(t))$ is integrable on $[t_0, T]$ and
- (iv) $(t_0, x(t_0), T, x(T)) \in \mathcal{B}$.

The trajectory x corresponding to an admissible control is an admissible trajectory and the corresponding pair (x, u) is an admissible pair.

Definition 1.19. For any $\hat{b} = (b_0, b_1, \dots, b_n) \in \mathbb{R}^{n+1}$ there is a corresponding value $b = (b_1, b_2, \dots, b_n) \in \mathbb{R}^n$. Define $\hat{f} : \mathbb{R}^{n+1} \times U \rightarrow \mathbb{R}^{n+1}$ by $\hat{f}^i(\hat{b}, u) = f^i(b, u)$ for all $i \in \{0, 1, \dots, n\}$. We now define the extended system of differential equations by

$$\begin{aligned}\dot{\hat{x}}^0 &= \hat{f}^0(\hat{x}, u), \\ \dot{\hat{x}}^j &= \hat{f}^j(\hat{x}, u), \quad j \in \{1, \dots, n\}.\end{aligned}$$

In the sequel D_2H will denote the derivative H with respect to its second argument.

Definition 1.20. *The extended Hamiltonian is the function $H : \mathbb{R}^{n+1} \times \mathbb{R}^{n+1} \times U \rightarrow \mathbb{R}$ defined by*

$$H(\hat{a}, \hat{b}, c) = \sum_{k=0}^n \hat{a}_k \hat{f}^k(\hat{b}, c) \quad (1.13)$$

Problem Statement 1.1. Assume U is a bounded set in $\mathbb{R}^m$. Assume $\hat{f}$ is continuous on U and continuously differentiable on $\mathbb{R}^{n+1}$. Let $\mathcal{A}$ denote the set of all admissible pairs (x, u) and let $\mathcal{A}$ be non-empty. Find an admissible pair $(x^*, u^*) \in \mathcal{A}$ such that $J(x^*, u^*) \leq J(x, u)$ for every $(x, u) \in \mathcal{A}$.

Theorem 1.13. *(Pontryagin's Maximum Principle (PMP)).*

If (x^*, u^*) is a solution to Problem Statement 1.1 then there exists an absolutely continuous function $\hat{\lambda} : [t_0, T] \rightarrow \mathbb{R}^{n+1}$ such that

- (i) $\dot{\hat{\lambda}} = -D_2H(\hat{\lambda}, \hat{x}, u)$, *a.e. on* $[t_0, T]$,
- (ii) $\hat{\lambda}(t) \neq 0$ for all $t \in [t_0, T]$,
- (iii) $\hat{\lambda} \in \{0, 1\}$,
- (iv) $H(\hat{\lambda}(t), \hat{x}^*(t), u^*(t)) = \sup_{u \in U} H(\hat{\lambda}(t), \hat{x}^*(t), u)$, *a.e. on* $[t_0, T]$,
- (v) *there exists* $c \in \mathbb{R}$ *such that* $H(\hat{\lambda}(t), \hat{x}^*(t), u^*(t)) = c$, *a.e. on* $[t_0, T]$,
- (vi) *if the end time* T *is free then* c *can be taken to be zero, and*
- (vii) $\lambda(t_0)$ *is orthogonal to* $\ker(D\zeta_0(x^*(t_0)))$ *and* $\lambda(T)$ *is orthogonal to* $\ker(D\zeta_1(x^*(T)))$.

Remark 1.1. *Part (vii) of the PMP is often referred to as the transversality condition and it states that $\lambda(t_0)$ and $\lambda(T)$ must be perpendicular to the constrain sets S_0 and S_f respectively.*

An important subtlety of PMP is that it presupposes that an optimal control exists. Therefore, before applying the PMP the first step is to prove that the problem under consideration actually possesses a solution. The following theorem from Fleming and Rishel (1982), can be used to prove the existence of a solution for a number of optimal control problems.

Assumption 1.3. *Let U be a bounded subset of $\mathbb{R}^m$ and assume $f : \mathbb{R}^n \times U \rightarrow \mathbb{R}^n$ is continuous on both $\mathbb{R}^n$ and U . Furthermore, assume that there exists constants K_1 and K_2 such that*

$$(i) \|f(x, u)\| \leq K_1(1 + \|x\|) \text{ and}$$

$$(ii) \|f(\hat{\varrho}, u) - f(\varrho, u)\| \leq K_2\|\hat{\varrho} - \varrho\| \text{ for all } \hat{\varrho}, \varrho \in \mathbb{R}^n \text{ and } u \in U.$$

Theorem 1.14. *Suppose Assumption (1.3) holds. Furthermore, assume*

$$(i) f^0 : \mathbb{R}^n \times U \rightarrow \mathbb{R} \text{ is continuous,}$$

$$(ii) \text{ the set of admissible pairs } \mathcal{A} \text{ is not empty,}$$

$$(iii) U \text{ is compact,}$$

$$(iv) g \text{ is continuous on } \mathcal{B},$$

$$(v) \text{ the set of allowable boundary values } \mathcal{B} \text{ is compact and}$$

$$(vi) G(x) = \{(z_0, z) \mid z_0 \geq f^0(x, u), z = f(x, u), u \in U\} \text{ is convex.}$$

Then there exists a solution to Problem 1.11.

1.9. Motivation and thesis structure

In this study, mathematical models for estimating the transmission dynamics of HSV-2 have been proposed and qualitatively analysed. The models presented herein focus on the effects of behavioural change on the transmission dynamics of HSV-2 amongst adolescents and the general population with adolescents inclusive. Of all the STIs, in this thesis we focus on HSV-2 since it is on the rise in Sub-Saharan Africa, mostly amongst adolescents and in contrast to other STIs such as chlamydial, gonorrhoea, syphilis and trichomoniasis, the infection with HSV-2 is lifelong and once established, there is no treatment to eliminate it (Hill and Biro, 2009; Gupta et al., 2007). HSV-2 is somewhat difficult to determine, due to its asymptomatic nature (Hill and Biro, 2009). Current available strategies are not enough

(such as, use of antiviral therapy, disclosure of serostatus to susceptible partners and consistent condom use) they reduce the risk of HSV-2 transmission by approximately 50% (Johnston et al., 2013), while male circumcision decreases the risk of HSV-2 acquisition by nearly 30% (Tobian, 2009). HSV-2 infected individuals suffer from poor treatment adherence because the treatment is expensive, it needs to be taken twice or three times daily and individuals who do not have symptoms are unlikely to take long-term antiviral (Mindel, 1998; Corey, 2002; Johnston, 2013). The best and most effective way of curtailing the spread of HSV-2 is the introduction of an effective vaccine. Currently, without an effective vaccine, we seek to understand, weigh and investigate the effect of various behavioural changes combining them with the current available strategies such as condom use and treatment, on curtailing the spread of HSV-2.

In Chapter 2, we develop a mathematical model to forecast future trends in the incidence of HSV-2 epidemic and also to quantify the association between substance abuse and HSV-2 epidemic amongst adolescents in the community. Mathematical analysis of the model is done. Further, optimal control is applied, with the time dependent controls representing condom use and educational campaigns.

In Chapter 3, we propose and analyse the transmission dynamics of HSV-2 to assess the impact of HSV-2 treatment adherence. We apply some optimal control theory to investigate the impact of counselling and monitoring on controlling the dynamics of HSV-2 in a community where there is poor treatment adherence.

In Chapter 4, we study the effects of sexting and peer influence on the prevalence of HSV-2 amongst adolescents. Mathematical analysis of the model is done. Necessary intervention strategies are discussed and some time dependent controls assessed.

In Chapter 5, we formulate and discuss a mathematical model to explore the association between gender and HSV-2 treatment adherence. The models steady states

are calculated and their stabilities analysed. Mathematical analysis of the model is also done. Numerical simulations and sensitivity analysis are investigated.

In Chapter 6, here we discuss the main contributions of this thesis and highlight some possible refinement of the current research and potential directions for future work.

1.10. Publications

Part of the work presented in this thesis has been published in international journals.

Articles published in international peer reviewed journals

Chapter 2

A. Mhlanga, C.P. Bhunu, S. Mushayabasa, HSV-2 and substance abuse amongst adolescents: Insights through mathematical modelling. *Journal of Applied Mathematics*, (2014) Article ID 104819, <http://dx.doi.org/10.1155/2014/104819>.

Chapter 3

A. Mhlanga, C.P. Bhunu, S. Mushayabasa, A computational study of HSV-2 with poor treatment adherence. *Abstract and applied analysis*, (2015) Article ID 85067, <http://dx.doi.org/10.1155/2015/850670>.

Chapter 4

A. Mhlanga, C.P. Bhunu, S. Mushayabasa, Modelling the effects of sexting on the transmission dynamics of HSV-2 amongst adolescents. *Cogent Mathematics*, (2015) vol. 2: Article ID 1085940, <http://dx.doi.org/10.1080/23311835.2015.1085940>.

Chapter 5

A. Mhlanga, C.P. Bhunu, S. Mushayabasa, W. Mangezi, Exploring the association between gender and HSV-2 treatment adherence, *Submitted*.

Not included

A. Mhlanga, S. Mushayabasa, C.P. Bhunu, Modelling HSV-2 transmission dynamics with risk factor. *World journal of modelling and simulation*, (2015), vol 11, no. 3, 219-240.

Chapter 2

HSV-2 and substance abuse amongst adolescents: Insights through mathematical modelling

2.1. Introduction

Since the creation of human history and before, people have found ways to modify their bodies and their consciousness by taking substances such as herbs, alcohol and drugs. Substance abuse is a major public health concern in global settings due to its consequences, and is very common in adolescents (Birhanu, 2014). In Africa, there appears to be a decline in the age of substance abuse and it usually starts with alcohol and cigarettes at tender ages between 10 to 14 years (Obot 1990,2004; Odejide, 2006). An estimated 13 million adolescents aged 12 to 17 years old become involved into substance abuse annually (Lennox and Cecchini, 2008). Cannabis accounts for approximately 90% or more of illicit substance abuse in North America, Australia and Europe with tobacco and alcohol being the most frequently used substances by young people (Alexander, 2001). It has been found that adolescents start

abusing substances for four main reasons; to improve their mood, to receive social rewards, to reduce negative feelings and to avoid social rejection (Kuntsche et al., 2005), and these makes them fall victims to peer influence easily. Adolescents who are into substance abuse have multiple sex partners and thus making them to be at risk for STIs (Howard and Wang, 2004; Nkansah-Amankra et al., 2011; van Gelder, 2011; Morrison-Beedy et al., 2011).

Adolescents are the most vulnerable group to STIs, due to their risky sexual behaviours. Adolescents aged 15-19 years, account for approximately 3 million cases, meaning one out of four sexually active adolescents reports an STI every year (Cates and Pheeters, 1997). Prevalence estimates for HSV-2 among adolescents are available through community-based studies. A study in western Kenya found HSV-2 prevalence to be 9% for females and 4% for males aged 13-14 years, and 28% females and 17% for males aged 15-19 years (Amornkul et al., 2009). It was shown that sexual activity in Namibia begins at a very young age, often as low as 10 years (Chinsembu, 2009), and some 61% of twelfth graders in USA have had sexual intercourse at least once (CDC, 2004). Thus, as much as HSV-2 prevalence is high amongst adolescents, so is substance abuse. Some preventive efforts should be made to target adolescents before initiation of sexual activity, since prevention is always better than cure. Hence, it is vital to reduce substance abuse because it would further disturb their already poor judgements.

Based on the above we propose a mathematical model to investigate the effects of peer influence and substance abuse on HSV-2 dynamics among adolescents. Although several mathematical models have been proposed to investigate the effects of social issues on the prevalence of epidemics, see for example (Burattini et al., 1998; Bacaër et al., 2006; Podder et al., 2007; Mushayabasa and Bhunu, 2011; Bhunu et al., 2011; Bhunu and Mushayabasa, 2012) not much has been done on exploring the impact of peer influence and substance abuse on HSV-2.

2.2. Model formulation

The total sexually-active population at time t , denoted by N , is subdivided into mutually-exclusive compartments, namely susceptible adolescents who are non-substance abusers (S_n), susceptible adolescents who are substance abusers (S_a), adolescents infected with HSV-2 who are non-substance abusers (I_n) and adolescents infected with HSV-2 who are substance abusers (I_a). Although there are many causes of substance abuse amongst adolescents, here we will consider only by peer influence. The total population is given by

$$N(t) = S_n(t) + S_a(t) + I_n(t) + I_a(t). \quad (2.1)$$

The susceptible is increased by a constant inflow into the population at rate Λ . A fraction π_0 of these adolescents are assumed to be non-substance abusers and the complementary fraction, $\pi_1 = 1 - \pi_0$ being substance abusers. This is reasonable because the underlying population is made up of adolescents only into these two classes (influence from some peers is probably the main drive behind the adolescents abusing substances and hence their recruitment into the substance abusers class). Individuals in different human subgroups suffer from natural death, at rate μ . Assuming homogeneous mixing of the population, the susceptible individuals acquire HSV-2 infection at rate $\lambda(t)$, with

$$\lambda(t) = \frac{\beta(I_a(t) + (1 - \eta)I_n(t))}{N(t)}. \quad (2.2)$$

$\eta \in (0, 1)$ is a modification parameter accounting for reduced number a non-substance abuser would infect as compared to a substance abuser (Cook et al., 2000; Buchacz et al., 2000), perhaps because adolescents who engage in substance abuse also engage in other risky behaviours. Substance abuse diminishes judgement, leading to the engagement of the high risk behaviours (Auslander et al., 2005), and the same explanation also applies for the modification parameter $\alpha \in (0, 1)$. p is the probability of being infected from a sexual partner and c is the rate at which an individual acquires sexual partners per unit time and $\beta = pc$ is the effective con-

tact rate for HSV-2 infection (contact sufficient to result in HSV-2 infection). The role of condom use is represented by θ . If $\theta = 0$, then condom use is not effective; $\theta = 1$ corresponds to completely effective condom use, while $0 < \theta < 1$ implies that condom use would be effective to some degree. Substance abusers experience related diseases like liver cirrhosis, pancreatitis, heart disease among other substance abuse induced diseases and die at a rate v because of these diseases (Bhunu and Mushayabasa, 2012). Individuals are assumed to become substance abusers mostly by peer pressure, maybe by choice or any other reasons at rate ρ , and likewise individuals may cease being substance abusers due to educational campaigns (mostly), health reasons, pressure at work or school, poverty or any other reason at rate ϕ . The model flow diagram is depicted in Figure 2.1 below.

From the descriptions and assumptions on the dynamics of the epidemic made above, the following are the model equations.

$$\begin{aligned}
 \frac{dS_n}{dt} &= \pi_0\Lambda - \alpha(1 - \theta)\lambda S_n + \phi S_a - (\mu + \rho)S_n, \\
 \frac{dS_a}{dt} &= \pi_1\Lambda - (1 - \theta)\lambda S_a + \rho S_n - (\mu + v + \phi)S_a, \\
 \frac{dI_n}{dt} &= \alpha(1 - \theta)\lambda S_n + \phi I_a - (\mu + \rho)I_n, \\
 \frac{dI_a}{dt} &= (1 - \theta)\lambda S_a + \rho I_n - (\mu + v + \phi)I_a.
 \end{aligned} \tag{2.3}$$

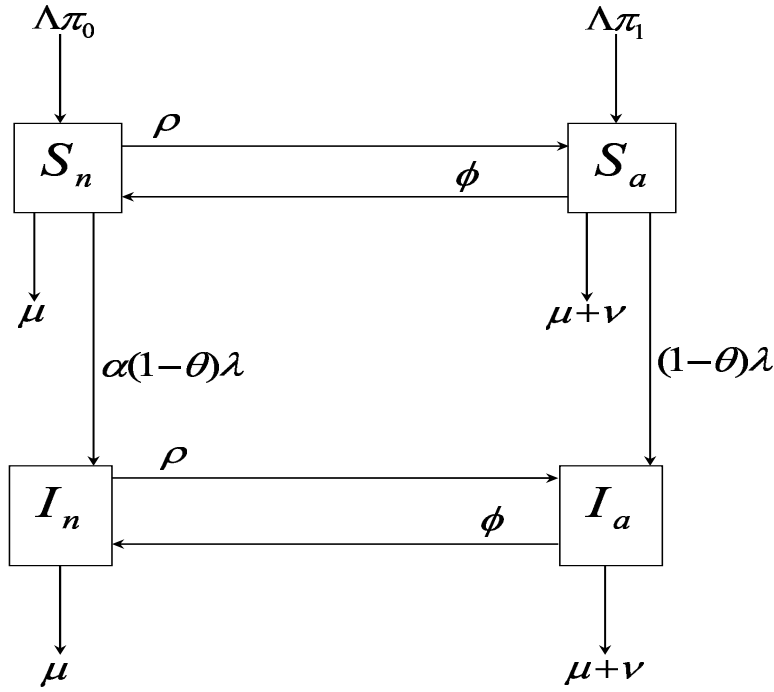


Figure 2.1: Structure of the model.

2.2.1. Positivity and boundedness of solutions

Model system (2.3) describes human population and therefore it is necessary to prove that all the variables $S_n(t)$, $S_a(t)$, $I_n(t)$ and $I_a(t)$ are non-negative for all time $t > 0$.

Theorem 2.1. *Let the initial data be $S_n(0) \geq 0$, $S_a(0) \geq 0$, $I_n(0) \geq 0$ and $I_a(0) \geq 0$. Then, the solutions $S_n(t)$, $S_a(t)$, $I_n(t)$ and $I_a(t)$ of model system (2.3) are positive for all $t > 0$.*

Proof. Under the given conditions, we prove that each solution component of model system (2.3) is positive, otherwise assume by contradiction that there exist a first time

$t_1 : S_n(t_1) = 0, S'_n(t_1) < 0$ and $S_n(t) > 0, S_a(t) > 0, I_n(t) > 0, I_a(t) > 0$ for $0 < t < t_1$

or there exists a

$t_2 : S_a(t_2) = 0, S'_a(t_2) < 0$ and $S_n(t) > 0, S_a(t) > 0, I_n(t) > 0, I_a(t) > 0$ for $0 < t < t_2$

or there exists a

$t_3 : I_n(t_3) = 0, I'_n(t_3) < 0$ and $S_n(t) > 0, S_a(t) > 0, I_n(t) > 0, I_a(t) > 0$ for $0 < t < t_3$
or there exists a

$t_4 : I_a(t_4) = 0, I'_a(t_4) < 0$ and $S_n(t) > 0, S_a(t) > 0, I_n(t) > 0, I_a(t) > 0$ for $0 < t < t_4$. In the first case we have,

$$S'_n(t_1) = \pi_0\Lambda + \phi S_a(t_1) > 0, \quad (2.4)$$

which is a contradiction and consequently $S_n(t)$ remains positive. In the second case we have,

$$S'_a(t_2) = \pi_1\Lambda + \rho S_n(t_2) > 0, \quad (2.5)$$

which is a contradiction, therefore $S_a(t)$ is positive. In the third case we have,

$$I'_n(t_3) = \alpha(1 - \theta)\lambda(t_3)S_n(t_3) + \phi I_a(t_3) > 0, \quad (2.6)$$

which is a contradiction, therefore $I_n(t)$ is positive. In the final case we have,

$$I'_a(t_4) = (1 - \theta)\lambda(t_4)S_a(t_4) + \rho I_s(t_4) > 0, \quad (2.7)$$

which is a contradiction, that is, $I_a(t)$ remains positive. Thus, in all cases $S_n(t), S_a(t), I_n(t), I_a(t)$ remain positive for all non-negative initial conditions, as required.

□

Adding all the equations of model system (2.3) we have,

$$\begin{aligned} \frac{dN}{dt} &= \frac{dS_n}{dt} + \frac{dS_a}{dt} + \frac{dI_n}{dt} + \frac{dI_a}{dt} \\ &= \Lambda - \mu N - v(S_a + I_a) \\ &\leq \Lambda - \mu N. \end{aligned} \quad (2.8)$$

Applying a theorem by Birkhof and Rota (1982), on differential inequality, we have

$$0 \leq N(t) \leq \frac{\Lambda}{\mu} + N(0)e^{-\mu t}, \quad (2.9)$$

where $N(0) = S_n(0) + S_a(0) + I_n(0) + I_a(0)$. Taking the limit as $t \rightarrow \infty$, we have that $0 \leq N(t) \leq \frac{\Lambda}{\mu}$. Thus, the state variables remain biologically meaningful in the set

$$\mathcal{G} = \left\{ (S_n(t), S_a(t), I_n(t), I_a(t)) \in \mathbb{R}_+^4 : N(t) \leq \frac{\Lambda}{\mu} \right\}, \quad (2.10)$$

for all positive initial conditions in $\mathbb{R}_+^4$. Thus, model system (2.3) will be analysed in $\mathcal{G}$. It is sufficient to consider solutions in $\mathcal{G}$ where existence, uniqueness and continuation results for model system (2.3) hold. Thus, the system is mathematically and epidemiologically well-posed.

2.3. Model Analysis

2.3.1. The reproductive number

A constant solution to a system of equations is referred to as an equilibrium solution. The disease free equilibrium point is defined as the point at which no disease is present in the population, which is presented in the model as $I_n = I_a = 0$. Then model system (2.3) reduces to

$$\begin{aligned} \frac{dS_n}{dt} &= \pi_0\Lambda + \phi S_a - (\mu + \rho)S_n, \\ \frac{dS_a}{dt} &= \pi_1\Lambda + \rho S_n - (\mu + v + \phi)S_a, \\ \frac{dI_n}{dt} &= 0, \\ \frac{dI_a}{dt} &= 0. \end{aligned} \quad (2.11)$$

Thus, model system (2.3) has the disease free equilibrium

$$\begin{aligned}\mathcal{E}^0 &= (S_a^0, S_n^0, 0, 0) \\ &= \left(\frac{\Lambda(\pi_0(\mu + v) + \phi)}{v(\mu + \rho) + \mu(\mu + \rho + \phi)}, \frac{\Lambda(\mu\pi_1 + \rho)}{v(\mu + \rho) + \mu(\mu + \rho + \phi)}, 0, 0 \right).\end{aligned}\tag{2.12}$$

The linear stability of $\mathcal{E}^0$ is governed by the basic reproductive number R_0 which is defined as the spectral radius of an irreducible or primitive non-negative matrix (Hethcote, 2000). Biologically, the basic reproductive number can be interpreted as the expected number of secondary infections produced by a single infectious individual during his/her infectious period when introduced in a completely susceptible population. Using the notation in van den Driessche and Watmough (2002), the non-negative matrix F and the non-singular matrix V for the new infection terms and the remaining transfer terms are respectively given (at DFE) by

$$F = \begin{bmatrix} \frac{\alpha\beta(1-\theta)(1-\eta)(\pi_0(\mu + v) + \phi)}{\mu + \rho + \phi + v\pi_0} & \frac{\alpha\beta(1-\theta)(\pi_0(\mu + v) + \phi)}{\mu + \rho + \phi + v\pi_0} \\ \frac{\beta(1-\theta)(1-\eta)(\mu\pi_1 + \rho)}{\mu + \rho + \phi + v\pi_0} & \frac{\beta(1-\theta)(\mu\pi_1 + \rho)}{\mu + \rho + \phi + v\pi_0} \end{bmatrix}\tag{2.13}$$

and

$$V = \begin{bmatrix} \mu + \rho & -\phi \\ -\rho & \mu + \phi + v \end{bmatrix}.\tag{2.14}$$

We now consider different possibilities in detail.

Case (a) There are no substance abusers in the community

We set $v = \phi = \rho = \pi_1 = 0$ and $\pi_0 = 1$. Then the spectral radius is given by

$$R_0 = R_n = \frac{\alpha\beta(1-\theta)(1-\eta)}{\mu}.\tag{2.15}$$

This reproductive rate is sometimes referred to as the back of the napkin (Arino et al., 2008) defined to be the number of secondary infections caused by a single infective introduced into a wholly susceptible population over the course of the infection of this single infective (van den Driessche and Watmough, 2002). Here, it is defined as the number of secondary HSV-2 cases produced by a single infected individual during his/her entire infectious period in a totally naive (susceptible) population in the absence of substance abusers.

Case (b) The entire population is made up of substance abusers

We set $\phi = \rho = \pi_0 = 0$ and $\pi_1 = 1$. Then the spectral radius is given by

$$R_a = \frac{\beta(1 - \theta)}{\mu + v}. \quad (2.16)$$

Biologically, R_a measures the average number of new infections generated by a single HSV-2 infective who is also a substance abuser during his/her entire infectious period when he/she is introduced into a susceptible population of substance abusers.

Case (c) The general case

Co-existence of non-substance abusers and substance abusers. Then the spectral radius is given by

$$R_{na} = \frac{\beta(1 - \theta)(k_1 + k_2 + k_3)}{(\mu + \rho + \phi + v\pi_0)((\mu + v)(\mu + \rho) + \mu\phi)}, \quad (2.17)$$

where

$$\begin{aligned} k_1 &= v\alpha((1 - \eta)(2\mu\pi_0 + \phi) + \pi_0(\rho + (1 - \eta)\phi)), \\ k_2 &= (\mu\pi_1 + \rho)(\mu + \rho + (1 - \eta)\phi) + v^2\alpha(1 - \eta)\pi_0, \\ k_3 &= \alpha(\mu\pi_0 + \phi)(\rho + (1 - \rho)(\mu + \phi) + \rho). \end{aligned}$$

Biologically, R_{na} measures the average number of new HSV-2 infections generated by a single HSV-2 infective during his/her infectious period within a community, in the presence of condom use, non-substance abusers and substance abusers adolescents.

Case (d) In the absence of condom use

We set $\theta = 0$ in R_{na} . Then the spectral radius is given by

$$R_c = \frac{\beta(k_1 + k_2 + k_3)}{(\mu + \rho + \phi + v\pi_0)((\mu + v)(\mu + \rho) + \mu\phi)}, \quad (2.18)$$

where,

$$\begin{aligned} k_1 &= v\alpha((1 - \eta)(2\mu\pi_0 + \phi) + \pi_0(\rho + (1 - \eta)\phi)), \\ k_2 &= (\mu\pi_1 + \rho)(\mu + \rho + (1 - \eta)\phi) + v^2\alpha(1 - \eta)\pi_0, \\ k_3 &= \alpha(\mu\pi_0 + \phi)(\rho + (1 - \rho)(\mu + \phi) + \rho). \end{aligned}$$

Biologically, R_c measures the average number of new secondary HSV-2 infections generated by a single HSV-2 infective during his/her infectious period whilst in a community of non-substance abusers and substance abusers, in the absence of condom use.

Theorem 2.2 follows from van den Driessche and Watmough (2002).

Theorem 2.2. *The disease-free equilibrium of model system (2.3) is locally asymptotically stable if $R_{na} \leq 1$, and unstable otherwise.*

Now we demonstrate that when $R_{na} \leq 1$ model system (2.3) admits a globally asymptotically stable disease-free equilibrium.

2.3.2. Global stability of the disease free equilibrium

Theorem 2.3. *The disease-free equilibrium $\mathcal{E}^0$ of model system (2.3) is globally asymptotically stable (GAS) if $R_{na} \leq 1$ and unstable if $R_{na} > 1$.*

Proof. Let $\Upsilon = (I_n, I_a)$. Given that

$$\begin{aligned} \frac{dI_n}{dt} &= \alpha(1 - \theta)\lambda S_n + \phi I_a - (\mu + \rho)I_n, \\ \frac{dI_a}{dt} &= (1 - \theta)\lambda S_a + \rho I_n - (\mu + v + \phi)I_a, \end{aligned} \quad (2.19)$$

it follows that $\frac{d\Upsilon}{dt} \leq (F - V)\Upsilon$, with F and V as defined in (2.13) and (2.14) respectively. It is worth noting that both F and V^{-1} are non-negative. By the Perron-Frobenius theorem (Horn and Johnson, 1985), the non-negative matrix $V^{-1}F$ has a non-negative left eigenvector $u \geq 0$ with respect to $\rho(V^{-1}F) = \rho(F^{-1}V) = R_{na}$, that is, $u^T V^{-1}F = R_{na}u^T$. Motivated by (Guo et al., 2006; Bani-Yaghoub et al., 2012), consider a Lyapunov function

$$V = u^T V^{-1} \Upsilon. \quad (2.20)$$

Then the derivative of V along model system (2.3) is

$$\begin{aligned} \frac{dV}{dt} &= u^T V^{-1} \frac{d\Upsilon}{dt} \\ &\leq u^T V^{-1} (F - V) \Upsilon \end{aligned} \quad (2.21)$$

$$\begin{aligned} &= u^T V^{-1} F \Upsilon - u^T \Upsilon \\ &\leq (R_{na} - 1) u^T \Upsilon \text{ if } R_{na} \leq 1. \end{aligned} \quad (2.22)$$

If $R_{na} < 1$, then $\frac{dV}{dt} \leq 0$. Let

$$\Psi = \left\{ (S_n, S_a, I_n, I_a) \in \mathcal{G} \mid \frac{dV}{dt} = 0 \right\} \quad (2.23)$$

If $R_{na} < 1$, $\frac{dV}{dt} \leq 0$, implies that $u^T \Upsilon = 0$, thus $I_n = 0$ and $I_a = 0$. Therefore, the largest invariant set of Ψ is the singleton $\mathcal{E}^0$. By LaSalle's Invariance Principle (LaSalle, 1976), $\mathcal{E}^0$ is globally asymptotically stable in the region $\mathcal{G}$ when $R_{na} < 1$.

If $R_{na} = 1$, $\frac{dV}{dt} = 0$ implies that $S_n = S_n^0$ and $S_a = S_a^0$, by (2.21) and (2.22) and the fact that $u^T V^{-1} > 0$. Then, adding the third equation and fourth equation for

model system (2.3), evaluated at the disease free equilibrium, we have

$$\begin{aligned} \frac{d(I_n + I_a)}{dt} &= -vI_a - \mu I_n - \mu I_a \\ &\leq -\mu(I_n + I_a), \end{aligned} \tag{2.24}$$

for which the invariant set satisfies $I_n + I_a = 0$. Therefore, the largest invariant set where $\frac{dV}{dT} = 0$ is the singleton $(S_n^0, S_a^0, 0, 0)$, and by the LaSalle Invariance Principle, the disease free equilibrium is globally asymptotically stable in $\mathcal{G}$ if $R_{na} = 1$.

If $R_{na} > 1$ and $\Psi > 0$, it follows that

$$(R_{na} - 1)u^T \Psi > 0. \tag{2.25}$$

The inequality (2.25) and the continuity imply that $\frac{dV}{dt} > 0$ in a small enough neighbourhood of $\mathcal{E}^0$ in the interior of $\mathcal{G}$. Therefore, solutions in the interior of $\mathcal{G}$ sufficiently close to $\mathcal{E}^0$ move away from $\mathcal{G}$ provided $R_{na} > 1$, and thus $\mathcal{E}^0$ is unstable. Using a uniform persistence result from Thieme (1993), it can be shown that, when $R_{na} > 1$, instability of $\mathcal{E}^0$ implies uniform persistence of model system (2.3).

□

2.3.3. Endemic equilibrium and stability analysis

The endemic equilibrium state is the state when the disease cannot be totally eradicated from the community but remains in the population. Model system (2.3) has three possible endemic equilibria, namely:

- (a) The (HSV-2 only) substance abuse-free endemic equilibria with a population of non-substance abusers only,
- (b) The endemic equilibrium when the whole population is made up of substance abusers only,

- (c) The equilibrium where non-substance abusers and substance abusers co-exist, herein refereed to as the interior equilibrium point.

(a) Non-substance abusers (only) endemic equilibrium

We set $\pi_1 = \rho = \phi = 0$ and $\pi_0 = 1$, so that there are no substance abusers in the community. Thus, model system (2.3), reduces to

$$\begin{aligned}\frac{dS_n}{dt} &= \Lambda - \frac{\alpha(1-\theta)(1-\eta)\beta S_n I_n}{N_n} - \mu S_n, \\ \frac{dI_n}{dt} &= \frac{\alpha(1-\theta)(1-\eta)\beta S_n I_n}{N_n} - \mu I_n.\end{aligned}\tag{2.26}$$

For system (2.26), it can be shown that the region

$$\mathcal{G}_n = \left\{ (S_n(t), I_n(t)) \in \mathbb{R}_+^2 : N_n(t) \leq \frac{\Lambda}{\mu} \right\},\tag{2.27}$$

is invariant and attracting. Thus, the dynamics of non-substance abusing (only) adolescents would be considered in $\mathcal{G}_n$.

At the endemic equilibrium point, we have

$$\begin{aligned}0 &= \Lambda - \frac{\alpha(1-\theta)(1-\eta)\beta S_n^* I_n^*}{N_n^*} - \mu S_n^*, \\ 0 &= \frac{\alpha(1-\theta)(1-\eta)\beta S_n^* I_n^*}{N_n^*} - \mu I_n^*.\end{aligned}\tag{2.28}$$

Let $\mathcal{E}_n^*$ denote the endemic equilibrium solution for model system (2.26). Summing the two equations in model system (2.26) above, we get

$$\frac{dN_n(t)}{dt} = \Lambda - \mu N_n(t)$$

so that, $N_n(t) \rightarrow \frac{\Lambda}{\mu} = N_n^*$ as $t \rightarrow \infty$. Furthermore, from the second equation of the two equations in (2.28), we let $I_n^* = 0$ or

$$\begin{aligned} 0 = \frac{\alpha(1-\theta)(1-\eta)\beta S_n^*}{N_n^*} - \mu &\Rightarrow \alpha(1-\theta)(1-\eta)\beta S_n^* = \mu N_n^* \\ &\Rightarrow S_n^* = \frac{\Lambda}{\mu R_n}, \end{aligned} \quad (2.29)$$

with R_n defined in (2.15).

Since $N_n^* = S_n^* + I_n^*$, hence $I_n^* = N_n^* - S_n^*$, thus

$$\begin{aligned} I_n^* &= \frac{\Lambda}{\mu} - \frac{\Lambda}{\mu R_n} \\ &= (R_n - 1)S_n^*. \end{aligned} \quad (2.30)$$

Thus, system (2.26) has an endemic equilibrium $\mathcal{E}_n^* = (S_n^*, I_n^*)$ which makes biological sense only when $R_n > 1$. This leads to Theorem 2.4 below.

Theorem 2.4. *The substance abuse free endemic equilibrium $\mathcal{E}_n^*$ exists whenever $R_n > 1$.*

The local stability of $\mathcal{E}_n^*$ is determined by the Jacobian evaluated at the point:

$$J(\mathcal{E}_n^*) = \begin{bmatrix} -\left(\frac{\alpha(1-\theta)(1-\eta)\beta I_n^*}{N_n^*} + \mu\right) & \frac{\alpha(1-\theta)(1-\eta)\beta S_n^*}{N_n^*} \\ \frac{\alpha(1-\theta)(1-\eta)\beta I_n^*}{N_n^*} & \frac{\alpha(1-\theta)(1-\eta)\beta S_n^*}{N_n^*} - \mu \end{bmatrix}. \quad (2.31)$$

From (2.28) we note that $\frac{\alpha(1-\theta)(1-\eta)\beta S_n^*}{N_n^*} = \mu$, which is obtained from the second equation of system (2.28) with the right-hand side set equal to zero. Thus, $J(\mathcal{E}_n^*)$ can be written as,

$$J(\mathcal{E}_n^*) = \begin{bmatrix} -\left(\frac{\alpha(1-\theta)(1-\eta)\beta I_n^*}{N_n^*} + \mu\right) & -\mu \\ \frac{\alpha(1-\theta)(1-\eta)\beta I_n^*}{N_n^*} & 0 \end{bmatrix}. \quad (2.32)$$

Hence the characteristic polynomial of the linearised system is given by

$$\Upsilon^2 + \left(\frac{\alpha(1-\theta)(1-\eta)\beta I_n^*}{N_n^*} + \mu\right)\Upsilon + \frac{\alpha(1-\theta)(1-\eta)\mu\beta I_n^*}{N_n^*} = 0, \quad (2.33)$$

$$\Rightarrow \Upsilon_1 = -\mu, \quad \Upsilon_2 = -\alpha(1-\alpha)(1-\eta)(R_n - 1)\frac{\beta I_n^*}{N_n^*}. \quad (2.34)$$

Thus, $\mathcal{E}_n^*$ is locally asymptotically stable for $R_n > 1$. We summarise the result in Theorem 2.5.

Theorem 2.5. *The endemic equilibrium $(\mathcal{E}_n^*)$ of system (2.26) is locally asymptotically stable whenever $R_n > 1$.*

We now study the global stability of system (2.26) using a Lyapunov function. We claim the following result.

Theorem 2.6. *The endemic equilibrium of the HSV-2 only model system (2.26) is globally asymptotically stable in $\mathcal{G}_n$ whenever $R_n > 1$.*

Proof. Consider the Lyapunov function

$$V(S, I) = \left[(S - S^*) + (I - I^*) - (S^* + I^*) \ln \frac{(S + I)}{(S^* + I^*)} \right] + \frac{2\mu(S^* + I^*)}{c\beta I^*} \left(I - I^* - I^* \ln \frac{I}{I^*} \right), \quad (2.35)$$

where $c = \alpha(1-\theta)(1-\eta)$. $V(S, I)$ is defined, continuous and positive definite for $S, I > 0$. It can be shown that the function $V(S, I)$ take the value $V(S, I) = 0$ at the equilibrium $\mathcal{E}_n^*$, and thus, the global minimum of $V(S, I)$ occurs at the endemic equilibrium point $\mathcal{E}_n^*$. Since $\mathcal{E}_n^* = (S_n^*, I_n^*)$ is an endemic equilibrium point of model

system (2.26), we have the following identities

$$\begin{aligned}\Lambda &= \mu(S^* + I^*), \\ \frac{c\beta S^*}{S^* + I^*} &= \mu.\end{aligned}\tag{2.36}$$

Computing the derivative of V along the solutions of model system (2.26), we obtain

$$\begin{aligned}\frac{dV}{dt} &= \frac{(S - S^*) + (I - I^*)}{S + I} \frac{d(S + I)}{dt} + \frac{2\mu(S^* + I^*)(I - I^*)}{c\beta I^* I} \frac{dI}{dt} \\ &= \frac{(S - S^*) + (I - I^*)}{S + I} (\Lambda - \mu(S + I)) + \frac{2\mu(S^* + I^*)(I - I^*)}{c\beta I^* I} \left(\frac{c\beta SI}{S + I} - \mu I \right)\end{aligned}\tag{2.37}$$

Substituting the identities in (2.36) into (2.37), we have

$$\frac{dV}{dt} = \frac{(S - S^*) + (I - I^*)}{S + I} (\mu(S^* + I^*) - \mu(S + I)) + \frac{2\mu(S^* + I^*)(I - I^*)}{\beta I^* I} \left(\frac{\beta SI}{S + I} - \frac{\beta S^* I^*}{S^* + I^*} \right)\tag{2.38}$$

but,

$$\left(\frac{S}{S + I} - \frac{S^*}{S^* + I^*} \right) = \frac{I^*(S - S^*) - S^*(I - I^*)}{(S^* + I^*)(S + I)}\tag{2.39}$$

thus, we now have

$$\begin{aligned}\frac{dV}{dt} &= \frac{(S - S^*) + (I - I^*)}{S + I} (-\mu(S - S^*) - \mu(I - I^*)) \\ &\quad + \frac{2\mu(S^* + I^*)(I - I^*)}{I^*} \left(\frac{I^*(S - S^*) - S^*(I - I^*)}{(S^* + I^*)(S + I)} \right) \\ &= -\mu \frac{(S - S^*)^2}{S + I} - \left(\mu + \frac{2\mu S^*}{I^*} \right) \frac{(I - I^*)^2}{S + I}.\end{aligned}\tag{2.40}$$

$\frac{dV}{dt} < 0$ always holds except at the endemic equilibrium, $\mathcal{E}_n^*$. Furthermore, $V(S, I) \rightarrow \infty$ as $S \rightarrow 0$ or $S \rightarrow \infty$ and $V(S, I) \rightarrow \infty$ as $I \rightarrow 0$ or $I \rightarrow \infty$. Therefore, we

may conclude that the function V is a Lyapunov function for system (2.26) and that, by the Lyapunov asymptotic stability theorem (LaSalle et al., 1961), the endemic equilibrium $\mathcal{E}_n^*$ is globally asymptotically stable in the interior of $\mathcal{G}_n$, when it exists. $\square$

(b) Substance abusers (only) endemic equilibrium

We set $\pi_0 = \rho = \phi = 0$ and $\pi_1 = 1$, so that there are substance abusers only in the community. Thus, model system (2.3), reduces to

$$\begin{aligned}\frac{dS_a}{dt} &= \Lambda - \frac{\alpha(1-\theta)\beta S_a I_a}{N_a} - \mu S_a, \\ \frac{dI_a}{dt} &= \frac{\alpha(1-\theta)\beta S_a I_a}{N_a} - \mu I_a.\end{aligned}\tag{2.41}$$

For system (2.41), it can be shown that the region

$$\mathcal{G}_a = \left\{ (S_a(t), I_a(t)) \in \mathbb{R}_+^2 : N_a \leq \frac{\Lambda}{\mu} \right\},\tag{2.42}$$

is invariant and attracting. Thus, the dynamics of substance abusing (only) adolescents would be considered in $\mathcal{G}_a$.

Using the similar analysis as for the non-substance abusers only adolescents case, it can be easily shown that the endemic equilibrium is

$$\mathcal{E}_a^* = \left\{ S_a^* = \frac{\Lambda}{\mu R_a}, I_a^* = (R_a - 1)S_a^* \right\},\tag{2.43}$$

with R_a as defined in (2.16), it follows that the endemic equilibrium $\mathcal{E}_a^*$ makes biological sense whenever $R_a > 1$. Furthermore, using the analysis done for the non-substance abusers only adolescents case, the stability of $\mathcal{E}_a^*$ can be established. We now discuss the co-existence of non-substance abusers and substance abusers in the community.

(c) Interior endemic equilibrium

This endemic equilibrium refers to the case where both, the non-substance abusers and the substance abusers co-exist. This state is denoted by $\mathcal{E}_{na}^*$, with

$$\mathcal{E}_{na}^* = \begin{cases} S_n^* = \frac{\pi_0 \Lambda + \phi S_a^*}{\alpha(1-\theta)\lambda_{na}^* + \mu + \rho}, \\ S_a^* = \frac{\pi_1 \Lambda + \rho S_n^*}{(1-\theta)\lambda_{na}^* + \mu + v + \phi}, \\ I_n^* = \frac{\alpha(1-\theta)\lambda_{na}^* S_n^* + \phi I_a^*}{\mu + \rho}, \\ I_a^* = \frac{(1-\theta)\lambda_{na}^* S_a^* + \rho I_n^*}{\mu + v + \phi}, \text{ with } \lambda_{na}^* = \frac{\beta(I_a^* + (1-\eta)I_n^*)}{N^*}. \end{cases}$$

We now study the global stability of the interior equilibrium of model system (2.3). The permanence of the disease destabilises the disease-free equilibrium $\mathcal{E}^0$ since $R_{na} > 1$, thus, the equilibrium $\mathcal{E}_{na}^*$ exists.

Theorem 2.7. *If $R_{na} > 1$, then model system (2.3) admits at least one positive endemic equilibrium, and there is a positive constant ϵ such that every solution $(S_n(t), S_a(t), I_n(t), I_a(t))$ of model system (2.3) with $(S_n(0), S_a(0), I_n(0), I_a(0)) \in X_0$ satisfies*

$$\min \left\{ \liminf_{t \rightarrow \infty} I_n, \liminf_{t \rightarrow \infty} I_a \right\} \geq \epsilon,$$

meaning model system (2.3) is uniformly persistent.

Proof. Now we prove that model system (2.3) is uniformly persistent with respect to $(X_0, \partial X_0)$. For ease of notation, we still use the notation $\mathcal{E}^0$ to denote the disease free equilibrium of model system (2.3).

Define

$$X = \left\{ (S_n, S_a, I_n, I_a) \mid S_n \geq 0, S_a \geq 0, I_n \geq 0, I_a \geq 0 \right\},$$

$$X_0 = \left\{ (S_n, S_a, I_n, I_a) \in X \mid S_n \geq 0, S_a \geq 0, I_n > 0, I_a > 0 \right\},$$

$$\partial X_0 = X \setminus X_0.$$

Following model system (2.3), it can be shown that X and X_0 are positively invariant and ∂X_0 is relatively closed in X . Furthermore, model system (2.3) is point dissipative. Let

$$M_\partial = \{(S_n(0), S_a(0), I_n(0), I_a(0)) \mid (S_n(t), S_a(t), I_n(t), I_a(t)) \in \partial X_0, \forall t \geq 0\}.$$

We now show that

$$M_\partial = \{(S_n(t), S_a(t), 0, 0) \mid S_n(t), S_a(t) \geq 0\}. \quad (2.44)$$

Noting that $\{(S_n(t), S_a(t), 0, 0) \mid S_n(t), S_a(t) \geq 0\} \subseteq M_\partial$, we only need to prove

$$M_\partial \subseteq \{(S_n(t), S_a(t), 0, 0) \mid S_n(t), S_a(t) \geq 0\}.$$

Assume $(S_n(0), S_a(0), I_n(0), I_a(0)) \in M_\partial$. It is sufficient to show that $I_n(t) = 0$ and $I_a(t) = 0, \forall t \geq 0$. Suppose not, then there exists $t_0 \geq 0$ such that $I_n(t_0) = 0$ and $I_a(t_0) > 0$, from the equation

$$\begin{aligned} \frac{dI_n(t_0)}{dt} &= \frac{\alpha(1-\theta)\beta(I_n(t_0)(1-\eta) + I_a(t_0))}{S_n(t_0) + S_a(t_0) + I_n(t_0) + I_a(t_0)} + \phi I_a(t_0) - (\mu + \rho)I_n(t_0) \\ &\geq \frac{\alpha(1-\theta)\beta I_a(t_0)}{S_n(t_0) + S_a(t_0) + I_a(t_0)} + \phi I_a(t_0). \end{aligned}$$

It follows that there is an $\eta > 0$ such that $I_a(t_0) > 0$, for $t_0 < t < t_0 + \eta$. This means that $(S_n(t), S_a(t), I_n(t), I_a(t))$ does not belong to ∂X_0 for $t_0 < t < t_0 + \eta$, which contradicts the assumption that $(S_n(0), S_a(0), I_n(0), I_a(0)) \in M_\partial$. This proves system

(2.44),

$$M_{\partial} = \{(S_n(t), S_a(t), 0, 0) | S_n(t), S_a(t) \geq 0\}. \quad (2.45)$$

As to $\mathcal{E}^0$ is globally asymptotically stable for model system (2.3). It is clear that there is only an equilibrium $\mathcal{E}^0$ in M_{∂} , by the afore-mentioned claim, it then follows that $\mathcal{E}^0$ is an isolated invariant set in X , $W^s(\mathcal{E}^0) \cap X_0 = \emptyset$. It is worth noting that, every orbit in M_{∂} converges to $\mathcal{E}^0$, where $\mathcal{E}^0$ is acyclic in M_{∂} . Using Theorem 4.6 in Thieme (1993), we conclude that model system (2.3) is uniformly persistent with respect to $(X_0, \partial X_0)$.

By the result in (Zhao, 1995; Wang et al., 2003; Wang, 2004), model system (2.3) has an equilibrium $(S_n^*, S_a^*, I_n^*, I_a^*) \in X_0$. We further claim that $S_n^* > 0$ and $S_a^* > 0$. Suppose that $S_n^* = 0$ and $S_a^* = 0$, then from model system (2.3), we can get $I_a = 0$ and $I_n = 0$ hence a contradiction. Then $(S_n^*, S_a^*, I_n^*, I_a^*)$ is a componentwise positive equilibrium of model system (2.3). This completes the proof.

□

From the epidemiological point of view, this result means that the disease persists at endemic state, which is not good news from the public health viewpoint. We then now explore the global stability of the endemic equilibrium for the case $R_{na} > 1$.

Global stability of the interior endemic equilibrium point

It is helpful to rescale model system (2.3) so that we have dimensionless variables. We let

$$S_1 = \frac{S_a}{N}, \quad S_2 = \frac{S_n}{N}, \quad I_1 = \frac{I_n}{N}, \quad I_2 = \frac{I_a}{N}, \quad \beta_1 = (1 - \eta)\beta, \quad \beta_2 = \beta. \quad (2.46)$$

We now denote the total population with $N = S_1 + S_2 + I_1 + I_2$, and our new model

takes the form

$$\begin{aligned}
\frac{dS_1}{dt} &= b_1 - \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j S_1 + \phi S_2 - (\mu + \rho) S_1, \\
\frac{dS_2}{dt} &= b_2 - (1 - \theta) \sum_{j=1}^2 \beta_j I_j S_2 + \rho S_1 - (\mu + v + \phi) S_2, \\
\frac{dI_1}{dt} &= \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j S_1 + \phi I_2 - (\mu + \rho) I_1, \\
\frac{dI_2}{dt} &= (1 - \theta) \sum_{j=1}^2 \beta_j I_j S_2 + \rho I_1 - (\mu + v + \phi) I_2.
\end{aligned} \tag{2.47}$$

Set

$$V = \left\{ S_1^* g\left(\frac{S_1}{S_1^*}\right) + I_1^* g\left(\frac{I_1}{I_1^*}\right) \right\} + \left\{ a_1 S_2^* g\left(\frac{S_2}{S_2^*}\right) + a_2 I_2^* g\left(\frac{I_2}{I_2^*}\right) \right\} \tag{2.48}$$

where $g(x) = x - 1 - \ln x \geq g(1) = 0$, for any $x > 0$. The positive constants a_1 and a_2 will be appropriately chosen later.

Differentiating V , we have

$$\frac{dV}{dt} = \left(1 - \frac{S_1^*}{S_1}\right) \frac{dS_1}{dt} + \left(1 - \frac{S_2^*}{S_2}\right) \frac{dS_2}{dt} + a_1 \left(1 - \frac{I_1^*}{I_1}\right) \frac{dI_1}{dt} + a_2 \left(1 - \frac{I_2^*}{I_2}\right) \frac{dI_2}{dt} \tag{2.49}$$

At the endemic equilibrium point, system (2.47) has the following identities

$$\begin{aligned}
b_1 &= \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^* - \phi S_2^* + (\mu + \rho) S_1^*, \\
b_2 &= (1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_2^* - \rho S_1^* + (\mu + v + \phi) S_2^*, \\
(\mu + \rho) I_1^* &= \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^* + \phi I_2^*, \\
(\mu + v + \phi) I_2^* &= (1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_2^* + \rho I_1^*, \quad j = 1, 2,
\end{aligned} \tag{2.50}$$

and we let $x_j = \frac{S_j}{S_j^*}$, $y_j = \frac{I_j}{I_j^*}$, $j = 1, 2$.

From the first equation of system (2.47) and the identities in (2.50) we have

$$\begin{aligned}
\frac{dS_1}{dt} &= b_1 - \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j S_1 + \phi S_2 - (\mu + \rho) S_1 \\
&= \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^* - \phi S_2^* + (\mu + \rho) S_1^* - \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j S_1 + \phi S_2 - (\mu + \rho) S_1 \\
&= -(\mu + \rho)(S_1 - S_1^*) - \left[\alpha(1 - \theta) \sum_{j=1}^2 (I_j S_1 - I_j S_1^*) - \phi(S_2 - S_2^*) \right] \\
&= -(\mu + \rho) S_1^* (x_1 - 1) - \left[\alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^* (x_1 y_j - 1) - \phi S_2^* (x_2 - 1) \right], \\
&\quad j = 1, 2.
\end{aligned} \tag{2.51}$$

From the second equation of system (2.47) and the identities in (2.50) we have

$$\begin{aligned}
\frac{dS_2}{dt} &= b_2 - (1 - \theta) \sum_{j=1}^2 \beta_j I_j S_2 + \rho S_1 - (\mu + v + \phi) S_2 \\
&= (1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_2^* - \rho S_1^* + (\mu + v + \phi) S_2^* \\
&\quad - (1 - \theta) \sum_{j=1}^2 \beta_j I_j S_2 + \rho S_1 - (\mu + v + \phi) S_2 \\
&= -(\mu + v + \phi)(S_2 - S_2^*) - \left[\sum_{j=1}^2 (1 - \theta) \beta_j (I_j S_2 - I_j^* S_2^*) - \rho(S_1 - S_1^*) \right] \\
&= -(\mu + v + \phi) S_2^* (x_2 - 1) - \left[\sum_{j=1}^2 (1 - \theta) \beta_j I_j^* S_2^* (x_2 y_j - 1) - \rho S_1^* (x_1 - 1) \right], \\
&\quad j = 1, 2.
\end{aligned} \tag{2.52}$$

From the third equation of system (2.47) and the identities in (2.50) we have

$$\begin{aligned}
\frac{dI_1}{dt} &= \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j S_1 + \phi I_2 - (\mu + \rho) I_1 \\
&= \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^* x_1 y_j + \phi I_2^* y_2 - (\mu + \rho) I_1^* y_1 \\
&= \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^* x_1 y_j + \phi I_2^* y_2 - y_1 \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^* - \phi y_1 I_2^* \\
&= \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^* (x_1 y_j - y_1) + \phi I_2^* (y_2 - y_1), \\
j &= 1, 2.
\end{aligned} \tag{2.53}$$

From the fourth equation of system (2.47) and the identities in (2.50) we have

$$\begin{aligned}
\frac{dI_2}{dt} &= (1 - \theta) \sum_{j=1}^2 \beta_j I_j S_2 + \rho I_1 - (\mu + v + \phi) I_2, \\
&= (1 - \theta) \sum_{j=1}^2 \beta_j I_j S_2 x_2 y_j + \rho I_1 y_1 - (\mu + v + \phi) I_2 y_2, \\
&= (1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_2^* x_2 y_j + \rho I_1^* y_1 - (1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_2^* y_2 - \rho I_1^* y_2, \\
&= (1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_2^* (x_2 y_j - y_2) + \rho I_1^* (y_1 - y_2), \\
j &= 1, 2.
\end{aligned} \tag{2.54}$$

Then,

$$\begin{aligned}
\frac{dV}{dt} = & \left(1 - \frac{1}{x_1}\right) \left\{ -(\mu + \rho)S_1^*(x_1 - 1) - \left[\alpha(1 - \theta) \sum_{j=1}^2 (x_1 y_j - 1) - \phi S_2^*(x_2 - 1) \right] \right\} \\
& + a_1 \left(1 - \frac{1}{x_2}\right) \left\{ -(\mu + v + \phi)S_2^*(x_2 - 1) \right. \\
& \left. - \left[\sum_{j=1}^2 (1 - \theta) \beta_j I_j^* S_2^*(x_2 y_j - 1) - \rho S_1^*(x_1 - 1) \right] \right\} \\
& + \left(1 - \frac{1}{y_1}\right) \left\{ \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^*(y_j x_1 - y_1) + \phi I_2^*(y_2 - y_1) \right\} \\
& + a_2 \left(1 - \frac{1}{y_2}\right) \left\{ (1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_2^*(y_j x_2 - y_2) + \rho I_1^*(y_1 - y_2) \right\} \quad (2.55)
\end{aligned}$$

$$\begin{aligned}
= & -(\mu + \rho)S_1^* \left(1 - \frac{1}{x_1}\right) (x_1 - 1) - \alpha(1 - \theta) \sum_{j=1}^2 \beta_j (x_1 y_j - 1) \left(1 - \frac{1}{x_1}\right) \\
& + \phi S_2^*(x_2 - 1) \left(1 - \frac{1}{x_1}\right) + \phi I_2^*(y_2 - y_1) \left(1 - \frac{1}{y_1}\right) \\
& + a_1 \rho S_1^*(x_1 - 1) \left(1 - \frac{1}{x_2}\right) + \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^*(x_1 y_j - y_1) \left(1 - \frac{1}{y_1}\right) \\
& - a_1 (\mu + v + \phi) S_2^*(x_2 - 1) \left(1 - \frac{1}{x_2}\right) - a_1 (1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_2^*(x_2 y_j - 1) \left(1 - \frac{1}{x_2}\right) \\
& + a_2 (1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_2^*(x_2 y_j - y_2) \left(1 - \frac{1}{y_2}\right) + a_2 \rho I_1^*(y_1 - y_2) \left(1 - \frac{1}{y_2}\right) \quad (2.56)
\end{aligned}$$

$$\begin{aligned}
&= -\left[(\mu + \rho)S_1^*(1 - x_1)\left(1 - \frac{1}{x_1}\right) - \phi S_2^*(x_2 - 1)\left(1 - \frac{1}{x_1}\right)\right] \\
&\quad + \phi I_2^*(y_2 - y_1)\left(1 - \frac{1}{y_1}\right) + a_2 \rho I_1^*(y_1 - y_2)\left(1 - \frac{1}{y_2}\right) \\
&\quad + \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_1^* \left\{ \left(1 - x_1 y_j\right)\left(1 - \frac{1}{x_1}\right) + \left(x_1 y_j - y_1\right)\left(1 - \frac{1}{y_1}\right) \right\} \\
&\quad - a_1 \left[(\mu + v + \phi) S_2^*(x_2 - 1)\left(1 - \frac{1}{x_2}\right) - \rho S_1^*(x_1 - 1)\left(1 - \frac{1}{x_2}\right) \right] \\
&\quad + (1 - \theta) \sum_{j=1}^2 \beta_j I_j^* S_2^* \left\{ a_1 (1 - x_2 y_j)\left(1 - \frac{1}{x_2}\right) + a_2 (x_2 y_j - y_2)\left(1 - \frac{1}{y_2}\right) \right\}, \\
&\quad j = 1, 2.
\end{aligned} \tag{2.57}$$

Considering the first part without the constants (a_1 and a_2) in (2.57), we have

$$\begin{aligned}
(x_1 - 1)\left(1 - \frac{1}{x_1}\right) &= -2 + \frac{1}{x_1} + x_1 = g(x_1) + g\left(\frac{1}{x_1}\right), \\
(x_2 - 1)\left(1 - \frac{1}{x_1}\right) &= x_2 - \frac{x_2}{x_1} + \frac{1}{x_1} - 1 = g(x_2) - g\left(\frac{x_2}{x_1}\right) + g\left(\frac{1}{x_1}\right), \\
(y_2 - y_1)\left(1 - \frac{1}{y_1}\right) &= y_2 - \frac{y_2}{y_1} - y_1 + 1 = -g\left(\frac{y_2}{y_1}\right) + g(y_2) - g(y_1), \\
(1 - x_1 y_j)\left(1 - \frac{1}{x_1}\right) + (x_1 y_j - y_1)\left(1 - \frac{1}{y_1}\right) &= 2 - \frac{1}{x_1} + y_j - \frac{x_1 y_j}{y_1} - y_1 \\
&= -g\left(\frac{1}{x_1}\right) - g\left(\frac{x_1 y_j}{y_1}\right) + g(y_j) - g(y_1).
\end{aligned} \tag{2.58}$$

Considering the second part with the constants (a_1 and a_2) in (2.57), we have

$$\begin{aligned}
(x_2 - 1) \left(1 - \frac{1}{x_2}\right) &= 2 - \frac{1}{x_2} + x_2 = g(x_2) + g\left(\frac{1}{x_2}\right), \\
(x_1 - 1) \left(1 - \frac{1}{x_2}\right) &= x_1 - \frac{x_1}{x_2} + \frac{1}{x_2} - 1 = g(x_1) - g\left(\frac{x_1}{x_2}\right) + g\left(\frac{1}{x_2}\right), \\
(y_1 - y_2) \left(1 - \frac{1}{y_2}\right) &= y_1 - \frac{y_1}{y_2} - y_2 + 1 = -g\left(\frac{y_1}{y_2}\right) + g(y_1) - g(y_2), \\
(1 - x_2 y_j) \left(1 - \frac{1}{x_2}\right) &+ (x_2 y_j - y_2) \left(1 - \frac{1}{y_2}\right) \\
&= \left(1 - \frac{1}{x_2} - x_2 y_j + y_j\right) + \left(1 - x_2 y_j - y_2 - \frac{x_2 y_j}{y_2}\right) \\
&= -\left\{g\left(\frac{1}{x_2}\right) + g(x_2 y_j) - g(y_j)\right\} + \left\{g\left(\frac{x_2 y_j}{y_2}\right) + g(x_2 y_j) + g(y_2)\right\}.
\end{aligned} \tag{2.59}$$

Then, substituting our functions we got from (2.58) and (2.59) into (2.57), we have

$$\begin{aligned}
\frac{dV}{dt} &= -\left[(\mu + \rho)S_1^* \left\{g(x_1) + g\left(\frac{1}{x_1}\right)\right\} + \phi S_2^* \left\{g\left(\frac{x_2}{x_1}\right) - g(x_2) - g\left(\frac{1}{x_1}\right)\right\}\right] \\
&\quad - \phi I_2^* \left\{g\left(\frac{y_2}{y_1}\right) + g(y_1) - g(y_2)\right\} - a_2 \rho I_1^* \left\{g\left(\frac{y_1}{y_2}\right) + g(y_2) - g(y_1)\right\} \\
&\quad - \alpha(1 - \theta) \sum_{j=1}^2 \beta_j I_j S_1^* \left\{g\left(\frac{1}{x_1}\right) + g(x_1 y_j) - g(y_j) + g\left(\frac{x_1 y_j}{y_1}\right) + g(y_1) - g(x_1 y_j)\right\} \\
&\quad - a_1 \left[(\mu + v + \phi)S_2^* \left\{g(x_2) + g\left(\frac{1}{x_2}\right)\right\} + \rho S_1^* \left\{g\left(\frac{x_1}{x_2}\right) - g(x_1) - g\left(\frac{1}{x_2}\right)\right\}\right] \\
&\quad - (1 - \theta) \sum_{j=1}^2 \beta_j I_j S_2^* \left[a_1 \left\{g\left(\frac{1}{x_2}\right) + g(x_2 y_j) - g(y_j)\right\} + a_2 \left\{g\left(\frac{x_2 y_j}{y_2}\right) + g(y_2) - g(x_2 y_j)\right\}\right].
\end{aligned} \tag{2.60}$$

Since $\alpha, \theta \in (0, 1)$, are being multiplied with β throughout and they do not con-

tribute in the stability of our endemic equilibrium point, we then assume that, $\alpha = 1$ and $\theta = 0$. Thus

$$\begin{aligned}
\frac{dV}{dt} = & -\{(\mu + \rho) + \beta_1 I_1^* - a_1 \rho\} S_1^* g(x_1) - \{a_1(\mu + v + \phi) + a_2 \beta_2 I_2^* - \phi\} S_2^* g(x_2) \\
& - (a_1 - a_2) \beta_1 S_2^* I_1^* g(x_2 y_1) - (a_1 - a_2) \beta_2 S_2^* I_2^* g(x_2 y_2) \\
& - \{(\beta_2 S_1^* + \phi) I_2^* - (a_1 \beta_1 S_2^* + a_2 \rho) I_1^*\} g(y_1) \\
& + [(a_1 - a_2) S_2^* (\beta_1 I_1^* + \beta_2 I_2^*) + (\beta_2 S_1^* + \phi) I_2^* - (a_1 \beta_1 S_2^* + a_2 \rho) I_1^*] g(y_2) \\
& - [\{(\mu + \rho) + (\beta_1 I_1^* + \beta_2 I_2^*)\} S_1^* - \phi S_2^*] g\left(\frac{1}{x_1}\right) \\
& - a_1 [\{(\mu + v + \phi) + (\beta_1 I_1^* + \beta_2 I_2^*)\} S_2^* - \rho S_1^*] g\left(\frac{1}{x_2}\right) \\
& - \left\{ \phi S_2^* g\left(\frac{x_2}{x_1}\right) + a_1 \rho S_1^* g\left(\frac{x_1}{x_2}\right) \right\} - \left\{ \beta_2 I_2^* S_1^* g\left(\frac{x_1 y_2}{y_1}\right) + \phi I_2^* g\left(\frac{y_2}{y_1}\right) \right\} \\
& - a_2 \left\{ \beta_1 S_2^* I_1^* g\left(\frac{x_2 y_1}{y_2}\right) + \rho I_1^* g\left(\frac{y_1}{y_2}\right) \right\}. \tag{2.61}
\end{aligned}$$

Using the identities in (2.50) we have that

$$\begin{aligned}
& -[\{(\mu + \rho) + (\beta_1 I_1^* + \beta_2 I_2^*)\} S_1^* - \phi S_2^*] g\left(\frac{1}{x_1}\right) \\
& -a_1[\{(\mu + v + \phi) + (\beta_1 I_1^* + \beta_2 I_2^*)\} S_2^* - \rho S_1^*] g\left(\frac{1}{x_2}\right) \\
& = -b_1 g\left(\frac{1}{x_1}\right) - a_1 b_2 g\left(\frac{1}{x_2}\right) \leq 0.
\end{aligned} \tag{2.62}$$

Moreover,

$$\begin{aligned}
& - \left\{ \phi S_2^* g\left(\frac{x_2}{x_1}\right) + a_1 \rho S_1^* g\left(\frac{x_1}{x_2}\right) \right\} - \left\{ \beta_2 I_2^* S_1^* g\left(\frac{x_1 y_2}{y_1}\right) + \phi I_2^* g\left(\frac{y_2}{y_1}\right) \right\} \\
& - a_2 \left\{ \beta_1 S_2^* I_1^* g\left(\frac{x_2 y_1}{y_2}\right) + \rho I_1^* g\left(\frac{y_1}{y_2}\right) \right\} \leq 0.
\end{aligned} \tag{2.63}$$

Thus,

$$\begin{aligned}
\frac{dV}{dt} & \leq -\{(\mu + \rho) + \beta_1 I_1^* - a_1 \rho\} S_1^* g(x_1) - \{a_1(\mu + v + \phi) + a_2 \beta_2 I_2^* - \phi\} S_2^* g(x_2) \\
& - (a_1 - a_2) \beta_1 S_2^* I_1^* g(x_2 y_1) - (a_1 - a_2) \beta_2 S_2^* I_2^* g(x_2 y_2) \\
& - \{(\beta_2 S_1^* + \phi) I_2^* - (a_1 \beta_1 S_2^* + a_2 \rho) I_1^*\} g(y_1) \\
& + [(a_1 - a_2) S_2^* (\beta_1 I_1^* + \beta_2 I_2^*) + (\beta_2 S_1^* + \phi) I_2^* - (a_1 \beta_1 S_2^* + a_2 \rho) I_1^*] g(y_2). \tag{2.64}
\end{aligned}$$

Lemma 2.1. *For system (2.47), assume $R_{na} > 1$ and consider a Lyapunov function*

(2.48) such that the positive constants a_1 and a_2 satisfy the following condition

$$\frac{\phi}{(\mu + v + \phi) + \beta_2 I_2^*} \leq a_1 = a_2 = \frac{(\beta_2 S_1^* + \phi) I_2^*}{(\beta_1 S_2^* + \rho) I_1^*} \leq \frac{(\mu + \rho) + \beta_1 I_1^*}{\rho}, \quad (2.65)$$

where

$$\frac{(\beta_2 S_1^* + \phi) I_2^*}{(\beta_1 S_2^* + \rho) I_1^*} = \frac{(\mu + \rho) - \beta_1 S_1^*}{\beta_1 S_2^* + \rho} = \frac{(\beta_2 S_1^* + \phi)}{(\mu + v + \phi) - \beta_2 S_2^*}, \quad (2.66)$$

Then, $\frac{dV}{dt} \leq 0$.

Proof. For system (2.47), assume $R_{na} > 1$ and consider a Lyapunov function (2.48) such that the constants a_1 and a_2 are positive and satisfy the following conditions that

$$(a_1 - a_2)\beta_1 = 0, \quad (a_1 - a_2)\beta_2 = 0, \quad (\beta_2 S_1 + \phi)I_2^* - (a_1\beta_1 S_2^* + a_2\rho)I_1^* = 0, \quad (2.67)$$

$$(\mu + \rho) + \beta_1 I_1^* - a_1 \rho \geq 0, \quad a_1(\mu + v + \phi) + a_2 \beta_2 I_2^* - \phi \geq 0,$$

then by (2.65) and the conditions in (2.67), we have that $\frac{dV}{dt} \leq 0$. Moreover, by (2.50), we can see that (2.66) holds and (2.67) is equivalent to (2.65). $\square$

Theorem 2.8. For system (2.47), if $R_{na} > 1$ and (2.65) holds, then the endemic equilibrium $\mathcal{E}^*$ is globally asymptotically stable in $\mathcal{G}$.

Proof. By Lemma (2.66), we obtain that $\frac{dV}{dt} \leq 0$ for the Lyapunov function (2.48) with (2.65). Moreover, $\frac{dV}{dt} = 0$ holds if and only if

$$x_j = 1, \quad y_j = y_k, \quad \text{for any } t > 0, \quad j = 1, 2 \text{ and } k = 1, 2. \quad (2.68)$$

Then, there exists a positive constant c such that

$$\frac{I_j(t)}{I_j^*} = c, \quad \text{for any } t > 0, \quad j = 1, 2. \quad (2.69)$$

Thus, substituting $S_j(t) = S_j^*$ and $I_j(t) = cI_j^*$ for any $t > 0$, $j = 1, 2$, into the first 2

equations of system (2.47) we obtain that

$$\begin{aligned}\frac{dS_1}{dt} &= b_1 - \alpha(1 - \theta)c \sum_{j=1}^2 \beta_j I_j^* S_1^* + \phi S_2^* - (\mu + \rho) S_1^*, \\ \frac{dS_2}{dt} &= b_2 - (1 - \theta)c \sum_{j=1}^2 \beta_j I_j^* S_2^* + \rho S_1^* - (\mu + v + \phi) S_2^*.\end{aligned}\tag{2.70}$$

Since the right hand side of (2.70) is strictly decreasing in c , thus it only holds at the point $c = 1$, namely at $\mathcal{E}_{na}^*$. Therefore, the only compact invariant subset where $\frac{dV}{dt} = 0$ is the singleton $\{\mathcal{E}_{na}^*\}$. By proposition 3.1 in Muroya et al. (2012), $\mathcal{E}_{na}^*$ is globally asymptotically stable in $\mathcal{G}$, if $R_{na} > 1$. Hence, the proof for this Theorem is complete.

□

2.4. Numerical results

In order to illustrate the results of the foregoing analysis, we have simulated model system (2.3) using the parameters in Table 2.1. Unfortunately, the scarcity of the data on HSV-2 and substance abuse correlation with a focus on adolescents limits our ability to calibrate. Nevertheless, we assume some of the parameters in the realistic range for illustrative purpose. These parsimonious assumptions reflect the lack of information currently available on HSV-2 and substance abuse with a focus on adolescents. Reliable data on the risk of transmission of HSV-2 among adolescents would enhance our understanding and aid in the possible intervention strategies to be implemented.

- (i) We set the recruitment rate $\Lambda = 10000$ per year and this value was adopted from the work of Podder and Gumel (2009).
- (ii) The average life expectancy in the sub-Saharan Africa is around 50 years

(Bhunu and Mushayabasa, 2011; Jamison et al., 2006) and thus $\mu = 1/50 = 0.02$ per year.

- (iii) Our sexual contact rate c , on adolescents is assumed to have a range of 0.3-0.4 per annum based on a research done by the CDC (2015) in the USA. These estimates were further supported by the CDC report of 2014 focusing on the USA adolescents and young adults, in which a programme known as The Youth Risk Behaviour Surveillance System (YRBSS) was executed (Kann et al., 2014).
- (iv) In this section we adopt the HSV-2 transmission probability p , of 0.01 per sex act when averaged over both sexes and all infection states (including latent periods) from several studies (Mertz et al., 1988; Bryson et al., 1993; Corey et al., 2004; Wald et al., 2001).
- (v) We used the substance abuse induced death rate, $v = 0.035$ per year, based on a research by Mokdad et al. (2004), which was meant to identify and quantify the leading causes of mortality in the USA.
- (vi) Proportions of the recruited individuals π_0 and π_1 , are derived from the Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Episode Data Set (TEDS), (2011), prepared by the Centre for behavioural health statistics and quality, focusing on the adolescents. In this report, it was observed that among the adolescents aged 12 to 14 years, 15 to 17 years and those above 18 years were initiated at a rate of 29.7%, 34.1% and 23.4% respectively. Thus we estimated our fraction of the recruitment of substance abusing adolescents by averaging the three rates $(29.7\% + 34.1\% + 23.4\%)/3 = 29.1\%$. We then took our point estimate as 30% per year. Our estimate is also supported by some previous research by Ayatollahi et al., (2005).
- (vii) We assumed the condom use efficacy for HSV-2 θ , to be around 50%. Comparing groups using condoms in $< 25\%$ of sex acts with those using condoms in $> 75\%$, produced an estimated reduction in risk of HSV-2 of 45% in one study

(Wald et al., 2005). Observing and comparing with some other studies, we took the now standard condom use efficacy estimate for HSV-2 which is 50% per year (Wald et al., 2001; Martins et al., 2009).

Definition	Symbol	B^* (Range)	Source
Recruitment rate	Λ	10000yr^{-1}	(Podder and Gumel, 2009)
Proportion of recruited individuals	π_0, π_1	0.7, 0.3	Assumed
Natural death rate	μ	$0.02(0.015-0.02)\text{yr}^{-1}$	(Bhunu and Mushayabasa, 2011)
Contact rate	c	0.3	(CDC, 2015)
HSV-2 transmission probability	p	$0.01(0.001-0.03)\text{yr}^{-1}$	(Mertz et al., 1988 Bryson et al., 1993 Corey et al., 2004 Wald et al., 2001)
Substance abuse induced death rate	v	0.035yr^{-1}	(Mokdad et al., 2004)
Rate of change in substance abuse habit	ρ, ϕ	variable	Assumed
Condom use efficacy	θ	0.5	(Wald et al., 2001 Martin et al., 2009)
Modification parameter	η	0.6(0-1)	Assumed
Modification parameter	α	0.4(0-1)	Assumed

Table 2.1: Model parameters and their interpretations (B^* represents the Baseline values.)

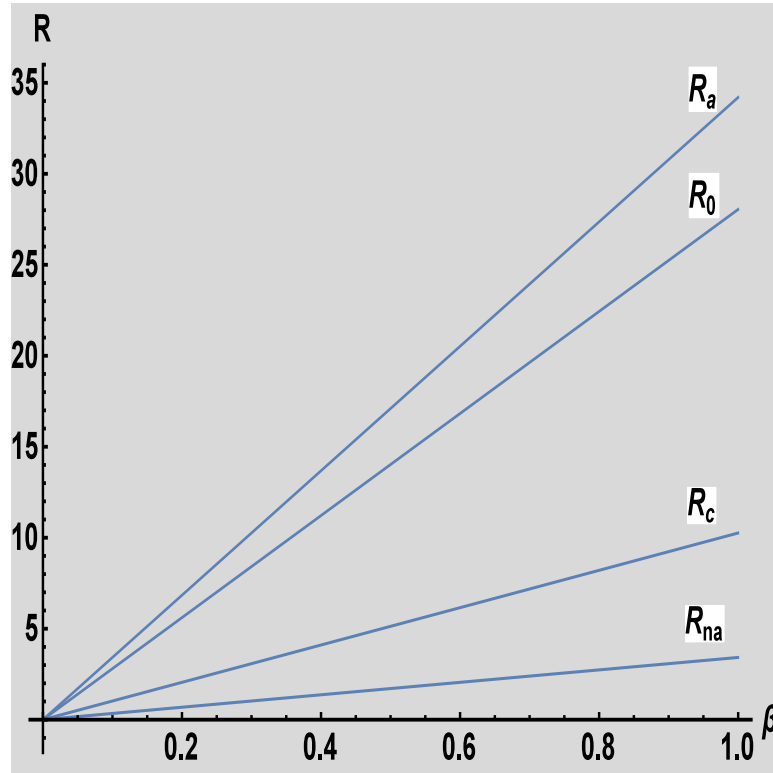


Figure 2.2: Effects of varying the effective contact rate (β) on the reproduction numbers. R represents the Reproduction number.

R_j	R_a	R_0	R_c	R_{na}
K_j	34.2β	27.7β	10.26β	3.5β

Table 2.2: The linear dependence of the reproduction number R_j on the constant rate β , for $j = 0, a, c, na$.

Figure 2.2 shows the effects of varying the effective contact rate on the reproduction number. The results demonstrate that an increase or the existence of substance abusers may increase the reproduction number. Figure 2.2 also shows that, in a population that consists of non-substance abusers and substance abusers adolescents, condom use remains a vital preventive measure in reducing the reproduction number. Further analysis of Figure 2.2 reveals that the combined use of condoms and educational campaigns as HSV-2 intervention strategies among substance abusing adolescents in a community, have an impact on reducing the magnitude of HSV-2 cases, as shown by the lowest graph for R_{na} .

Table (2.2) outlines the numerical values of the relationship of the linear equation $R_j = K_j\beta$, for $j = 0, a, c, ac$ with respect to each reproductive number plotted in Figure 2.2. From the equation $R_j = K_j\beta$, R_j represents the respective reproduction number, K_j is the respective constant of proportionality (gradient of each respective straight line graph) and β being the effective contact rate.

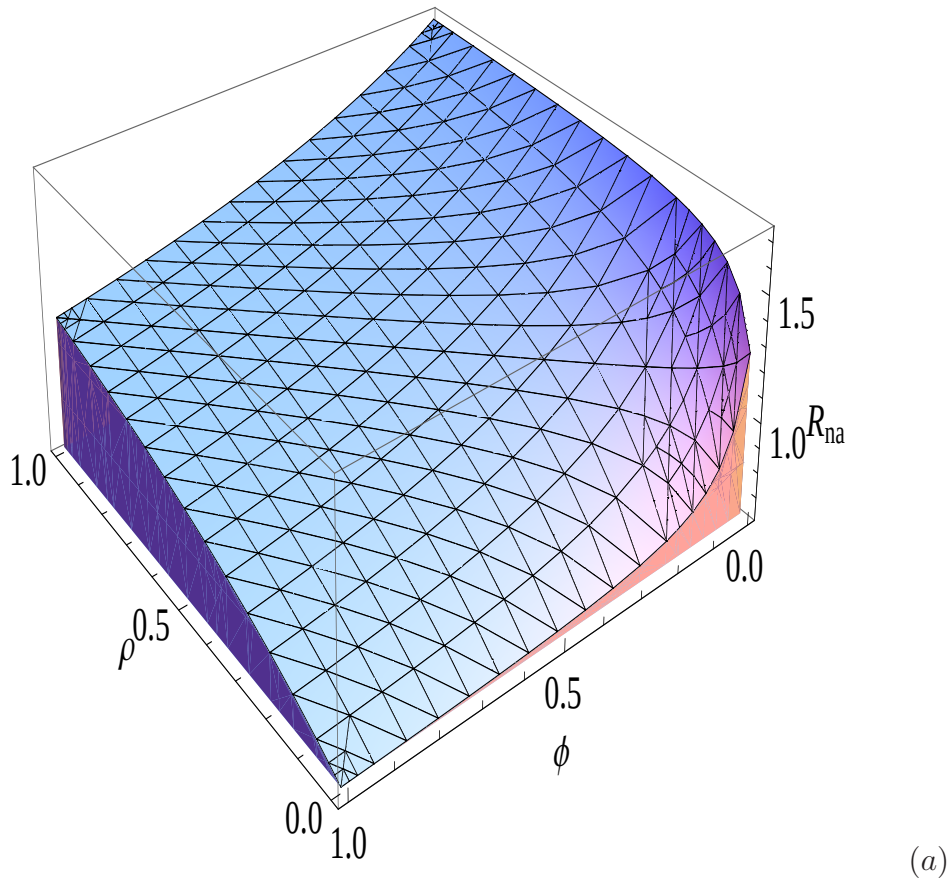


Figure 2.3: The relationship between the reproduction number (R_{na}), rate of becoming a substance abuser (ρ), and rate of quitting substance abuse (ϕ).

Figure 2.3 demonstrate that the reduction on the rate of non-substance abusers to become substance abusers has an influence on the reproductive number. Thus, intervention strategies aimed at minimising the rate of non-substance abusers on becoming substance abusers could be useful on controlling the spread of HSV-2.

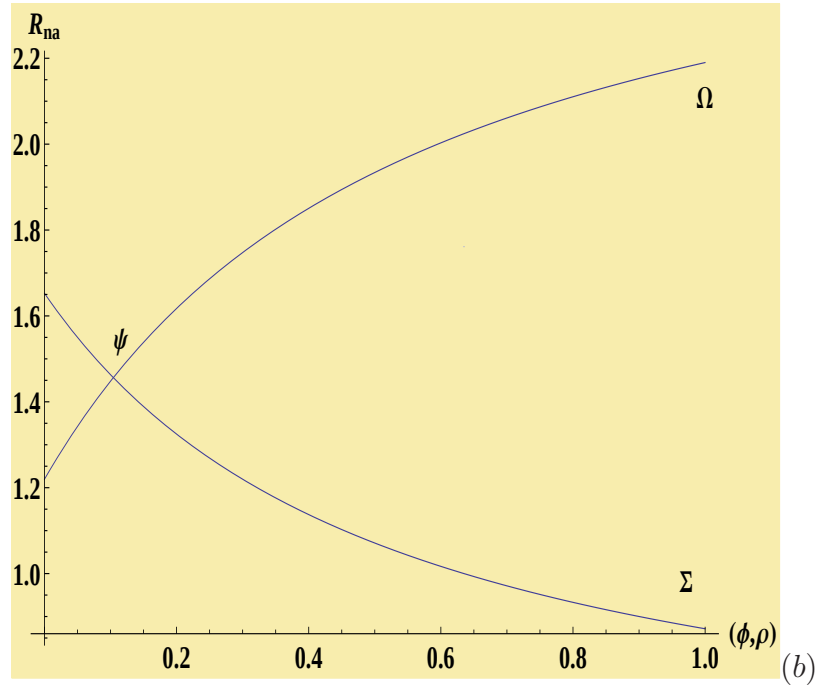


Figure 2.4: Numerical results of model system (2.3) showing the effect in the change of substance abusing habits. Parameter values used are in Table 2.1 with ϕ and ρ , varying from 0.0 to 1.0.

Numerical results in Figure 2.4 suggest that more adolescents should desist from substance abuse, since the trend Σ shows a decrease in the reproduction number R_{na} with increasing ϕ . Trend line Ω shows the effects of increasing ρ which results in an increase of the reproductive number R_{na} thereby increasing the prevalence of HSV-2 in community. The point ψ depicts the balance in transfer rates from being a substance abuser to a non-substance abuser or from a non-substance abuser to a substance abuser at the point $(\rho = \phi = 0.1)$, corresponding to $R_{na} = 1.45$. This suggests that changes in the substance abusive habit will not have an impact on the reproduction number. Point ψ also suggests that besides substance abuse among adolescents, other factors are influencing the spread of HSV-2 amongst them in the community. Measures such as educational campaigns and counselling may be introduced so as to reduce ρ while increasing ϕ .

In many epidemiological models, the magnitude of the reproductive number is associated with the level of infection. The same is true in model system (2.3). Sen-

sitivity analysis assesses the amount and type of change inherent in the model as captured by the terms that define the reproductive number (R_{na}). If R_{na} is very sensitive to a particular parameter, then a perturbation of the conditions that connect the dynamics to such a parameter may prove useful in identifying policies or intervention strategies that reduce epidemic prevalence.

Partial rank correlation coefficients (PRCCs) were calculated to estimate the degree of correlation between values of R_{na} and the ten model parameters across 1000 random draws from the empirical distribution of R_{na} and its associated parameters.

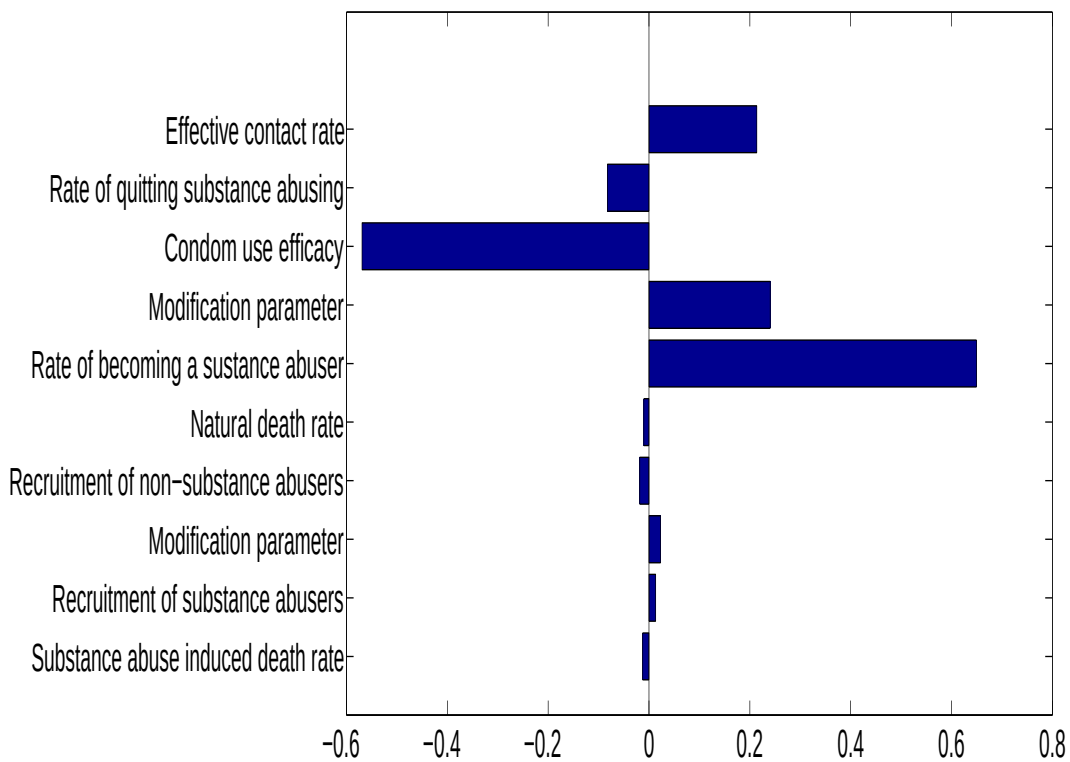


Figure 2.5: Partial rank correlation coefficients showing the effect of parameter variations on R_{na} using ranges in Table 2.1. Parameters with positive PRCCs will increase R_{na} when they are increased, whereas parameters with negative PRCCs will decrease R_{na} when they are increased.

Figure 2.5 illustrates the PRCCs using R_{na} as the output variable. PRCCs show that the rate of becoming substance abusers by the adolescents has the most impact in the spread of HSV-2 among adolescents. Effective contact rate is found to support the spread of HSV-2 as noted by its positive PRCC. However, condom use efficacy is shown to have a greater impact on reducing R_{na} .

Since the rate of becoming a substance abuser (ρ), condom use efficacy (θ), and the effective contact rate (β) have significant effects on R_{na} , we examine their dependence on R_{na} in more detail. We used Latin Hypercube Sampling and Monte Carlo simulations to run 1000 simulations, where all parameters were simultaneously drawn from across their ranges.

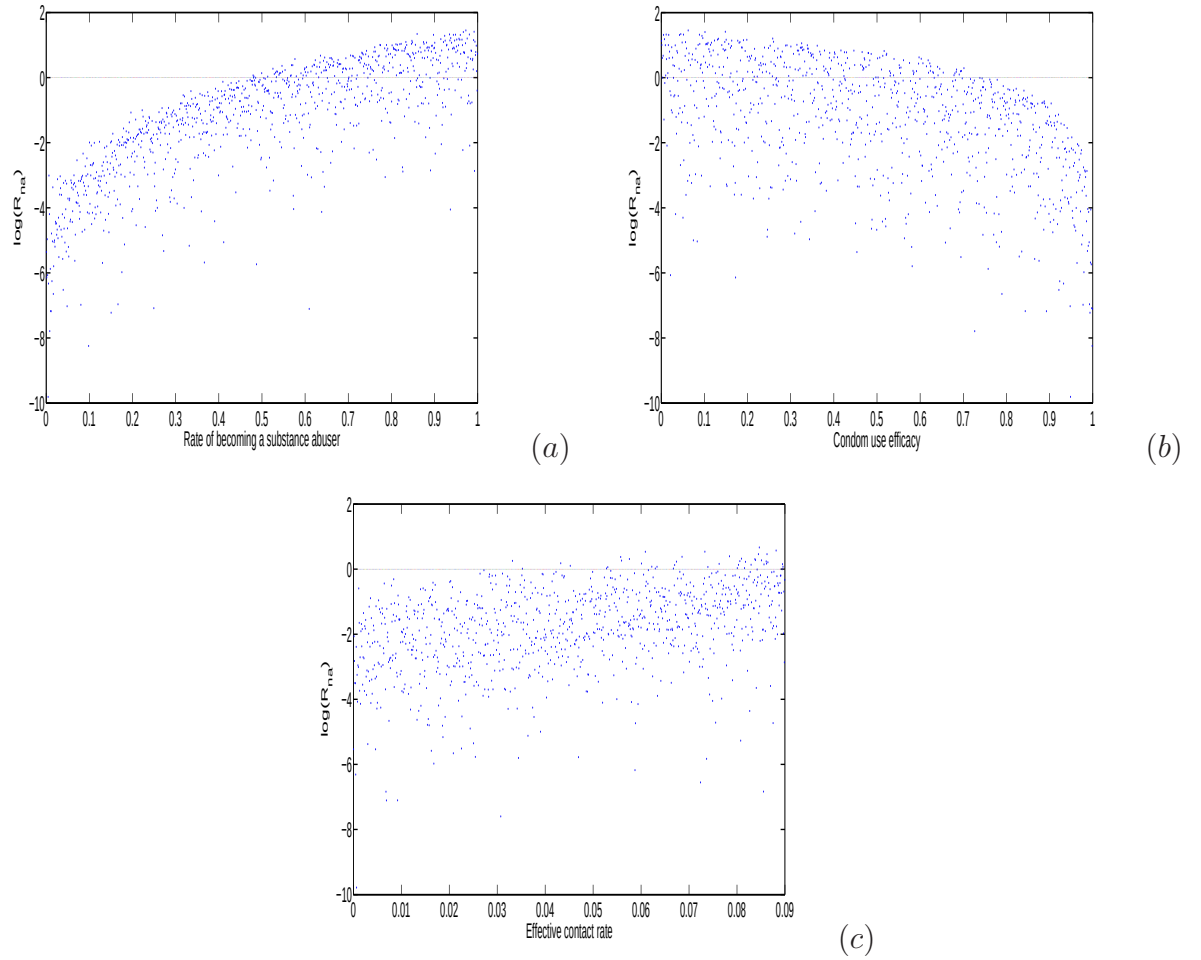


Figure 2.6: Monte Carlo Simulations of 1000 sample values for three illustrative parameters (ρ , θ , and β) chosen via Latin Hypercube Sampling.

Figure 2.6 illustrates the effect that varying three sample parameters will have on R_{na} . In Figure 2.6(a), if the rate of becoming a substance abuser is sufficiently high, then $R_{na} > 1$ and the disease will persist. However, if the rate of becoming a substance abuser is low, then $R_{na} < 1$ and the disease can be controlled. Figure 2.6(b) illustrates the effect of condom use efficacy on controlling HSV-2. The result demonstrates that an increase in θ results in a decrease in the reproduction number. Figure 2.6(b) demonstrates that if condom use efficacy is more than 70% of the time, then the reproduction number is less than unity, then the disease will be controlled.

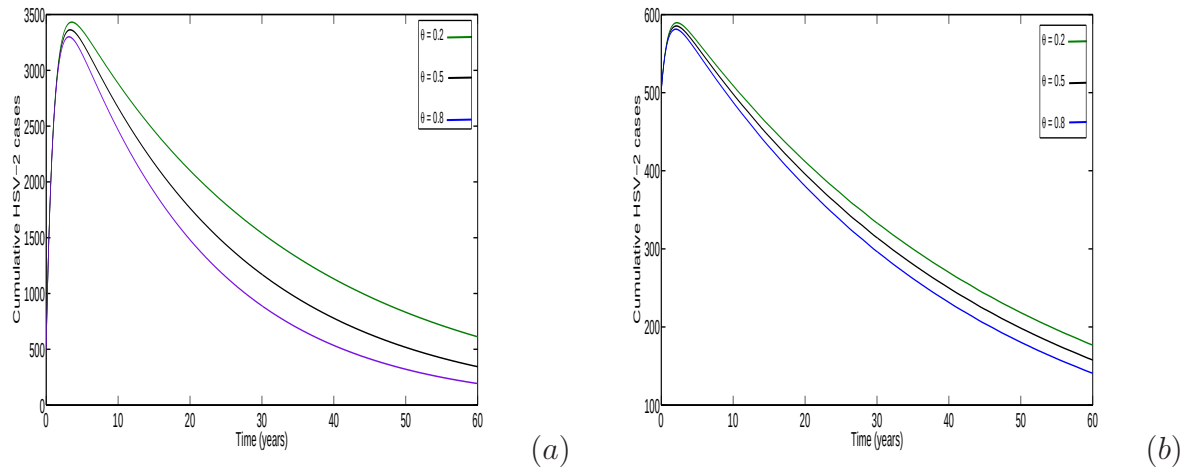


Figure 2.7: Simulations of model system (2.3) showing the effects of an increase on condom use efficacy on the HSV-2 cases ($I_a + I_n$) over a period of 60 years. The rest of the parameters are fixed on their baseline values, with Figure 2.7(a) having $\rho > \phi$ and Figure 2.7(b) having $\phi > \rho$.

Numerical results on Figure 2.7 are in agreement with the earlier findings, which have shown that condom use has a significant effect on HSV-2 cases among adolescents. However, Figure 2.7(b) shows that for more adolescents changing their behaviour by leaving their substance abuse habit than becoming substance abusers, condom use is more effective. Figure 2.7(b) also shows that, more adolescents should desist from substance abuse to reduce the HSV-2 cases. It is also worth noting that, as the condom use efficacy is increasing, the cumulative HSV-2 cases also reduces.

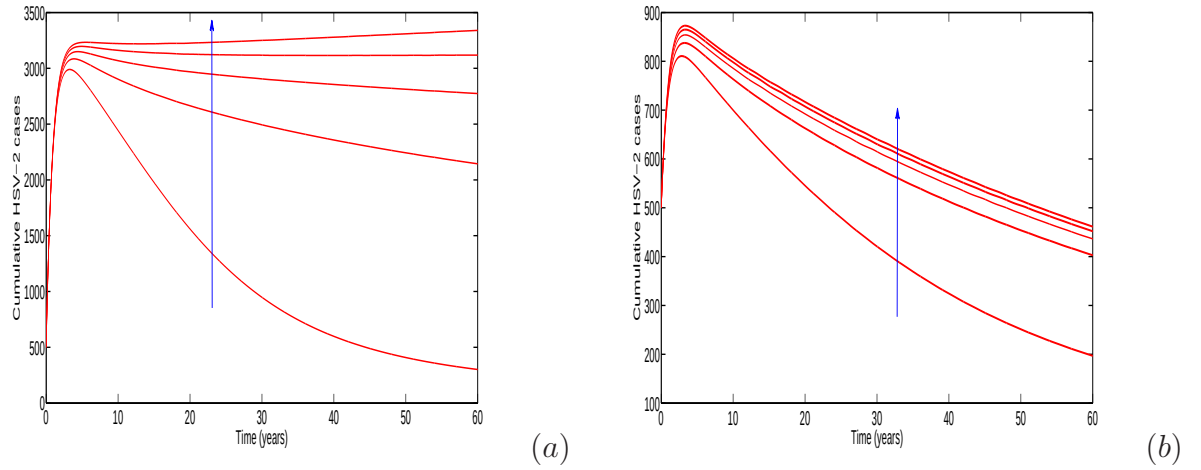


Figure 2.8: Simulations of model system (2.3) showing the effects of increasing the proportion of recruited substance abusers (π_1), varying from 0.0 to 1.0 with a step size of 0.25, for the 2 cases where (a) $\rho > \phi$ and (b) $\phi > \rho$.

In general, simulations in Figure 2.8 suggest that an increase in recruitment of substance abusing adolescents into the community will increase the prevalence of HSV-2 cases. It is worth noting that the prevalence is much higher when we have more adolescents becoming substance abusers than quitting the substance abusing habit, that is for $\rho > \phi$.

2.5. Optimal condom use and educational campaigns

In this section our goal is to solve the following maximisation problem: *given initial population sizes of all the four subgroups, S_n , S_a , I_n and I_a , we seek to find the best strategy in terms of intervention strategies that would maximise the susceptible non-substance abusing adolescents while at the same time minimising the susceptible substance abusing adolescents, the cumulative HSV-2 cases and the the cost of intervention strategies.* Naturally, there are various ways of expressing such a goal mathematically. In this section, for a fixed (time) T , we consider the following

objective functional:

$$J(u_1, u_2) = \int_0^{t_f} [S_n - B_1 S_a - B_2 I_n - B_3 I_a - (A_1 u_1^2 + A_2 u_2^2)] dt, \quad (2.71)$$

subject to

$$\begin{aligned} \frac{dS_n}{dt} &= \pi_0 \Lambda - \alpha(1 - u_1) \lambda S_n + \phi S_a - (1 - u_2) \rho S_n - \mu S_n, \\ \frac{dS_a}{dt} &= (1 - u_2) \pi_1 \Lambda - (1 - u_1) \lambda S_a + (1 - u_2) \rho S_n - (\mu + v + \phi) S_a, \\ \frac{dI_n}{dt} &= \alpha(1 - u_1) \lambda S_n + \phi I_a - (1 - u_2) \rho I_n - \mu I_n, \\ \frac{dI_a}{dt} &= (1 - u_1) \lambda S_a + (1 - u_2) \rho I_n - (\mu + v + \phi) I_a. \end{aligned} \quad (2.72)$$

The parameter B_1 , B_2 and B_3 represent the weight constants of the susceptible substance abusers, the infectious non-substance abusers and the infectious substance abusers, while the parameters A_1 and A_2 are the weights and cost of condom use and educational campaigns for the controls u_1 and u_2 , respectively. The weight constants help to balance each term in the integrand so that none of the terms dominates. The terms u_1^2 and u_2^2 reflect the severity of condom use and educational campaigns in the control of the disease. The values $u_1 = u_2 = 1$ represent maximum effectiveness of condom use and educational campaigns. We therefore seek optimal controls u_1^* and u_2^* such that

$$J(u_1^*, u_2^*) = \max\{J(u_1, u_2) | u_1, u_2 \in \mathcal{U}\} \quad (2.73)$$

where

$$\mathcal{U} = \{u_1(t), u_2(t) | u_1(t), u_2(t) \text{ is measurable} : 0 \leq a_{11} \leq u_1(t) \leq b_{11} \leq 1, 0 \leq a_{22} \leq u_2(t) \leq b_{22} \leq 1, t \in [0, t_f]\},$$

The basis framework of this problem is to characterise the optimal control and prove the existence of the optimal control and uniqueness of the optimality system.

In our analysis, we assume $\Lambda = \mu N$ and $v = 0$, as applied in (Jung et al., 2002). Thus the total population N is constant. We can also treat the nonconstant population case by these same techniques, but we choose to present the constant population case here.

2.5.1. Existence of an optimal control

The existence of an optimal control is proved by a result from Fleming and Rishel (1975). The boundedness of solutions of system (2.72) for a finite interval is used to prove the existence of an optimal control. To determine existence of an optimal control to our problem, we use a result from Fleming and Rishel (1975) (Thm 4.1 pg 68-69), where the following properties are satisfied,

1. The class of all initial conditions with an optimal control set u_1 and u_2 in the admissible control set along with each state equation being satisfied is not empty.
2. The control set $\mathcal{U}$ is convex and closed.
3. The right-hand side of the state is continuous, is bounded above by a sum of the bounded control and the state, and can be written as a linear function of each control in the optimal control set u_1 and u_2 with coefficients depending on time and the state variables.
4. The integrand of the functional is concave on $\mathcal{U}$ and is bounded above by $c_2 - c_1(|u_1|^2 + |u_2|^2)$, where $c_1, c_2 > 0$.

An existence result in Lukes (1982) (Theorem 9.2.1) for the system of equations (2.72) for bounded coefficients is used to give condition 1. The control set is closed and convex by definition. The right hand side of the state system equation (2.72)

satisfies condition 3 since the state solution are *a priori* bounded. The integrand in the objective functional, $S_n - B_1 S_a - B_2 I_n - B_3 I_a - (A_1 u_1^2 + A_2 u_2^2)$, is Lebesgue integrable and concave on $\mathcal{U}$. Furthermore, $c_1, c_2 > 0$ and $B_1, B_2, B_3, A_1, A_2 > 1$, hence satisfying

$$S_n - B_1 S_a - B_2 I_n - B_3 I_a - (A_1 u_1^2 + A_2 u_2^2) \leq c_2 - c_1(|u_1|^2 + |u_2|^2),$$

hence the optimal control exist, since the states are bounded.

2.5.2. Characterisation

Since there exists an optimal control for maximising the functional (2.74) subject to equation (2.72), we use Pontryagin's Maximum Principle to derive the necessary conditions for this optimal control. The Lagrangian is defined as,

$$\begin{aligned} L = & S_n - B_1 S_a - B_2 I_n - B_3 I_a - (A_1 u_1^2 + A_2 u_2^2) \\ & + \lambda_1 \left[\pi_0 \Lambda - \frac{\alpha(1-u_1)\beta(I_a + (1-\eta)I_n)S_n}{N} + \phi S_a - (1-u_2)\rho S_n - \mu S_n \right] \\ & + \lambda_2 \left[(1-u_2)\pi_1 \Lambda - \frac{(1-u_1)\beta(I_a + (1-\eta)I_n)S_a}{N} + (1-u_2)\rho S_n - (\mu + v + \phi)S_a \right] \\ & + \lambda_3 \left[\frac{\alpha(1-u_1)\beta(I_a + (1-\eta)I_n)S_n}{N} + \phi I_a - (1-u_2)\rho I_n - \mu I_n \right] \\ & + \lambda_4 \left[\frac{(1-u_1)\beta(I_a + (1-\eta)I_n)S_a}{N} + (1-u_2)\rho I_n - (\mu + v + \phi)I_a \right] \\ & + \omega_{11}(t)(b_1 - u_1(t)) + \omega_{12}(t)(u_1(t) - a_1) \\ & + \omega_{21}(t)(b_2 - u_2(t)) + \omega_{22}(t)(u_2(t) - a_2), \end{aligned} \tag{2.74}$$

where $\omega_{11}(t), \omega_{12}(t) \geq 0, \omega_{21}(t), \omega_{22}(t) \geq 0$ are penalty multipliers satisfying $\omega_{11}(t)(b_1 - u_1(t)) = 0$ and $\omega_{12}(t)(u_1(t) - a_1) = 0$, $\omega_{21}(t)(b_2 - u_2(t)) = 0$ and $\omega_{22}(t)(u_2(t) - a_2) = 0$, at the optimal point u_1^* and u_2^* .

Theorem 2.9. *Given optimal controls u_1^* and u_2^* and solutions of the corresponding*

state system (2.72), there exist adjoint variables $\lambda_i, i = 1, \dots, 4$ satisfying

$$\begin{aligned}
 \frac{d\lambda_1}{dt} &= -\frac{\partial L}{\partial S_n} \\
 &= -1 + \frac{\alpha(1-u_1)\beta I_a[\lambda_1 - \lambda_3]}{N} + \frac{\alpha(1-u_1)(1-\eta)\beta I_n[\lambda_1 - \lambda_3]}{N} \\
 &\quad + (1-u_2)\rho[\lambda_1 - \lambda_2] + \mu\lambda_1, \\
 \frac{d\lambda_2}{dt} &= -\frac{\partial L}{\partial S_a} \\
 &= B_1 + \phi[\lambda_2 - \lambda_1] + \frac{(1-u_1)\beta I_a[\lambda_2 - \lambda_4]}{N} + \frac{(1-u_1)(1-\eta)\beta I_n[\lambda_2 - \lambda_4]}{N} \\
 &\quad + (\mu + v)\lambda_2, \\
 \frac{d\lambda_3}{dt} &= -\frac{\partial L}{\partial I_n} \\
 &= B_2 + \frac{\alpha(1-u_1)(1-\eta)\beta S_n[\lambda_1 - \lambda_3]}{N} + \frac{(1-u_1)(1-\eta)\beta S_a[\lambda_2 - \lambda_4]}{N} \\
 &\quad + (1-u_2)\rho[\lambda_3 - \lambda_4] + \mu\lambda_3, \\
 \frac{d\lambda_4}{dt} &= -\frac{\partial L}{\partial I_a} \\
 &= B_3 + \frac{\alpha(1-u_1)\beta S_n[\lambda_1 - \lambda_3]}{N} + \frac{(1-u_1)\beta S_a[\lambda_2 - \lambda_4]}{N} + \phi[\lambda_4 - \lambda_3] + (\mu + v)\lambda_4.
 \end{aligned} \tag{2.75}$$

Proof. The form of the adjoint equation and transversality conditions are standard results from Pontryagin's Maximum Principle (Fleming and Rishel, 1975; Pontryagin et al., 1985); therefore, solutions to the adjoint system exist and are bounded. To determine the interior maximum of our Lagrangian, we take the partial derivative L with respect to $u_1(t)$ and $u_2(t)$ and set to zero. Thus,

Making $u_1(t)^*$ subject of formulae

$$u_1(t)^* = \frac{\beta(I_a + (1 - \eta)I_n)}{2A_1N} [\alpha S_n(\lambda_1 - \lambda_3) + S_a(\lambda_2 - \lambda_4)] + \frac{\omega_{12}(t) - \omega_{11}(t)}{2A_1}. \quad (2.76)$$

Making $u_2(t)^*$ subject of formulae

$$u_2(t)^* = \frac{\rho}{2A_2} [S_n(\lambda_1 - \lambda_2) + I_n(\lambda_3 - \lambda_4)] - \frac{\pi_1 \Lambda \lambda_2}{2A_2} + \frac{\omega_{22}(t) - \omega_{21}(t)}{2A_2}. \quad (2.77)$$

To determine the explicit expression for the control without $\omega_1(t)$ and $\omega_2(t)$, a standard optimality technique is utilised. The specific characterisation of the optimal controls $u_1(t)^*$ and $u_2(t)^*$ is

$$u_1(t)^* = \min\{\max\{a_1, \frac{\beta(I_a + (1 - \eta)I_n)}{2A_1N} [\alpha S_n(\lambda_1 - \lambda_3) + S_a(\lambda_2 - \lambda_4)]\}, b_1\}, \quad (2.78)$$

$$u_2(t)^* = \min\{\max\{a_2, \frac{\rho}{2A_2} [S_n(\lambda_1 - \lambda_2) + I_n(\lambda_3 - \lambda_4)] - \frac{\pi_1 \Lambda \lambda_2}{2A_2}\}, b_2\}. \quad (2.79)$$

The optimality system consists of the state system coupled with the adjoint system with the initial conditions, the transversality conditions and the characterisation of the optimal control. Substituting $u_1(t)^*$ and $u_2(t)^*$ for $u_1(t)$ and $u_2(t)$, in equations (2.75) gives the optimality system. The state system and adjoint system have finite upper bounds. These bounds are needed in the uniqueness proof of the optimality system. Due to *a priori* boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ordinary differential equations (ODEs), we obtain the uniqueness of the optimal control for small t_f (Magombedze et al., 2011). The uniqueness of the optimal control follows from the uniqueness of the optimality system. $\square$

2.5.3. Numerical Simulations

The optimality system is solved using an iterative method with Runge-Kutta fourth order scheme. Starting with a guess for the adjoint variables, the state equations are solved forward in time. Then these state values are used to solve the adjoint equations backward in time, and the iterations continue until convergence. The

simulation were carried out using parameter values in Table 2.1 and the following values $A_1 = 0.005$, $A_2 = 0.005$, $B_1 = 0.06$, $B_2 = 0.05$, $B_3 = 0.05$. The assumed initial conditions for the differential equations are $S_{n_0} = 0.4$, $S_{a_0} = 0.3$, $I_{n_0} = 0.2$ and $I_{a_0} = 0.1$.

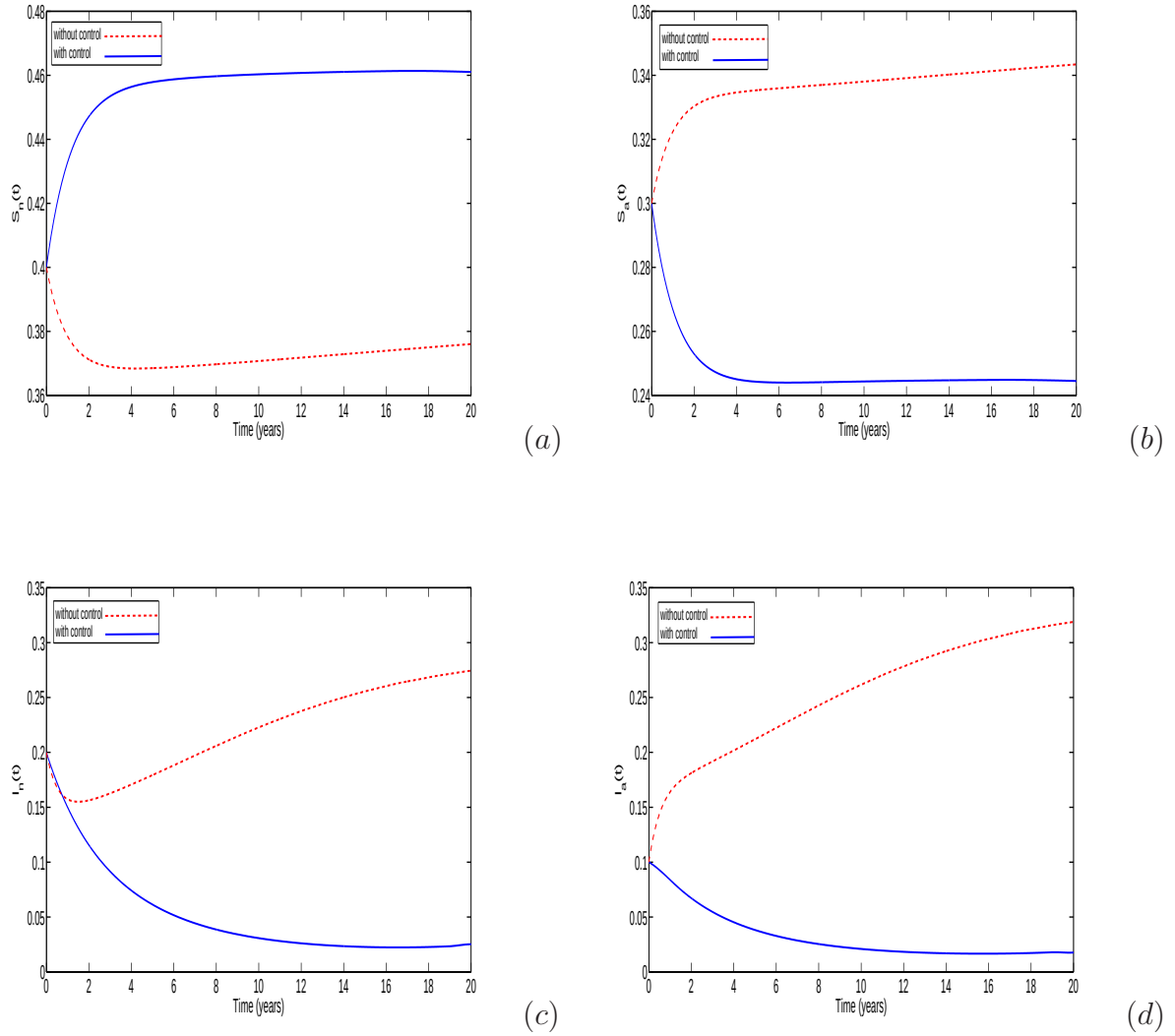


Figure 2.9: Time series plots showing the effects of optimal control on the susceptible non-substance abusing adolescents S_n , susceptible substance abusing adolescents S_a , infectious non-substance abusing adolescents I_n and the infectious substance abusing I_a , over a period of 20 years

Figure 2.9(a) illustrates the population of the susceptible non-substance abusing adolescents in the presence and absence of the controls over a period of 20 years. For the period 0-3 years, in the absence of the control, the susceptible non-substance abusing adolescents have a sharp increase, and for the same period when

there is no control the population of the non-substance abusing adolescents decreases sharply. Further, we note that for the case when there is no control, for the period 3-20 years, the population of the susceptible non-substance abusing adolescents increases slightly.

Figure 2.9(b) illustrates the population of the susceptible substance abusers adolescents in the presence and absence of the controls over a period of 20 years. For the period 0-3 years, in the presence of the controls, the susceptible substance abusing adolescents have a sharp decrease, and for the same period when there are controls the population of the susceptible substance abusers increases sharply. It is worth noting that after 3 years, the population for the substance abusers with control remains constant while the population of the susceptible substance abusers without control continues increasing gradually.

Figure 2.9(c) highlights the impact of controls on the population of infectious non-substance abusing adolescents. For the period 0-2 years, in the absence of the control, cumulative HSV-2 cases for the non substance abusing adolescents decreases rapidly, before starting to increase moderately for the remaining years under consideration. The cumulative HSV-2 cases for the non-substance abusing adolescents decrease sharply for the whole 20 years under consideration. It is worth noting that for the infectious non-substance abusing adolescents, the controls yield positive results after a period of 2 years, hence the controls have an impact in controlling cumulative HSV-2 cases, within a community.

Figure 2.9(d) highlights the impact of controls on the population of infectious substance abusing adolescents. For the whole period under investigation, in the absence of the control, cumulative infectious substance abusing HSV-2 cases increase rapidly, and for the similar period, when there is a control the population of the exposed individuals decreases sharply. Results on Figure 2.9(d) clearly, suggests that, the presence of controls have an impact on reducing cumulative HSV-2 cases within a society with substance abusing adolescents.

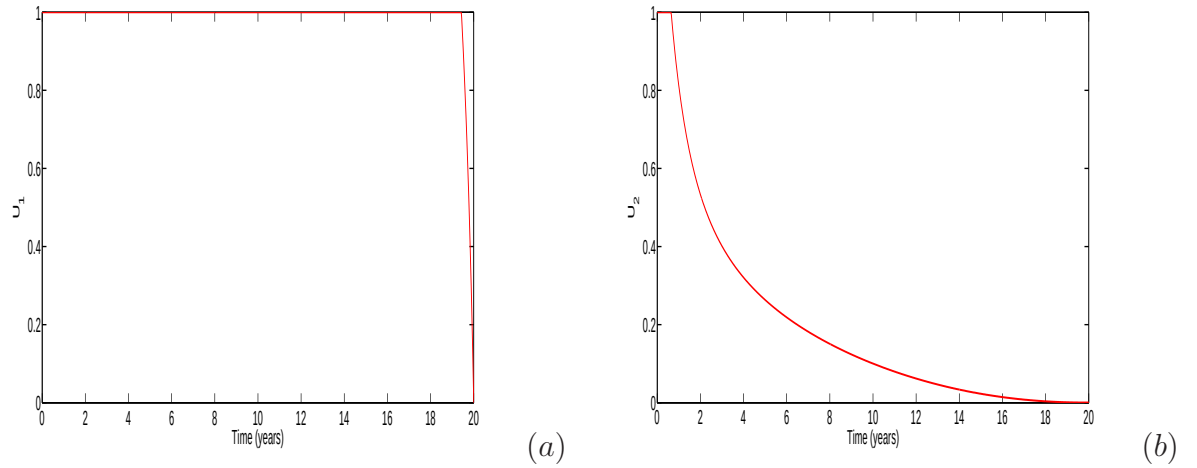


Figure 2.10: The optimal control graphs for the two controls, namely, condom use (u_1) and educational campaigns (u_2).

Figure 2.10 represents the controls u_1 and u_2 . The condom use control u_1 is at the upper bound b_1 for approximately 20 years and has a steady drop until it reaches the lower bound $a_1 = 0$. Treatment control u_2 , is at the upper bound for approximately half a year and has a sharp drop until it reaches the lower bound $a_2 = 0$.

These results suggest that more effort should be devoted to condom use (u_1), as compared to educational campaigns (u_2).

2.6. Concluding remarks

Adolescents who abuse substances have higher rates of HSV-2 infection, since adolescents who engage in substance abuse also engage in risky behaviours, hence most of them do not use condoms. In general adolescents are not fully educated on HSV-2. A mathematical model for investigating the effects of substance abuse amongst adolescents on the transmission dynamics of HSV-2 in the community is formulated and analysed. We computed and compared the reproduction numbers. Results from the analysis of the reproduction numbers suggest that condom use

and educational campaigns have a great impact in the reduction of HSV-2 cases in the community. The PRCCs were calculated to estimate the correlation between values of the reproduction number and the epidemiological parameters. It has been seen that an increase in condom use and a reduction on the number of adolescents becoming substance abusers, have the greatest influence on reducing the magnitude of the reproduction number than any other epidemiological parameters. This result is further supported by numerical simulations which show that condom use is highly effective when we are having more adolescents quitting substance abusing habit than those becoming ones, where as it is less effective when we have more adolescents becoming substance abusers than quitting. Substance abuse amongst adolescents increases disease transmission, and prevalence of disease increases with increased rate of becoming a substance abuser. Thus, in the event when we have more individuals becoming heavy substance abusers, there is urgent need for intervention strategies such as counselling and educational campaigns in order to curtail the HSV-2 spread. Numerical simulations also suggest that an increase in recruitment of substance abusers in the community will increase the prevalence of HSV-2 cases.

The optimal control results show how a cost effective combination of aforementioned HSV-2 intervention strategies (condom use and educational campaigns) amongst adolescents, may influence cumulative cases over a period of 20 years. Overall, optimal control theory results suggest that more effort should be devoted to condom use compared to educational campaigns.

Chapter 3

A computational study of HSV-2 with poor treatment adherence

3.1. Introduction

Sexually transmitted infections (STIs) are responsible for an enormous burden of morbidity and mortality in many developing countries because of their effects on reproductive and child health and their role in facilitating the transmission of HIV infection (Laga et al., 1994). Some of the reasons why STIs incidence and prevalence rates are generally high in developing nations are: inadequacies in health service provision and health care seeking, (Aral and Wasserheit, 1999) delayed and poor treatment adherence (Kalichman and Rompa, 2003). Adhering to a treatment schedule and successfully completing it are crucial to the control of any global disease (Mushayabasa and Bhunu, 2013). Poor adherence to treatment can be influenced by a couple of issues such as personal, psychosocial, economic, medical and health service factors (Mushayabasa and Bhunu, 2013). Prior studies suggests that rates of non-adherence to treatment generally range from 20 to 40% for acute illness regimen and 50 to 80% for preventive regimens (Christensen, 2005).

Plummer et al. (2010) conducted a qualitative study on HSV-2 treatment adherence in Tanzania, and observed an 8% (7/86) adherence for HSV-2 patients who were on Acyclovir. Despite numerous research efforts that have been devoted to the study of HSV-2, the aspect of poor treatment adherence and its impact on infection and spread of HSV-2 has not yet been investigated. It is against this background that this chapter finds its relevance. In this chapter we propose a compartmental model for the spread of HSV-2 incorporating all the essential biological details. The model incorporates the aspect of poor treatment adherence and allows optimal control methods to be used. We conduct both epidemic and endemic analysis, with a focus on the threshold dynamics characterised by the basic reproduction numbers. In addition, we explored the role of time dependent intervention strategy of controlling HSV-2 incidence and prevalence.

3.2. Model Framework

Our objective is to formulate a deterministic model for HSV-2 that includes relevant biological detail, accounts for HSV-2 treatment, and allows optimal control methods to be used. To begin, we partition the sexual active population into the following epidemiological classes or subgroups: susceptibles ($\bar{S}$), infected with acute HSV-2 and also under anti-viral treatment ($\bar{A}_a$), infected with acute HSV-2 and not under anti-viral treatment after quitting before completion ($\bar{A}_u$), infected with latent HSV-2 after undergoing successful anti-viral treatment ($\bar{L}_a$) and the infected with latent HSV-2 after undergoing natural healing ($\bar{L}_u$). Thus, the total population is given by $\bar{N} = \bar{S} + \bar{A}_a + \bar{A}_u + \bar{L}_a + \bar{L}_u$. We assume a constant size population with a birth and non-disease related death rate given by μ . The recruitment of susceptible is proportional to the population and is given by $\mu\bar{N}(t)$. Assuming homogeneous mixing of the population, the susceptible individuals acquire acute HSV-2 infection at rate $\bar{\lambda}$, given by

$$\bar{\lambda}(t) = \frac{\beta(\bar{A}_a(t)(1 - \eta) + \bar{A}_u(t))}{\bar{N}(t)},$$

where $\beta = \rho c$ is the effective contact rate for HSV-2 infection (contact sufficient to result in HSV-2 infection), ρ is the probability of being infected from a sexual partner and c is the rate at which an individual acquires sexual partners per unit time. $\eta \in (0, 1)$ is a modification factor accounting for the assumed reduced likelihood for individuals in class $\bar{A}_a$ to pass on the infection compared to individuals in class $\bar{A}_u$. This is due to the fact that individuals in treatment have reduced viral load compared to those who have failed to adhere to anti-viral treatment guidelines. Upon being infected with acute HSV-2, the individuals become latent at constant rate κ . Following an appropriate stimulus in individuals with latent HSV-2, reactivation may occur (Blower et al., 1998). The anti-viral treatment rates for the individuals with acute HSV-2 is denoted by ψ . Since the anti-viral medication will also suppress reactivation of latent HSV-2, we assume that the reactivation rate of people with latent HSV-2 is at rate $\gamma(\psi)$, where $\gamma(\psi)$ is a decreasing function of ψ (Feng et al., 2013). Thus,

$$\gamma(\psi) = \gamma(0) \frac{\alpha}{\alpha + \psi},$$

in which the factor $\frac{\alpha}{\alpha + \psi}$ represents reduced reactivation to class $\bar{A}_a$ due to anti-viral treatment. In the case, where there is no treatment, we have that $\psi = 0$, thus $\gamma(\psi_0) = \gamma(0) = \gamma_0$. A proportion $(1 - \theta)$ of individuals on treatment fail to adhere to treatment at rate δ , and they move to class $\bar{A}_u$. Since HSV-2 is not fatal, we assume that individuals in different human sub groups suffer from natural death at a rate μ . The model flow diagram is shown in Figure 3.2 below.

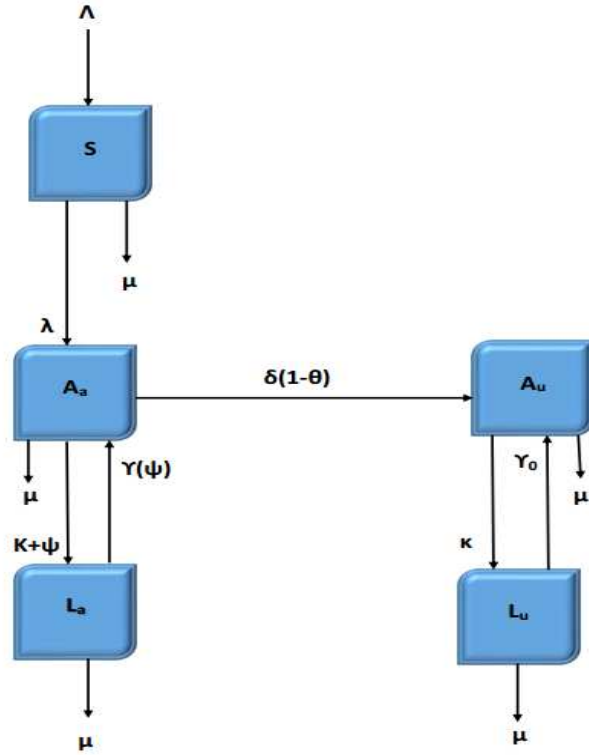


Figure 3.1: Structure of the model.

HSV-2 dynamics in this study are governed by the following system of nonlinear differential equations:

$$\left\{ \begin{array}{l} \frac{d\bar{S}}{dt} = \mu\bar{N} - \bar{\lambda}\bar{S} - \mu\bar{S}, \\ \frac{d\bar{A}_a}{dt} = \bar{\lambda}\bar{S} + \gamma(\psi)\bar{L}_a - (\mu + \kappa + \psi + \delta(1 - \theta))\bar{A}_a, \\ \frac{d\bar{A}_u}{dt} = \delta(1 - \theta)\bar{A}_a + \gamma_0\bar{L}_u - (\mu + \kappa)\bar{A}_u, \\ \frac{d\bar{L}_a}{dt} = (\kappa + \psi)\bar{A}_a - (\mu + \gamma(\psi))\bar{L}_a, \\ \frac{d\bar{L}_u}{dt} = \kappa\bar{A}_u - (\mu + \gamma_0)\bar{L}_u. \end{array} \right. \quad (3.1)$$

It is helpful to re-scale system (3.1) so that we have dimensionless variables. We

let

$$S = \frac{\bar{S}}{\bar{N}}, \quad L_a = \frac{\bar{L}_a}{\bar{N}}, \quad L_u = \frac{\bar{L}_u}{\bar{N}}, \quad A_a = \frac{\bar{A}_a}{\bar{N}}, \quad A_u = \frac{\bar{A}_u}{\bar{N}}.$$

We now denote the total population with $N = S + L_a + L_u + A_a + A_u$, and our new model takes the form

$$\left\{ \begin{array}{l} \frac{dS}{dt} = \mu - \lambda S - \mu S, \\ \frac{dA_a}{dt} = \lambda S + \gamma(\psi)L_a - (\mu + \kappa + \psi + \delta(1 - \theta))A_a, \\ \frac{dA_u}{dt} = \delta(1 - \theta)A_a + \gamma_0 L_u - (\mu + \kappa)A_u, \\ \frac{dL_a}{dt} = (\kappa + \psi)A_a - (\mu + \gamma(\psi))L_a, \\ \frac{dL_u}{dt} = \kappa A_u - (\mu + \gamma_0)L_u, \end{array} \right. \quad (3.2)$$

with $\lambda = \beta(A_a(1 - \eta) + A_u)$. The model parameters and their baseline values are given in Table 3.1. We begin by estimating the parameters for model system (3.2) in details.

- (i) Average sexual lifespan μ : the world's average rate of exiting sexual activity is around 35 years (420 months), the 15-49 years of age (Abu-Raddad et al., 2008). Thus, we set $\mu = 1/420$ per month (Abu-Raddad et al., 2008; Foss et al., 2013).
- (ii) Effective contact rate β : we set $\beta = 0.002$ per year and this value was adopted from the work of Feng et al., (2013).
- (iii) Rate of acute becoming latent κ : we adopt the value of $\kappa = 2.3805$ per year from the work of Abu Raddad et al., (2008).
- (iv) Treatment rate of acute HSV-2 ψ : we assume it varies without any point

estimate, as applied in the work of Feng et al., (2013).

- (v) Baseline re-activation rate of latent HSV-2 γ_0 : we set $\gamma_0 = 0.3875$ per annum from the work of Abu-Raddad et al., (2008).
- (vi) Proportion of patient who complete treatment θ : we adopt $\theta = 0.6$ per year, from a study which was conducted in Tanzania by Watson-Jones et al., (2009).
- (vii) The re-activation rate with an effect of treatment γ : we vary γ without any point estimate and this variation was adopted from the work of Feng et al., (2008).
- (viii) Treatment quitting rate δ : we assume $\delta = 0.3$, we adopted this value from the works Golin et al., (2001) and (Bangsberg et al., 2001).

Table 3.1: Model parameters and their baseline values. The time unit is in months

Definition	Symbol	Baseline values	Source
Reactivation rate with an effect of treatment	$\gamma(\psi)$	Varies	(Feng et al., 2013)
Proportion of patients who complete treatment	θ	0.7(0-1)	Estimate
Effective contact rate	β	0.2	(Feng et al., 2013; Foss et al., 2009)
Baseline reactivation rate of latent HSV-2	γ_0	0.3875(0.339-0.436)	a*
Rate of acute becoming latent	κ	2.3805(2.083-2.678)	a*
Treatment rate of acute HSV-2	ψ	Varied	(Feng et al., 2013)
Average sexual lifespan	μ	0.002(0.003-0.005)	(Foss et al., 2013; a*)
Modification parameter	η	0.4(0-1)	Estimate
Treatment quitting rate	δ	0.3	(Golin et al., 2001 b*)

In Table 3.1 above, a* represents (Abu-Raddad et al., 2008) and b* represents (Bangsberg et al., 2001).

3.3. Model Analysis and Results

3.3.1. Positivity and boundedness of solutions

In this Section we study the basic properties of the solutions of model system (3.2), which are essential to the proofs of stability.

Theorem 3.1. *The equations preserve positivity of solutions.*

Proof. Let $t_1 = \sup\{t > 0 : S > 0, A_a > 0, A_u > 0, L_a > 0, L_u > 0 \in [0, t]\}$. Thus, $t_1 > 0$. It follows from the first equation of model system (3.2) that

$$\frac{dS}{dt} = \mu - \mu S \geq \mu - \lambda S - \mu S, \quad (3.3)$$

which can be rewritten as

$$\frac{d}{dt} \left(S(t) \exp \left\{ \mu t + \int_0^t \lambda(\tau) d\tau \right\} \right) \geq \mu \exp \left\{ \mu t + \int_0^t \lambda(\tau) d\tau \right\}. \quad (3.4)$$

Hence,

$$S(t_1) \exp \left\{ \mu t_1 + \int_0^{t_1} \lambda(\tau) d\tau \right\} - S(0) \geq \int_0^{t_1} \mu \exp \left\{ \mu y + \int_0^y \lambda(\tau) d\tau \right\} dy, \quad (3.5)$$

so that

$$\begin{aligned} S(t_1) &\geq S(0) \exp \left\{ -\mu t_1 - \int_0^{t_1} \lambda(\tau) d\tau \right\} \left(\exp \left\{ -\mu t_1 - \int_0^{t_1} \lambda(\tau) d\tau \right\} \right) \\ &\times \left(\int_0^{t_1} \mu \exp \left\{ \mu y + \int_0^y \lambda(\tau) d\tau \right\} dy \right) > 0. \end{aligned} \quad (3.6)$$

Similarly, it can be shown that $A_a > 0$, $A_u > 0$, $L_a > 0$ and $L_u > 0$ for all time $t > 0$. $\square$

Theorem 3.2. *All solutions of model system (3.2) are bounded.*

Proof. Using model system (3.2), we have

$$\begin{aligned} \frac{dN}{dt} &= \frac{dS}{dt} + \frac{dA_a}{dt} + \frac{dA_u}{dt} + \frac{dL_a}{dt} + \frac{dL_u}{dt} \\ &= \mu - \mu N. \end{aligned}$$

The initial value problem $d\Theta/dt = \mu - \mu\Theta$ with $\Theta(0) = N(0)$, has the solution $\Theta(t) = 1 - ce^{-\mu t}$ and $\lim_{t \rightarrow \infty} \Theta(t) = 1$. Therefore, $N(t) \leq \Theta(t)$, which implies that $\lim_{t \rightarrow \infty} \sup N(t) \leq 1$.

Therefore all feasible solutions of system (3.2) enter the region

$$\Omega = \left\{ (S, A_a, A_u, L_a, L_u) \in \mathbb{R}_+^5 : S + A_a + A_u + L_a + L_u \leq 1 \right\}.$$

Thus, Ω is positively invariant and it is sufficient to consider solutions of model system (3.2) in Ω . Existence, uniqueness and continuation results for model system (3.2) starting in Ω remain in Ω for all $t \geq 0$. All parameters and state variables for model system (3.2) are assumed to be non-negative (for biological relevance) for all $t \geq 0$ since it monitors human population.

□

3.3.2. Equilibrium points and their stability analysis

Disease-free equilibrium

The disease-free equilibrium point is a steady-state solution where there is no disease in the population. In this section, we define the *diseased* classes as the human populations that are either quiescent or infectious. In the absence of the disease, we have that $A_a = A_u = L_a = L_u = 0$, hence model system (3.2) reduces to $\frac{dS}{dt} = \mu - \mu S$ only.

Thus, model system (3.2) has an evident disease free equilibrium (DFE) given by

$$\mathcal{C}^0 = (S^0, A_a^0, A_u^0, L_a^0, L_u^0) = (1, 0, 0, 0, 0).$$

The Jacobian of model system (3.2) evaluated at the disease free equilibrium is given by Π ,

$$\Pi = \begin{bmatrix} -\mu & -(1-\eta)\beta & -\beta & 0 & 0 \\ 0 & (1-\eta)\beta - (\delta(1-\theta) + \mu + \kappa + \psi) & \beta & \gamma(\psi) & 0 \\ 0 & \delta(1-\theta) & -(\mu + \kappa) & 0 & \gamma_0 \\ 0 & \kappa + \psi & 0 & -(\mu + \gamma(\psi)) & 0 \\ 0 & 0 & \kappa & 0 & -(\mu + \gamma_0) \end{bmatrix}. \quad (3.7)$$

It is clear from (3.7) that $\lambda_1 = -\mu$ is an eigenvalue and the other four eigenvalues are obtained from the matrix,

$$\Delta = \begin{bmatrix} (1-\eta)\beta - (\delta(1-\theta) + \mu + \kappa + \psi) & \beta & \gamma(\psi) & 0 \\ \delta(1-\theta) & -(\mu + \kappa) & 0 & \gamma_0 \\ \kappa + \psi & 0 & -(\mu + \gamma(\psi)) & 0 \\ 0 & \kappa & 0 & -(\mu + \gamma_0) \end{bmatrix}. \quad (3.8)$$

The trace and determinant of (3.8) are, respectively, given by

$$\left\{ \begin{array}{l} \text{tr}(\Delta) = -(4\mu + 2\kappa + \psi + \gamma(\psi) + \gamma_0 + \delta(1 - \theta)) + (1 - \eta)\beta < 0, \\ \text{for } (1 - \eta)\beta < (\delta(1 - \theta) + \mu + \kappa + \psi), \\ \det(\Delta) = \varpi \left(1 - \frac{\beta(\mu + \gamma(\psi))[\delta(1 - \theta)(\mu + \gamma_0) + \mu(1 - \eta)(\mu + \kappa + \gamma_0)]}{\mu(\mu + \kappa + \gamma_0)[\gamma(\psi)(\delta(1 - \theta) + \mu) + \mu(\delta(1 - \theta) + \mu + \kappa + \psi)]} \right) > 0, \\ \text{where, } \varpi = \mu(\mu + \kappa + \gamma_0)[\gamma(\psi)(\delta(1 - \theta) + \mu) + \mu(\delta(1 - \theta) + \mu + \kappa + \psi)]. \end{array} \right. \quad (3.9)$$

Let the spectral radius of model system (3.2) be

$$R_{ac} = \frac{\beta(\mu + \gamma(\psi))[\delta(1 - \theta)(\mu + \gamma_0) + \mu(1 - \eta)(\mu + \kappa + \gamma_0)]}{\mu(\mu + \kappa + \gamma_0)[\gamma(\psi)(\delta(1 - \theta) + \mu) + \mu(\delta(1 - \theta) + \mu + \kappa + \psi)]}. \quad (3.10)$$

Biologically, the reproductive number is defined as the number of secondary cases generated by a primary case when the virus is introduced in a population of wholly susceptible individuals at a demographic steady state. Based on (3.9) we have Theorem 3.3.

Theorem 3.3. *If $R_{ac} < 1$, then $\mathcal{C}^0$ is locally asymptotically stable.*

We now investigate the global stability of the disease-free equilibrium $\mathcal{C}^0$. We claim the following result:

Theorem 3.4. *Whenever $R_{ac} < 1$, it follows that the equilibrium point $\mathcal{C}^0$ of model system (3.2) is globally asymptotically stable.*

Proof. From the first equation of model system (3.2), we have that

$$\frac{dS}{dt} = \mu - \beta(A_a(1 - \eta) + A_u)S - \mu S \leq \mu - \mu S.$$

Choosing a small enough positive number v , there exists a $t_1 > 0$ such that for all $t > t_1$,

$$S \leq 1 + v = S^0 + v.$$

From model system (3.2) and that $S \leq S^0 + v$, $t > t_1$, we also know that

$$\left\{ \begin{array}{l} \frac{dA_a}{dt} \leq \beta(A_a(1 - \eta) + A_u)(S^0 + v) + \gamma(\psi)L_a - (\mu + \kappa + \psi + \delta(1 - \theta))A_a, \\ \frac{dA_u}{dt} = \delta(1 - \theta)A_a + \gamma_0L_u - (\mu + \kappa)A_u, \\ \frac{dL_a}{dt} = (\kappa + \psi)A_a - (\mu + \gamma(\psi))L_a, \\ \frac{dL_u}{dt} = \kappa A_u - (\mu + \gamma_0)L_u, \end{array} \right. \quad (3.11)$$

for all $t > t_1$. Considering the following auxiliary system

$$\left\{ \begin{array}{l} \frac{dA_a}{dt} = \beta(A_a^{**}(1 - \eta) + A_u^{**})(S^0 + v) + \gamma(\psi)L_a^{**} - (\mu + \kappa + \psi + \delta(1 - \theta))A_a^{**}, \\ \frac{dA_u}{dt} = \delta(1 - \theta)A_a^{**} + \gamma_0L_u^{**} - (\mu + \kappa)A_u^{**}, \\ \frac{dL_a}{dt} = (\kappa + \psi)A_a^{**} - (\mu + \gamma(\psi))L_a^{**}, \\ \frac{dL_u}{dt} = \kappa A_u^{**} - (\mu + \gamma_0)L_u^{**}. \end{array} \right. \quad (3.12)$$

Let Δ_0 be the matrix defined as

$$\Delta_0 = \begin{bmatrix} (1 - \eta)\beta & \beta & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}.$$

Setting $\Delta_1 = \Delta + v\Delta_0$, it follows from Theorem 2 in van den Driessche and Wat-

mough (2002) that $R_{ac} < 1$ if and only if $\rho(\Delta) < 0$. Thus, there exists an $v > 0$ small enough such that $\rho(\Delta_1) < 0$. By the Perron-Frobenius theorem (Horn and Johnson, 1985), all eigenvalues of the matrix Δ_1 have negative real parts where $\rho(\Delta_1) < 0$. Therefore it has

$$(A'_a(t), A'_u(t), L'_a(t), L'_u(t)) \rightarrow (0, 0, 0, 0), \text{ as } t \rightarrow \infty,$$

which implies that the zero solution of model system (3.2) is globally asymptotically stable.

By the comparison principle of Smith and Waltman (1995), we know that

$$(A_a(t), A_u(t), L_a(t), L_u(t)) \rightarrow (0, 0, 0, 0) \text{ as } t \rightarrow \infty.$$

By the theory of asymptotic autonomous system of Thieme (1993), it is also known that $S(t) \rightarrow S^0$ as $t \rightarrow \infty$. So C^0 is globally attractive when $R_{ac} < 1$. It follows that the disease-free equilibrium C^0 of model system (3.2) is globally asymptotically stable when $R_{ac} < 1$. $\square$

Endemic equilibrium

The endemic equilibrium of model system (3.2) is given by,

$$C^* = \begin{cases} S = \frac{\mu}{\mu + \lambda^*}, & L_a = \frac{\mu(\kappa + \psi)\lambda^*}{(\mu + \lambda^*)[\gamma(\delta(1 - \theta) + \mu) + \mu(\delta(1 - \theta) + \kappa + \mu + \psi)]}, \\ L_u = \frac{\mu\kappa\delta(1 - \theta)(\mu + \gamma)\lambda^*}{(\mu + \lambda^*)(\kappa + \mu + \gamma_0)[\gamma(\delta(1 - \theta) + \mu) + \mu(\delta(1 - \theta) + \kappa + \mu + \psi)]}, \\ A_a = \frac{\mu(\mu + \gamma)\lambda^*}{(\mu + \lambda^*)[\gamma(\delta(1 - \theta) + \mu) + \mu(\delta(1 - \theta) + \kappa + \mu + \psi)]}, \\ A_u = \frac{\mu\delta(1 - \theta)(\mu + \gamma_0)(\mu + \gamma)\lambda^*}{(\mu + \lambda^*)[\gamma(\delta(1 - \theta) + \mu) + \mu(\delta(1 - \theta) + \kappa + \mu + \psi)]}. \end{cases} \quad (3.13)$$

in terms of the force of infection λ^* . Substituting (3.13) into the equation of the force of infection λ^* we have

$$\lambda^* h(\lambda^*) = \lambda^* (\mathcal{H}_1 \lambda^* + \mathcal{H}_2) = 0,$$

where $\lambda^* = 0$ corresponds to the disease free equilibrium and $h(\lambda^*) = 0$ corresponds to the existence of the endemic equilibrium point where

$$\mathcal{H}_1 = \frac{1}{\mu}, \quad \mathcal{H}_2 = 1 - R_{ac}.$$

$\mathcal{H}_1$ is always positive and $\mathcal{H}_2$ is negative or positive depending on if R_{ac} is greater or less than unity.

Theorem 3.5. *The endemic equilibrium $\mathcal{C}^*$ exists whenever $R_{ac} > 1$.*

Proof. By looking at the linear equation of $\mathcal{H}_1 \lambda^* + \mathcal{H}_2 = 0$ we have that

$$\lambda^* = -\frac{\mathcal{H}_2}{\mathcal{H}_1} = \frac{R_{ac} - 1}{\mathcal{H}_1}. \quad (3.14)$$

But the disease is endemic when the force of infection $\lambda^* > 0$ which implies that $R_{ac} > 1$. Therefore the endemic equilibrium $\mathcal{C}^*$ exists whenever $R_{ac} > 1$. $\square$

Since the disease free equilibrium is globally asymptotically stable, it is evident that $\mathcal{C}^*$ is unique, and it has been shown that our endemic equilibrium exists for $R_{ac} > 1$. When $R_{ac} > 1$, the disease free equilibrium becomes unstable and it is natural to expect that the infectious populations will remain persistent in this case.

Theorem 3.6. *If $R_{ac} > 1$, model system (3.2) is uniformly persistent, namely, there exists a constant $\xi > 0$ such that,*

$$\begin{aligned} \liminf_{t \rightarrow \infty} S(t) &> \xi, & \liminf_{t \rightarrow \infty} A_a(t) &> \xi, & \liminf_{t \rightarrow \infty} A_u(t) &> \xi, \\ \liminf_{t \rightarrow \infty} L_a(t) &> \xi \text{ and } & \liminf_{t \rightarrow \infty} L_u(t) &> \xi. \end{aligned} \quad (3.15)$$

here, ξ is independent of the initial data in Ω .

Proof. When $t \rightarrow \infty$, from system (3.2), we obtain the following limiting system

$$\left\{ \begin{array}{l} \frac{dS}{dt} = \mu - \beta S(A_a(1 - \eta) + A_u) - \mu S, \\ \frac{dA_a}{dt} = \beta S(A_a(1 - \eta) + A_u) + \gamma(\psi)L_a - (\mu + \kappa + \psi + \delta(1 - \theta))A_a, \\ \frac{dA_u}{dt} = \delta(1 - \theta)A_a + \gamma_0 L_u - (\mu + \kappa)A_u, \\ \frac{dL_a}{dt} = (\kappa + \psi)A_a - (\mu + \gamma(\psi))L_a, \\ \frac{dL_u}{dt} = \kappa A_u - (\mu + \gamma_0)L_u. \end{array} \right. \quad (3.16)$$

We shall also denote the disease free equilibrium for model system (3.16) as C^0 . We set

$$X = \left\{ (S, A_a, A_u, L_a, L_u) \in S \geq 0, A_a \geq 0, A_u \geq 0, L_a \geq 0, L_u \geq 0 \right\},$$

$$X_0 = \left\{ (S, A_a, A_u, L_a, L_u) \in S \geq 0, A_a > 0, A_u > 0, L_a > 0, L_u > 0 \right\},$$

$$Y = X \setminus X_0.$$

Now, we have to show that model system (3.16) is uniformly persistent with respect to (X_0, Y) .

Firstly, by the form of model system (3.16), it can be easily shown that both X and X_0 are positively invariant. Clearly, Y is relatively closed in X and model system (3.16) is point dissipative. Consider the following set using solutions

$(S(t), A_a(t), A_u(t), L_a(t), L_u(t))$ of model system (3.16),

$$M_Y = \left\{ (S(0), A_a(0), A_u(0), L_a(0), L_u(0)) : (S(t), A_a(t), A_u(t), L_a(t), L_u(t)) \in Y, \forall t \geq 0 \right\}.$$

We now show that

$$M_Y = \left\{ (S(0), A_a(0), A_u(0), L_a(0), L_u(0)) : S \geq 0 \right\}. \quad (3.17)$$

Assume that $(S(0), A_a(0), A_u(0), L_a(0), L_u(0)) \in M_Y$. It suffices to show that $A_a(t) = A_u(t) = L_a(t) = L_u(t) = 0$. Suppose not, then there exists a $t_0 \geq 0$ such that:

$$\begin{aligned} & (A_a > 0, A_u = 0, L_a = 0, L_u = 0) \text{ or } (A_a > 0, A_u > 0, L_a = 0, L_u = 0) \text{ or} \\ & (A_a > 0, A_u > 0, L_a > 0, L_u = 0) \text{ or } (A_a > 0, A_u = 0, L_a > 0, L_u > 0) \text{ or} \\ & (A_a > 0, A_u = 0, L_a = 0, L_u > 0) \text{ or } (A_a > 0, A_u > 0, L_a = 0, L_u > 0) \text{ or} \\ & (A_a > 0, A_u = 0, L_a > 0, L_u = 0) \text{ or } (A_a = 0, A_u > 0, L_a = 0, L_u = 0) \text{ or} \\ & (A_a = 0, A_u > 0, L_a > 0, L_u = 0) \text{ or } (A_a = 0, A_u > 0, L_a = 0, L_u > 0) \text{ or} \\ & (A_a = 0, A_u > 0, L_a > 0, L_u = 0) \text{ or } (A_a = 0, A_u = 0, L_a > 0, L_u = 0) \text{ or} \\ & (A_a = 0, A_u = 0, L_a > 0, L_u > 0) \text{ or } (A_a = 0, A_u = 0, L_a = 0, L_u > 0). \end{aligned} \quad (3.18)$$

For $(A_a > 0, A_u = 0, L_a = 0, L_u = 0)$, we have

$$A'_u(t_0) = \delta(1 - \theta)A_a, \quad (3.19)$$

$$L'_a(t_0) = (\kappa + \psi)A_a.$$

It follows that there is an $\epsilon_0 > 0$ such that $A_u > 0$ and $L_a > 0$ for $t_0 < t < t_0 + \epsilon_0$. Clearly, we can restrict $\epsilon_0 > 0$ small enough such that $A_a > 0$ for $t_0 < t < t_0 + \epsilon_0$. This means that $(S(t), A_a(t), A_u(t), L_a(t), L_u(t)) \notin Y$ for $t_0 < t < t_0 + \epsilon_0$, which contradicts with the assumption that $(S(0), A_a(0), A_u(0), L_a(0), L_u(0)) \in M_Y$. For the other cases, we can also show these contradict the assumption that $(S(0), A_a(0), A_u(0), L_a(0), L_u(0)) \in M_Y$, respectively. Thus, (3.16) holds.

It is worth noting that $\mathcal{C}^0$ is globally asymptotically stable in the interior of M_Y . Moreover, $\mathcal{C}^0$ is an isolated invariant set in X , every orbit in M_Y converges to $\mathcal{C}^0$, and $\mathcal{C}^0$ is acyclic in M_Y . By Theorem 4.6 (Thieme, 1993), we only need to show that $W^S(\mathcal{C}^0) \cap X_0 = \emptyset$ if $R_{ac} > 1$.

In the following, we now prove that $W^S(\mathcal{C}^0) \cap X_0 = \emptyset$. Suppose not, that is, $W^S(\mathcal{C}^0) \cap X_0 \neq \emptyset$. Then there exists a positive solution $(S^*(t), A_a^*(t), A_u^*(t), L_a^*(t), L_u^*(t))$ with $(S^*(0), A_a^*(0), A_u^*(0), L_a^*(0), L_u^*(0)) \in X_0$, such that,

$$(S^*(t), A_a^*(t), A_u^*(t), L_a^*(t), L_u^*(t)) \longrightarrow \mathcal{C}^0 \text{ as } t \longrightarrow \infty.$$

Since $R_{ac} > 1$, we can choose a $\nu > 0$ small enough such that

$$R_{ac} - \nu R_{ac} > 1. \quad (3.20)$$

Thus, when t is sufficiently large, we have

$$\begin{aligned} S^0 - \nu &\leq S^*(t) \leq S^0 + \nu, \quad 0 \leq A_a^*(t) \leq \nu, \quad 0 \leq A_u^*(t) \leq \nu, \\ 0 &\leq L_a^*(t) \leq \nu, \quad 0 \leq L_u^*(t) \leq \nu, \end{aligned} \quad (3.21)$$

and

$$\left\{ \begin{aligned} \frac{dA_a}{dt} &\geq \beta S(A_a(1 - \eta) + A_u) + \gamma(\psi)L_a - (\mu + \kappa + \psi + \delta(1 - \theta))A_a, \\ \frac{dA_u}{dt} &\geq \delta(1 - \theta)A_a + \gamma_0 L_u - (\mu + \kappa)A_u, \\ \frac{dL_a}{dt} &\geq (\kappa + \psi)A_a - (\mu + \gamma(\psi))L_a, \\ \frac{dL_u}{dt} &\geq \kappa A_u - (\mu + \gamma_0)L_u. \end{aligned} \right. \quad (3.22)$$

By the comparison principle, it can be established that

$$A_a^*(t) \longrightarrow \infty, \quad A_u^*(t) \longrightarrow \infty, \quad L_a^*(t) \longrightarrow \infty, \quad L_u^*(t) \longrightarrow \infty,$$

which contradicts to

$$A_a^*(t) \longrightarrow 0, \quad A_u^*(t) \longrightarrow 0, \quad L_a^*(t) \longrightarrow 0, \quad L_u^*(t) \longrightarrow 0,$$

as $t \longrightarrow \infty$. This proves $W^S(\mathcal{C}^0) \cap X_0 = \emptyset$.

Since $W^S(\mathcal{C}^0) \cap X_0 = \emptyset$, $\bigcup_{x \in M_Y} \omega(x) = \{\mathcal{C}^0\}$, $\mathcal{C}^0$ is isolated invariant set in X , and $\mathcal{C}^0$ is acyclic in M_Y by Theorem 4.6 (Thieme, 1993), we are able to conclude that model system (3.16) is uniformly persistent with respect to (X_0, Y) . Hence, model system (3.2) is uniformly persistent.

□

Theorem 3.7. *If $R_{ac} > 1$, the endemic equilibrium point is globally asymptotically stable.*

Proof. To study the global asymptotic stability of the endemic equilibrium, following (Li et al., 2011; Huo and Chen, 2014), we use a Lyapunov function V as follows,

$$\begin{aligned} V = & \left(S - S^* - S^* \ln \frac{S}{S^*} \right) + V_1 \left(A_a - A_a^* - A_a^* \ln \frac{A_a}{A_a^*} \right) + V_2 \left(A_u - A_u^* - A_u^* \ln \frac{A_u}{A_u^*} \right) \\ & + V_3 \left(L_a - L_a^* - L_a^* \ln \frac{L_a}{L_a^*} \right) + V_4 \left(L_u - L_u^* - L_u^* \ln \frac{L_u}{L_u^*} \right), \end{aligned} \quad (3.23)$$

where $V_1, V_2, V_3, V_4 > 0$, are constants to be determined later. Applying the replacements

$$\frac{S}{S^*} = m, \quad \frac{A_a}{A_a^*} = n, \quad \frac{A_u}{A_u^*} = x, \quad \frac{L_a}{L_a^*} = y, \quad \frac{L_u}{L_u^*} = z, \quad (3.24)$$

the derivative of V is given by

$$\begin{aligned}
 \frac{dV}{dt} &= \left(1 - \frac{S^*}{S}\right) \frac{dS}{dt} + V_1 \left(1 - \frac{A_a^*}{A_a}\right) \frac{dA_a}{dt} + V_2 \left(1 - \frac{A_u^*}{A_u}\right) \frac{dA_u}{dt} \\
 &\quad + V_3 \left(1 - \frac{L_a^*}{L_a}\right) \frac{dL_a}{dt} + V_4 \left(1 - \frac{L_u^*}{L_u}\right) \frac{dL_u}{dt}. \\
 &= \left(1 - \frac{1}{m}\right) [\mu - \beta A_a(1 - \eta)S - \beta A_u S - \mu S] \\
 &\quad + V_1 \left(1 - \frac{1}{n}\right) [\beta A_a(1 - \eta)S + \beta A_u S + \gamma(\psi)L_a - (\mu + \kappa + \psi + \delta(1 - \theta))A_a] \\
 &\quad + V_2 \left(1 - \frac{1}{x}\right) [\delta(1 - \theta)A_a + \gamma_0 L_u - (\mu + \kappa)A_u] \\
 &\quad + V_3 \left(1 - \frac{1}{y}\right) [(\kappa + \psi)A_a - (\mu + \gamma(\psi))L_a] + V_4 \left(1 - \frac{1}{z}\right) [\kappa A_u - (\mu + \gamma_0)L_u].
 \end{aligned} \tag{3.25}$$

At the endemic equilibrium point, model system (3.2) has the following identities

$$\left\{ \begin{array}{ll} \mu &= \beta A_a^*(1 - \eta)S^* + \beta A_u^* S^* + \mu S^*, \\ (\mu + \kappa + \psi + \delta(1 - \theta))A_a^* &= \beta A_a^*(1 - \eta)S^* + \beta A_u^* S^* + \gamma L_a^*, \\ (\mu + \kappa)A_u^* &= \delta(1 - \theta)A_a^* + \gamma_0 L_u^*, \\ (\mu + \gamma(\psi))L_a^* &= (\kappa + \psi)A_a^*, \\ (\mu + \gamma_0)L_u^* &= \kappa A_u^*. \end{array} \right. \tag{3.26}$$

Thus,

$$\begin{aligned}
\frac{dV}{dt} = & \left(1 - \frac{1}{m}\right) [\beta A_a^*(1 - \eta)S^* + \beta A_u^*S^* + \mu S^* - \beta A_a^*(1 - \eta)S^*mn - \beta A_u^*S^*mx - \mu S^*m] \\
& + V_1 \left(1 - \frac{1}{n}\right) [\beta A_a^*(1 - \eta)S^*mn + \beta A_u^*S^*mx + \gamma L_a^*y - \beta A_a^*(1 - \eta)S^*n - \beta A_u^*S^*n - \gamma L_a^*n] \\
& + V_2 \left(1 - \frac{1}{x}\right) [\delta(1 - \theta)A_a^*n + \gamma_0 L_u^*z - \delta(1 - \theta)A_a^*x - \gamma_0 L_u^*x] \\
& + V_3 \left(1 - \frac{1}{y}\right) [(\kappa + \psi)A_a^*n - (\kappa + \psi)A_a^*y] + V_4 \left(1 - \frac{1}{z}\right) [\kappa A_u^*x - \kappa A_u^*z]. \tag{3.27}
\end{aligned}$$

$$\begin{aligned}
= & \beta A_a^*(1 - \eta)S^* + \beta A_u^*S^* + \mu S^* - \beta A_a^*(1 - \eta)S^*mn - \beta A_u^*S^*mx - \mu S^*m \\
& - \beta A_a^*(1 - \eta)S^*\frac{1}{m} - \beta A_u^*S^*\frac{1}{m} - \mu S^*\frac{1}{m} + \beta A_a^*(1 - \eta)S^*n + \beta A_u^*S^*x + \mu S^* \\
& + V_1 \left(\beta A_a^*(1 - \eta)S^*mn + \beta A_u^*S^*mx + \gamma L_a^*y - \beta A_a^*(1 - \eta)S^*n - \beta A_u^*S^*n - \gamma L_a^*n \right. \\
& \left. - \gamma L_a^*\frac{y}{n} - \beta A_a^*(1 - \eta)S^*m - \beta A_u^*S^*\frac{mx}{n} + \beta A_a^*(1 - \eta)S^* + \beta A_u^*S^* + \gamma L_a^* \right) \\
& + V_2 \left(\delta(1 - \theta)A_a^*n + \gamma_0 L_u^*z - \delta(1 - \theta)A_a^*x - \gamma_0 L_u^*x - \delta(1 - \theta)A_a^*\frac{n}{x} - \gamma_0 L_u^*\frac{z}{x} \right. \\
& \left. + \delta(1 - \theta)A_a^* + \gamma_0 L_u^* \right) \\
& + V_3 \left((\kappa + \psi)A_a^*n - (\kappa + \psi)A_a^*y - (\kappa + \psi)A_a^*\frac{n}{y} + (\kappa + \psi)A_a^* \right) \\
& + V_4 \left(\kappa A_u^*x - \kappa A_u^*z - \kappa A_u^*\frac{x}{z} + \kappa A_u^* \right). \tag{3.28}
\end{aligned}$$

We define the set $\mathcal{G}$ of all the above terms as,

$$\mathcal{G} = \left\{ m, n, x, y, z, \frac{1}{m}, \frac{y}{n}, \frac{n}{y}, \frac{x}{z}, \frac{z}{x}, \frac{n}{x}, \frac{mx}{n} \right\}. \tag{3.29}$$

Then we create some subsets of $\mathcal{G}$, where the product of each set equals one (like $\frac{y}{n} \times \frac{n}{y} = 1$).

$$\left\{ m, \frac{1}{m} \right\}, \left\{ \frac{y}{n}, \frac{n}{y} \right\}, \left\{ \frac{x}{z}, \frac{z}{x} \right\}, \left\{ \frac{1}{m}, \frac{n}{x}, \frac{mx}{n} \right\}. \tag{3.30}$$

Then, we let the coefficients of the terms that are not members of our subsets in

(3.30), for the function dV/dt be zero, that is, the coefficients of the terms

n, x, y, z, mn, mx . Thus, we have

$$\begin{cases} (V_1 - 1)\beta A_u^* S^* = 0, \\ (V_1 - 1)\beta A_a^*(1 - \eta)S^* = 0, \\ \gamma L_a^* V_1 - (\kappa + \psi)A_a^* V_3 = 0, \\ \gamma_0 L_u^* V_2 - \kappa A_u^* V_4 = 0, \\ \beta A_u^* S^* - \delta(1 - \theta)A_a^* V_2 - \gamma_0 L_u^* V_2 + \kappa A_u^* V_4 = 0, \\ \beta A_a^*(1 - \eta)S^* - \beta A_a^*(1 - \eta)S^* V_1 - \beta A_u^* S^* V_1 - \gamma L_a^* V_1 + \delta(1 - \theta)A_a^* V_2 + (\kappa + \psi)A_a^* V_3 = 0. \end{cases} \quad (3.31)$$

From (3.31), it follows that

$$V_1 = 1, \quad V_2 = \frac{\beta A_u^* S^*}{\delta(1 - \theta)A_a^*}, \quad V_3 = \frac{\gamma L_a^*}{(\kappa + \psi)A_a^*}, \quad V_4 = \frac{\gamma_0 L_u^* \beta A_u^* S^*}{\kappa A_u^* \delta(1 - \theta)A_a^*}. \quad (3.32)$$

From (3.32), the derivative of V is given by

$$\begin{aligned} \frac{dV}{dt} = & \beta A_a^*(1 - \eta)S^* + 2\beta A_u^* S^* + \mu S^* - \mu S^* m - \beta A_a^*(1 - \eta)S^* \frac{1}{m} - \beta A_u^* S^* \frac{1}{m} \\ & - \mu S^* \frac{1}{m} + \mu S^* + V_1 \left(-\beta A_u^* S^* \frac{mx}{n} - \gamma L_a^* \frac{y}{n} + \beta A_a^*(1 - \eta)S^* + \beta A_u^* S^* + \gamma L_a^* \right) \\ & + V_2 \left(\gamma_0 L_u^* + \delta(1 - \theta)A_a^* - \gamma_0 L_u^* \frac{z}{x} - \delta(1 - \theta)A_a^* \frac{n}{x} \right) \\ & + V_3 \left((\kappa + \psi)A_a^* - (\kappa + \psi)A_a^* \right) + V_4 \left(\kappa A_u^* - \kappa A_u^* \frac{x}{z} \right). \end{aligned} \quad (3.33)$$

After some tedious algebraic manipulations, then we have

$$\begin{aligned} \frac{dV}{dt} = & (\beta A_a^*(1 - \eta)S^* + \mu S^*) \left(2 - m - \frac{1}{m} \right) + \gamma_0 L_a^* \left(2 - \frac{n}{y} - \frac{y}{n} \right) \\ & + \frac{\gamma_0 L_u^* \beta A_u^* S^*}{\delta(1 - \theta)A_a^*} \left(2 - \frac{z}{x} - \frac{x}{z} \right) + \beta A_u^* S^* \left(3 - \frac{1}{m} - \frac{n}{x} - \frac{mx}{n} \right). \end{aligned} \quad (3.34)$$

By the property that the arithmetic mean is greater than or equal to the geometric mean, then $2 - m - 1/m \leq 0$ for $m > 0$ and $2 - m - 1/m = 0$ if and only if $m = 1$; $3 - 1/m - n/x - mx/n \leq 0$ for $m > 0$, $n > 0$ and $x > 0$ and

$3 - 1/m - n/x - mx/n = 0$ if and only if $m = n = x = 1$; $2 - x/z - z/x \leq 0$ for $x > 0$, $z > 0$ and $2 - x/z - z/x = 0$ if and only if $z = 1$ and $x = 1$, and lastly $2 - y/n - n/y \leq 0$ for $n > 0$, $y > 0$ and $2 - y/n - n/y = 0$ if and only if $n = 1$ and $y = 1$.

In conclusion, the limit cycle $dV/dt = 0$ if and only if $m = n = x = y = z = 1$. The maximum invariant set of system (3.2) on the set $\{(m, n, x, y, z) : \dot{V} = 0\}$ is the singleton $(1, 1, 1, 1, 1)$. Thus, for model system (3.2), the endemic equilibrium is globally asymptotically stable if $R_{ac} > 1$ by LaSalle invariance principle. $\square$

Analysis of the reproduction number

In this section we theoretically assess the effects of adherence on curtailing the spread of HSV-2 and also consider some different possibilities for our reproduction numbers.

Case (a) There is no treatment in the community

We set $\psi = \eta = 0$ and $\theta = 1$. Then the spectral radius is given by

$$R_0 = \frac{\beta(\mu + \gamma_0)}{\mu(\mu + \kappa + \gamma_0)}. \quad (3.35)$$

Biologically, R_0 represents the average number of secondary HSV-2 cases produced by a single HSV-2 infected individual during his/her infectious period in the absence of treatment and any other HSV-2 intervention strategies.

Case (b) Everyone is adhering to the HSV-2 anti-viral treatment in the community

We set $\theta = 1$. Then the spectral radius is given by

$$R_a = \frac{\beta(\mu + \gamma(\psi))}{\mu(\gamma(\psi) + \kappa + \psi + \mu)}. \quad (3.36)$$

Biologically, R_a represents the average number of secondary HSV-2 cases produced by a single HSV-2 infected individual during his/her infectious period in the presence of HSV-2 treatment where everyone is adhering to the HSV-2 anti-viral treatment.

Case (c) The general case

This is the general case which has been defined in equation 3.10 above, which is given by

$$\begin{aligned}
 R_{ac} &= \frac{\beta(\mu + \gamma(\psi))[\delta(1 - \theta)(\mu + \gamma_0) + \mu(1 - \eta)(\mu + \kappa + \gamma_0)]}{\mu(\mu + \kappa + \gamma_0)[\gamma(\psi)(\delta(1 - \theta) + \mu) + \mu(\delta(1 - \theta) + \mu + \kappa + \psi)]} \\
 &= R_{ac}^1 + R_{ac}^2 \\
 &= \frac{\beta(\mu + \gamma(\psi))(\mu + \gamma_0)\delta(1 - \theta)}{\mu(\mu + \kappa + \gamma_0)[\gamma(\psi)(\delta(1 - \theta) + \mu) + \mu(\delta(1 - \theta) + \mu + \kappa + \psi)]} \\
 &\quad + \frac{\beta(1 - \eta)(\mu + \gamma(\psi))}{[\gamma(\psi)(\delta(1 - \theta) + \mu) + \mu(\delta(1 - \theta) + \mu + \kappa + \psi)]}. \tag{3.37}
 \end{aligned}$$

R_{ac}^1 is the reproduction number induced by the individuals who do not fully adhere to HSV-2 anti-viral treatment, like those who quit treatment before completion and R_{ac}^2 is the reproduction number induced by the individuals who fully adhere to HSV-2 anti-viral treatment.

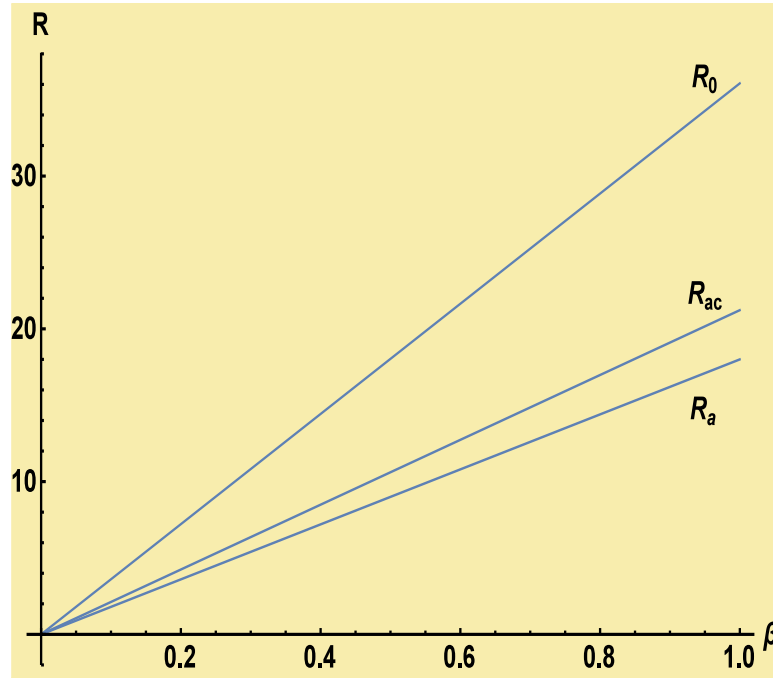


Figure 3.2: Effect of varying the effective contact rate β on the reproduction numbers. Where R represents the reproduction number(s).

R_j	R_0	R_a	R_{ac}
K_j	38.07	21.223	17.89

Table 3.2: The linear dependence of the reproduction number R_j on the constant rate β , for $j = 0, a, ac$.

Figure 3.2 shows that $R_0 > R_{ac} > R_a$, indicating that adherence has an effect on reducing the reproduction number. Furthermore, since R_{ac} represents 70% adherence and R_a , 100% adherence, it means that an increase in the level of adherence among individuals in a community has an effect on reducing the prevalence of HSV-2. The fact that $R_0 > R_a$, indicates that treatment also has an effect on reducing the reproduction number.

Table 3.2 depicts the numerical values of the relationship of the linear equation $R_j = K_j\beta$, for $j = 0, a, ac$ with respect to each reproductive number plotted in Figure 3.2. R_j is the reproduction number, β the effective contact rate and K_j is the respective constant of proportionality.

Sensitivity analysis

In this section we perform the sensitivity analysis of the reproductive number. Sensitivity analysis tells us how important each parameter is to disease transmission. Such information is crucial not only for experimental design, but also to data assimilation and reduction of complex nonlinear models (Powell et al., 2005). Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values, since there are usually errors in data collection and presumed parameter values. It is used to discover parameters that have a high impact on R_{ac} and should be targeted by intervention strategies.

Following Arriola and Hyman (2007), we present the normalised forward sensitivity indices of R_{ac} with respect to our model parameters in Table 3.1. The detailed sensitivity indices of R_{ac} resulting from the evaluation to other model parameters are shown in Table 3.3. The sensitivity index with respect to θ , for example is,

$$\Upsilon_{\theta}^{R_{ac}} = \frac{\partial R_{ac}}{\partial \theta} \times \frac{\theta}{R_{ac}} = -0.51079.$$

	Symbol	Definition	Sensitivity Index
1	$\gamma(\psi)$	Reactivation rate of latent HSV-2 with an effect of treatment	0.327651
2	γ_0	Baseline reactivation rate of latent HSV-2	0.691435
3	β	Effective contact rate for HSV-2 infection	1
4	κ	Rate of acute HSV-2 becoming latent	-0.976583
5	ψ	Treatment rate of acute HSV-2	-0.0538677
6	μ	Average sexual lifespan	-1.01589
7	θ	Proportion of adherence	-0.51079
8	δ	Treatment quitting rate	0.170263
9	η	Modification parameter	-0.130296

Table 3.3: Sensitivity indices of model parameters to R_{ac}

Since $\Upsilon_{\theta}^{R_{ac}} = -0.51079$, increasing (or decreasing) the proportion of individuals who

are adhering to HSV-2 anti-viral treatment by 51%, decrease (or increase) the reproduction number (R_{ac}) by 51%. Thus, increasing the number of individuals adhering to HSV-2 anti-viral treatment would be very crucial in curtailing the spread of HSV-2.

Similarly, increasing (or decreasing) the treatment rate of the acute HSV-2 infected individuals by 5% would also trigger an decrease (or increase) in R_{ac} by 5%. It is worth noting that an increase in treatment rate of the acute HSV-2 individuals automatically reduces the re-activation rate of latent HSV-2 individuals who came into the latent class through treatment. As illustrated in Table 3.3, re activation rate of the latent HSV-2 individuals who adhered to treatment has an effect of reducing the reproduction number (R_{ac}) by 33% if it has been increased or decreased by 33%. Thus, it would be very crucial to increase treatment rate of the acute HSV-2 individuals. Methods, such as the use of pre-packaged blister cards (Wrights et al., 1999), the use of follow-up telephone calls (Beaucage et al., 2006) and sharing of simple instructions about antimicrobial/anti-viral therapy which include information about adverse reactions (Reyes et al., 1997; Kardas, 2002), can be employed so as to improve and encourage adherence within the community.

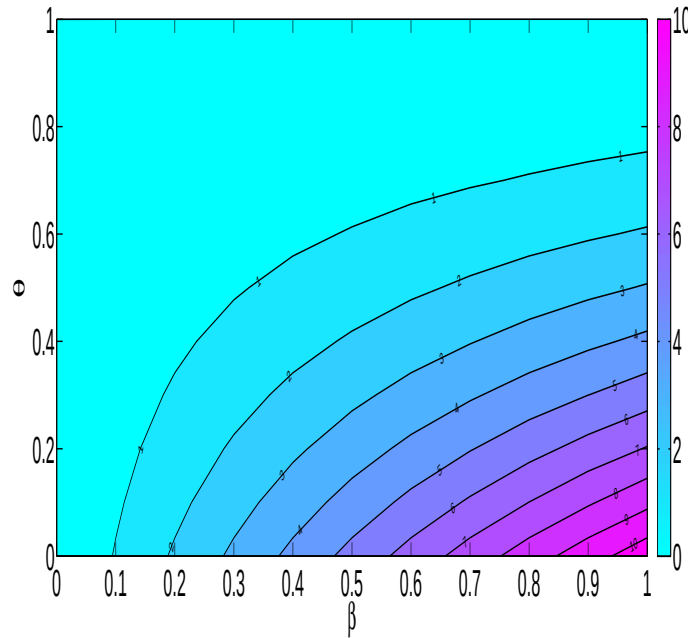


Figure 3.3: Simulations of model system (3.2) showing the contour plots of R_{ac} as a function of the effective contact rate for HSV-2 infection (β), and the proportion of individuals who are adhering to the HSV-2 anti-viral treatment (θ).

Figure 3.3 depicts the combined effect of the effective contact rate β and the proportion of individuals who are adhering to the HSV-2 anti-viral treatment θ on the reproduction number R_{ac} . These contour plots show a marked decrease in R_{ac} with increasing adherence and decreasing effective contact rate. Significantly high adherence and low effective contact rate are needed to reduce the prevalence of HSV-2 (achieve $R_{ac} < 1$).

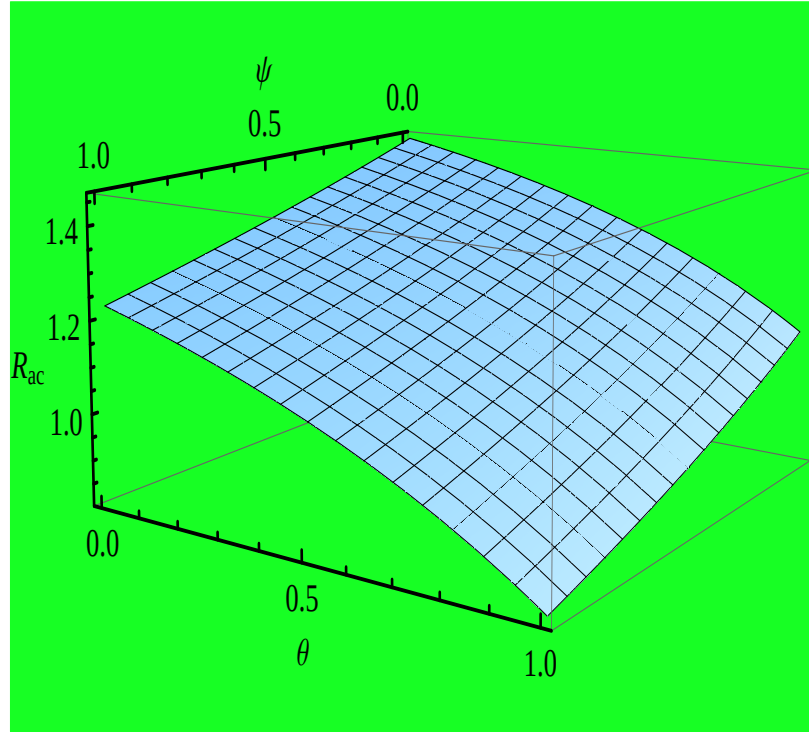


Figure 3.4: Simulations of model system (3.2) showing the effects of varying the treatment rate of acute HSV-2 and the proportion of individuals who are adhering to the HSV-2 anti-viral treatment (θ).

Figure 3.4 depicts the combined effect of proportion of individuals who are adhering to the HSV-2 anti-viral treatment θ and the treatment rate of acute HSV-2 on the reproduction number R_{ac} . Figure 3.4 shows that the reproduction number can be significantly reduced for high rates of adherence and high rates of treatment.

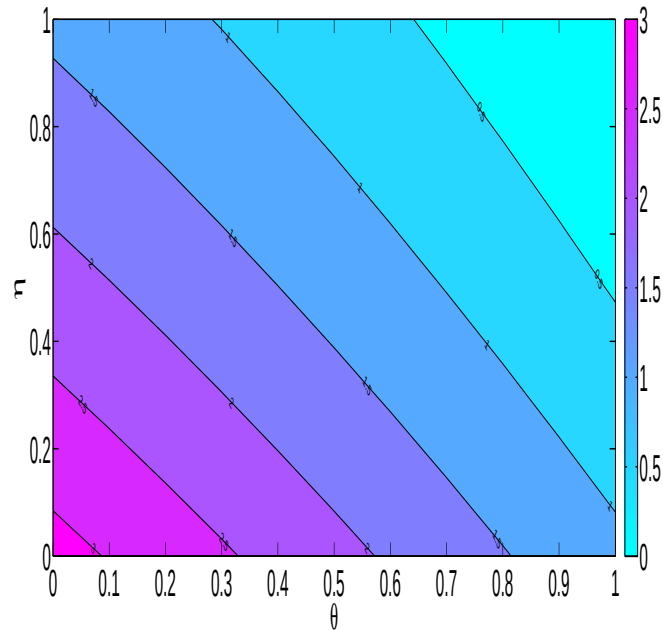


Figure 3.5: Simulations of model system (3.2) showing the contour plots of R_{ac} as a function of the modification parameter (η) and the proportion of individuals who are adhering to the HSV-2 anti-viral treatment (θ).

Figure 3.5 depicts that if more people are adhering to HSV-2 anti-viral treatment and at the same time having few infectious individuals who are not under treatment being infectious, then the disease can be curtailed. Conversely, low values of people adhering to HSV-2 anti-viral treatment and at the same time having more infectious individuals who are not under treatment being infectious, then HSV-2 will prevail.

3.4. Optimal control problem

We introduce into model system (3.2), a time-dependent control effort on counselling and monitoring (u), as a control to curtail the spread of HSV-2. The HSV-2

model system (3.2) becomes,

$$\left\{ \begin{array}{l} \frac{dS}{dt} = \mu - \lambda S - \mu S, \\ \frac{dA_a}{dt} = \lambda S + \gamma(\psi)L_a - (\mu + \kappa + \psi)A_a - \delta(1-u)A_a, \\ \frac{dA_u}{dt} = \delta(1-u)A_a + \gamma_0 L_u - (\mu + \kappa)A_u, \\ \frac{dL_a}{dt} = (\kappa + \psi)A_a - (\mu + \gamma(\psi))L_a, \\ \frac{dL_u}{dt} = \kappa A_u - (\mu + \gamma_0)L_u. \end{array} \right. \quad (3.38)$$

For this, we consider the objective functional

$$J(u) = \min_u \int_0^{t_f} (zA_u + \vartheta u^2) dt, \quad (3.39)$$

where t_f is the final time and where z is a positive weight constant to balance the factor. The term ϑu^2 is the cost of the control effort on counselling and monitoring of HSV-2 individuals under treatment. We choose a quadratic cost on the control, this is similar with that in other literature on epidemic controls (Joshi, 2002; Kirschner et al., 1997). With the given objective function $J(u)$, our goal is to minimise the number of HSV-2 individuals who would have failed to adhere to HSV-2 anti-viral treatment A_u , while minimising the cost of control u^* such that

$$J(u^*) = \min \{J(u) | u \in \mathcal{U}\}, \quad (3.40)$$

where $\mathcal{U} = \{u \text{ is such that } u \text{ is measurable with } 0 \leq u \leq 1 \text{ for } t \in [0, t_f]\}$ is the control set. The necessary conditions that an optimal must satisfy come from the Pontryagin's maximum principle (Pontryagin et al., 1985). This principle converts (3.38)-(3.39) into a problem of minimising point-wise a Hamiltonian H , with respect to u

$$\begin{aligned}
H = & \quad zA_u + \vartheta u^2 + \lambda_1[\mu - \lambda S - \mu S] \\
& + \lambda_2[\lambda S + \gamma(\psi)L_a - (\mu + \kappa + \psi)A_a - \delta(1 - u)A_a] \\
& + \lambda_3[\delta(1 - u_1)A_a + \gamma_0 L_u - (\mu + \kappa)A_u] \\
& + \lambda_4[(\kappa + \psi)A_a - (\mu + \gamma(\psi))L_a] \\
& + \lambda_5[\kappa A_u - (\mu + \gamma_0)],
\end{aligned} \tag{3.41}$$

where the λ_1 , λ_2 , λ_3 , λ_4 , and λ_5 are the adjoint variables or shadow price. By applying Pontryagin's maximum principle (Pontryagin et al., 1985), and the existence result for the optimal control from (Fleming and Rishel., 1975) we obtain

Theorem 3.8. *For the optimal control u^* that minimises $J(u)$ over $\mathcal{U}$, then there exist adjoint variables λ_1 , λ_2 , λ_3 , λ_4 , and λ_5 satisfying*

$$\left\{ \begin{aligned} \frac{d\lambda_1}{dt} &= \beta(A_a(1 - \eta) + A_u)[\lambda_1 - \lambda_2] + \mu\lambda_1, \\ \frac{d\lambda_2}{dt} &= \beta(1 - \eta)S[\lambda_1 - \lambda_2] + (\kappa + \psi)[\lambda_2 - \lambda_4] + \delta(1 - u)[\lambda_2 - \lambda_3] + \mu\lambda_2, \\ \frac{d\lambda_3}{dt} &= -z + \beta S[\lambda_1 - \lambda_2] + \kappa[\lambda_3 - \lambda_5] + \mu\lambda_3, \\ \frac{d\lambda_4}{dt} &= \gamma(\psi)[\lambda_4 - \lambda_2] + \mu\lambda_4, \\ \frac{d\lambda_5}{dt} &= \gamma_0[\lambda_5 - \lambda_3] + \mu\lambda_5. \end{aligned} \right. \tag{3.42}$$

with transversality conditions

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = \lambda_5(t_f) = 0, \quad (3.43)$$

additionally, the optimal control u^* that minimises $J(u)$ over $\mathcal{U}$ satisfies the optimality condition,

$$u^* = \max \left\{ 0, \min \left(1, \frac{(\lambda_3 - \lambda_2)\delta A_a}{2\vartheta} \right) \right\}. \quad (3.44)$$

Proof. Corollary 4.1 of (Fleming and Rishel., 1975) gives the existence of an optimal control due to the convexity of the integrand of J with respect to u , *a priori* boundedness of the state solutions, and the *Lipschitz* property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by differential of the Hamiltonian function, evaluated at the optimal control.

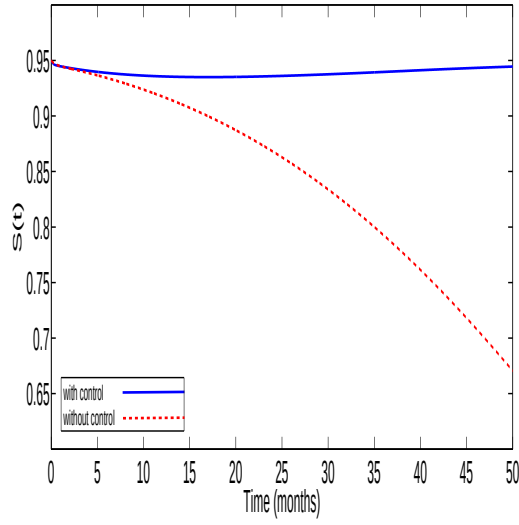
□

Due to the *a priori* boundedness of the state system, adjoint system and the resulting *Lipschitz* structure of the ODEs, we obtain the uniqueness of the optimal control for small t_f . The uniqueness of the optimal control follows from the uniqueness of the optimality system, which consists of (3.42) and (3.43) with characterisation (3.44). There is a restriction on the length of time interval in order to guarantee the uniqueness of the optimality system. The smallness restriction of the length on time is due to the opposite time orientations of (3.42) and (3.43), the state problem has initial values and the adjoint variable has final values. The restriction is common in control problems (Joshi, 2002 ; Kirschner et al., 1997).

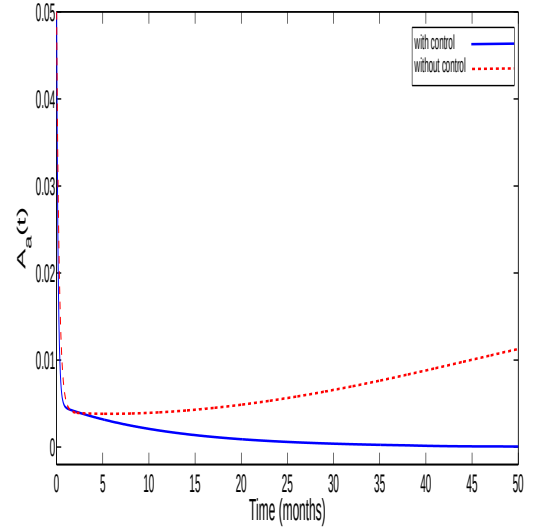
3.4.1. Numerical Simulations

The optimality system is solved using an iterative method with Runge-Kutta fourth order scheme. Starting with a guess for the adjoint variables, the state equations are solved forward in time. Then these state values are used to solve the adjoint equations backward in time, and the iterations continue until convergence. The

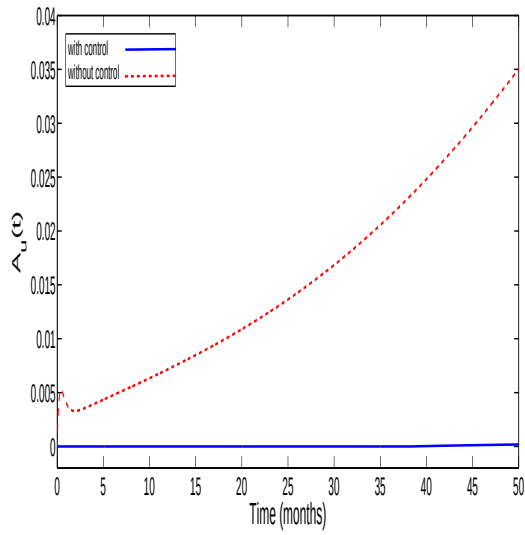
simulation were carried out using parameter values in Table 3.1 and the following values $z = 0.95$ and $\vartheta = 0.01$. The assumed initial conditions for the differential equations are $S = 0.95$, $A_a = 0.05$, $A_u = 0.0$, $L_a = 0.0$, $L_u = 0.0$.



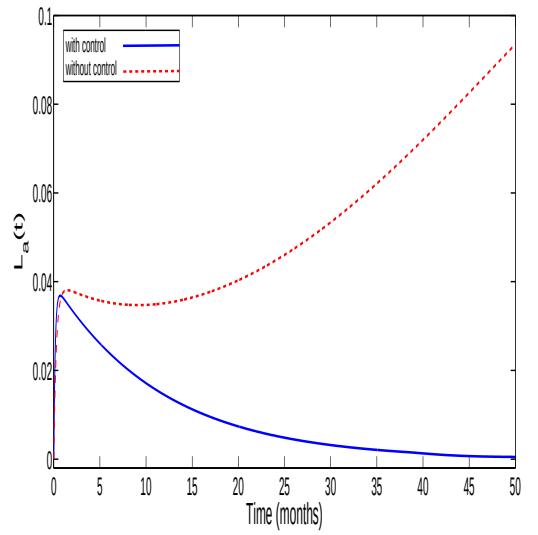
(a)



(b)



(c)



(d)

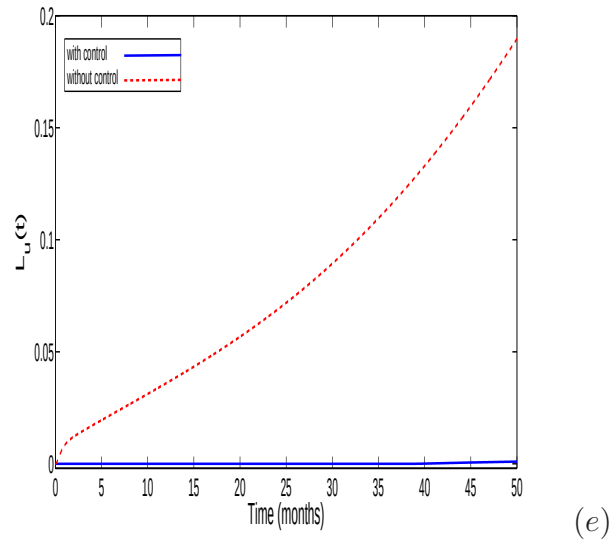


Figure 3.6: Graphs of the numerical solutions of the optimality system, showing propagation of, (a) susceptibles S , (b) infected with acute HSV-2 and also under anti-viral treatment A_a , (c) infected with latent HSV-2 after undergoing successful anti-viral treatment L_a , (d) infected with acute HSV-2 and not under anti-viral treatment after quitting before completion A_u , (e) and the infected with latent HSV-2 after undergoing natural healing L_u , over a period of 50 months.

In Figure 3.6(a) we note that for the whole interval under study, optimal counselling and monitoring leads to a very small decrease of the susceptible population. In the absence of the control, it is worth noting that the population of the susceptible individuals drops drastically. Thus, optimal counselling and monitoring has an effect on the susceptible population.

Figure 3.6(b) illustrates the population of the individuals with acute HSV-2 and also under anti-viral treatment in the presence and absence of the control over a period of 50 months. For both cases, in the presence and absence of the control there is no much difference since both populations have a sharp decrease for the period 0-2.5 months. For the period 2.5-50 months, the population of the individuals in the absence of a control increases gradually for that period under review. Further, we note that for the same period under review (2.5-50 months), the population of the individuals in the presence of the control reduces significantly signifying a positive effect of the control.

Figure 3.6(c) shows the individuals infected with acute HSV-2 and not under anti-viral treatment after quitting before completion, in the presence and absence of the control. In the absence of the control, the individuals increases gradually in the first month then reduce again a little, for the next two months before increasing rapidly for the remaining period under review, that is 3-50 months. In the presence of the control, we note that for the whole period under review the HSV-2 cases remain relatively insignificant.

In Figure 3.6(d), the population of the infected with latent HSV-2 after undergoing successful anti-viral treatment in the presence and absence of the controls, over a period of 50 months is presented. The population of the infected individuals with latent HSV-2 after undergoing successful anti-viral treatment have a sharp increase for the first month, for both cases (with or without the control). In the presence of the control, we then note that from 2-50 months the population of the HSV-2 cases decreases gradually until it almost reaches 0. In the absence of the control, the population of the individuals drops slightly over the period 2-9 months, further, it then increases rapidly in the interval 10-50 months.

In Figure 3.6(e) the dynamics of the infected with latent HSV-2 after undergoing natural healing are presented. In the absence of the control, the population of the individuals increases rapidly for the whole period under review. In the absence of the control, the population of the infected individuals remains very very low for the whole period under review, that is 0-50 months.

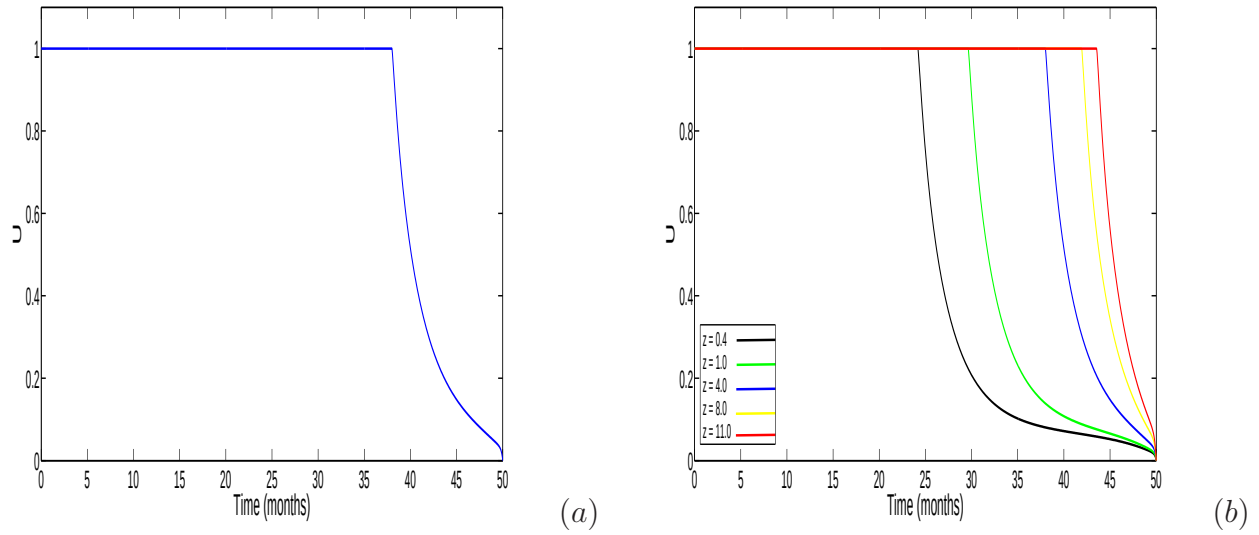


Figure 3.7: Graphs of the numerical solutions to the behaviour of the control constrain, (a) with the weight constant $z = 0.4$, (b) with the weight constant z being varied.

Figure 3.7(a) represents the control u . The control is at the upper bound 1 for approximately 37 months and has a sharp drop until it reaches the lower bound 0. Figure 3.7(b) shows the control u , being varied. It shows that the weight constant has been varied (increased or reduced about $z = 4$). Increasing z implies increasing the minimisation of A_u and A_u classes. Increasing the weight constant z implies the control effort on counselling and monitoring are implemented for a longer time. Further, reducing z implies a reduction in the minimisation of the of A_u and A_u classes. A reduction of the weight constant work against the efforts on counselling and monitoring since they will be implemented for a shorter period.

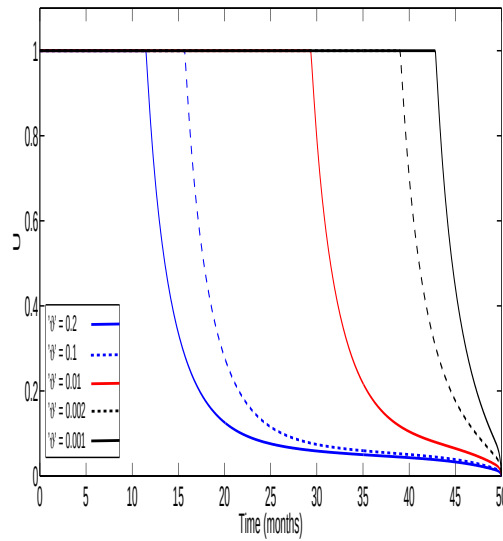


Figure 3.8: Graph of the numerical solutions to the behaviour of the control constrain, with the weight and cost factor ϑ being varied.

Figure 3.8 illustrates the range of values, that can be taken by ϑ (increasing or decreasing it around the value 0.01). Increasing the weight and cost factor (ϑ) works against the efforts on counselling and monitoring since they will be implemented for a shorter period, hence not suitable. Reducing the weight and cost factor (ϑ) works in favour of implementing the efforts on counselling and monitoring since they will be implemented for a longer period. It is worth noting that for our numerical simulations we assumed $\vartheta = 0.01$, since that was the feasible optimum value which was applicable.

3.5. Concluding remarks

HSV-2 is a significant factor for increased risk of acquisition and transmission of HIV and also being the leading disease in causing genital ulcers. In this study, a mathematical model to assess the impact of non-adherence to HSV-2 anti-viral treatment is developed and analysed. Qualitative analysis of the model has shown that the model has a globally asymptotically stable disease free equilibrium when-

ever the reproduction number is less than unity. The Lyapunov function approach was used to prove the global stability of the endemic equilibrium. Sensitivity analysis of the reproduction number suggested that increasing the rate of adherence by 51% has an effect of increasing the reproduction number by 51%. Furthermore, analysis of the reproduction number through the contour plots shows that the reproduction number can be reduced to very low levels by increasing the adherence rate and decreasing the effective contact rate. Our results are in agreement with some earlier findings which managed to suggest that adherence to HSV-2 anti-viral treatment is vital in the fight against HSV-2, although tailored adherence strategies may be needed (Retaino et al., 1998; Watson-Jones, 2009). Optimal control was then applied with the objective of minimising the number of individuals quitting HSV-2 anti-viral treatment. The technical tool used to determine the optimal strategy is the Pontryagin maximum principle. The control represent counselling and treatment. According to our optimal control results, we saw that a reduction of the weight constant work against the efforts on counselling and monitoring since they will be implemented for a shorter period. Our optimal control results also suggests that to successfully control HSV-2 prevalence we need to keep the cost of the control effort as low as possible. Overall, the study finds that in a community where HSV-2 is endemic the disease can be eliminated or controlled if optimal intervention strategies are implemented.

Chapter 4

Modelling the effects of sexting on the transmission dynamics of HSV-2 amongst adolescents

4.1. Introduction

Cellphone usage has increased dramatically in the United States of America (USA), with more than 320 million individual subscriber connections as of 2011 (CTIA, 2012). Adolescents are more likely to be cellphone users since they are individuals aged between 10-19 years old inclusive (WHO, 1998), and constituting approximately 20% of the world's population (Denhe and Riedner, 2005). Cellphone use has the potential for other negative outcomes and in recent years, a new trend of sexualised text communication has emerged, which is known as sexting. "Sexting" was listed in the Time magazine as the number one word buzzword of 2009 (Stephey, 2009), and was also a finalist for the 2009 word of the year by the New Oxford American Dictionary (Stangling, 2009).

The major force behind the majority of adolescents joining sexting is because of peer influence (Carter, 2009). Researchers suggest that the adolescents were amongst the group with the highest sexting rate, and they are also the group that reports the greatest use of these devices (Mitchell et al., 2012). Adolescents and people who seek partners online or who are involved in sexting, have a higher number of sexual partners, more unprotected sex acts, higher rates of substance abuse in conjunction with sexual activity and more sexually transmitted infections (Benotsch et al., 2011; Bolding et al., 2013; Bull and McFarlane, 2000; Grov et al., 2007; Horvath et al., 2006; McFarlane, 2000; McFarlane, 2002). With rapidly increasing popularity of smart phones as web platforms, there would appear to exist a potential for cell phone technology to also play a role in sexuality. Sexting plays a major role in polarising someone's sexual behaviour. Since sexting was found to be greatly associated with high risk sexual behaviour and higher rates of STIs (Benotsch et al., 2013), it would be very crucial to find ways of reducing sexting, especially amongst adolescents.

Most of the limited research on sexting to date focused on social and legal consequences of this behaviour (O'Keeffe et al., 2011). There is less research that has examined the potential health implications of sexting. Specifically, there has been limited research examining the relationship between sexting and sexual risk behaviour (Benotsch et al., 2013). A number of mathematical models have looked into mathematical modelling of STIs and high risk sexual behaviour (Pinkerton et al., 2011; Truong et al., 2006; Turner et al., 2004; Garnett, 2002; Garnett and Anderson, 1996; Zenilman, 2007; Gorbach and Holmes, 2003), to mention just a few. To date, a number of mathematical models have looked into mathematical modelling of HSV-2. To the best of our knowledge as authors, no mathematical model has looked into the effects of sexting and peer influence on the transmission dynamics of any STIs mainly HSV-2. It is against this background that our chapter finds relevance and motivation, by formulating a mathematical model to investigate the impact of sexting and peer influence on the transmission dynamics of HSV-2. The model incorporates some key epidemiological features such as the

impact of awareness campaigns and filtering. Filtering is a modern technology that prevent individuals from sending or accessing pornographic content and sexting on the internet, mobile phones, ipads, etc. These filters can operate at network and device level (Carter, 2009; Patlar et al., 2012; Eneman, 2006). The main objective of this study is to forecast future trends in the incidence of HSV-2 epidemic and also to quantify the association between sexting, peer influence and HSV-2 epidemic amongst adolescents in a society.

4.2. Model formulation

The model subdivides the population based on HSV-2 status and also on sexting amongst adolescents. The population is divided into the following classes: Susceptible adolescents who are not into sexting S_N , infected adolescents who are not into sexting I_N , susceptible adolescents who are into sexting S_T and infected adolescents who are into sexting I_T . Individuals in all sub-classes experience natural death only at a rate μ which is proportional to the number in each class and neither sexting nor HSV-2 cause death. The total sexually active population at time t , is given by $N(t) = N_N(t) + N_T(t)$, $N_N(t) = S_N(t) + I_N(t)$ and $N_T(t) = S_T(t) + I_T(t)$ with $N_T(t)$ and $N_N(t)$ being the total number of adolescents who are into sexting and non-sexting, respectively. The susceptible population is increased by a constant inflow into the population at a rate Λ . Assuming homogeneous mixing of the population, the sexting and non-sexting susceptibles acquire HSV-2 infection at a rate λ_h and $\alpha\lambda_h$ respectively, with

$$\lambda_h(t) = \frac{\beta_h(I_T(t) + (1 - \eta)I_N(t))}{N(t)}, \quad (4.1)$$

and where β_h is the effective contact rate for HSV-2 infection (contact sufficient to result in HSV-2 infection). The modification parameter η captures the fact that HSV-2 infectives who are into sexting are assumed to have a higher chance, relative to HSV-2 infectives who are not into sexting of generating new infections due

to their risky sexual behaviours (Benotsch et al., 2013; Ferguson, 2011). The modification parameter $\alpha \in (0, 1)$ accounts for the reduced chance of being infected with HSV-2 as non-sexting individuals have less risky sexual behaviours.

Susceptible adolescents who are not into sexting and the infectious adolescents who are not into sexting acquire sexting habits via effective contacts with those who are into sexting at a rate λ_p . With many reasons that can lead adolescents into sexting, we shall focus on peer influence as the main one (Carter, 2009). Thus, the force of peer influence is given by

$$\lambda_p(t) = \frac{\beta_p(S_T(t) + I_T(t))}{N(t)}, \quad (4.2)$$

where β_p is the effective contact rate for peer influence (contact sufficient enough to coerce a fellow adolescent to join sexting through peer influence). We assume that adolescents quit the behaviour of sexting at rate ϕ , and this may be due to some adverse outcomes for those involved, such as embarrassment, mental health problems, public dissemination of sexual photos and legal consequences if the images are of underage individuals, repenting due to various religions who do not encourage it and also through some educational campaigns (Lenhart, 2009; Mitchell et al., 2012; Ryan, 2010; Theodore, 2011). The model flow diagram is depicted in Figure 4.1.

From the descriptions and assumptions on the dynamics of the epidemic made above, the following are the model equations.

$$\frac{dS_N}{dt} = \Lambda - \alpha\lambda_h S_N - \lambda_p S_N - \mu S_N + \phi S_T,$$

$$\frac{dS_T}{dt} = \lambda_p S_N - \lambda_h S_T - (\mu + \phi) S_T,$$

$$\frac{dI_N}{dt} = \alpha\lambda_h S_N + \phi I_T - \lambda_p I_N - \mu I_N,$$

$$\frac{dI_T}{dt} = \lambda_h S_T + \lambda_p I_N - (\mu + \phi) I_T.$$

(4.3)

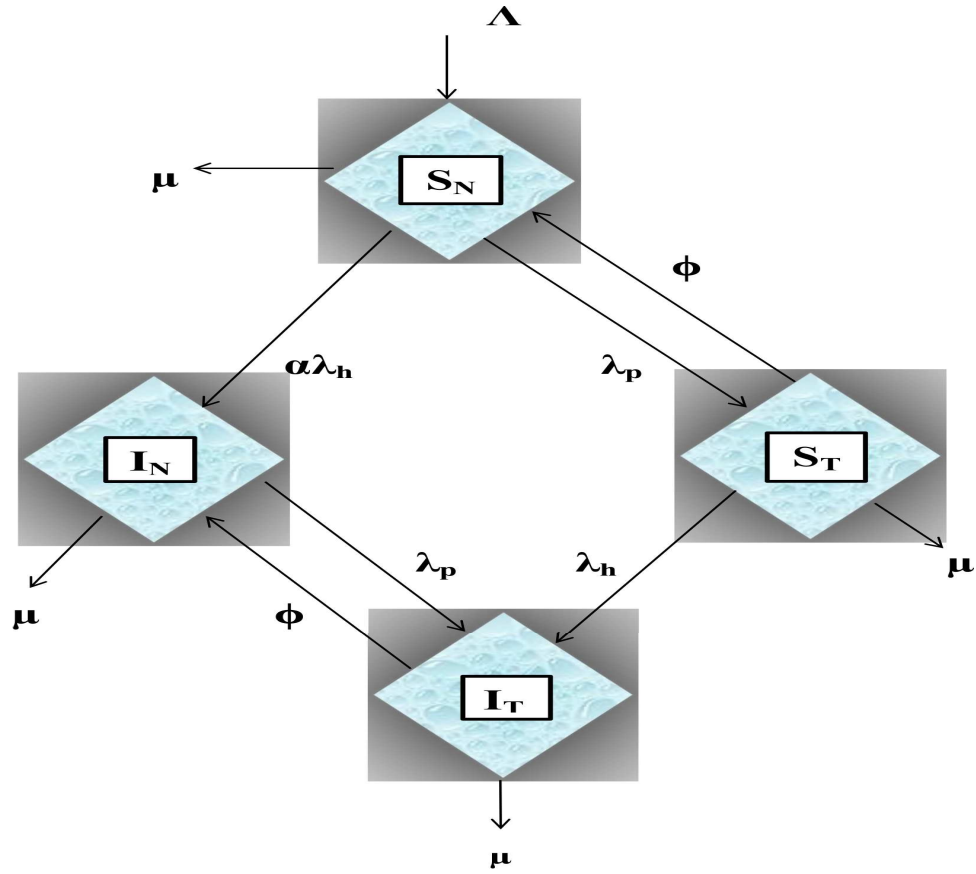


Figure 4.1: Model flow diagram.

4.3. Analytic Results

4.3.1. Basic properties of the model

In this section, we study the basic properties of the solutions of model system (4.3), which are used in the proofs of stability and persistence results. Let $\mathbb{R}_+^n = (0, \infty)$ denote the set $x = (x_1, x_2, x_3, x_4)$ with $x_j > 0$ for $j = 1, 2, \dots, n$. We will use the following results in Appendix A of Thieme (2003).

Lemma 4.1. *Let $F : \mathbb{R}_+^n \rightarrow \mathbb{R}^n$, $F(x) = (F_1(x), F_2(x), \dots, F_n(x))$, $x = (x_1, x_2, \dots, x_n)$ be continuous and have partial derivatives $\frac{\partial F_j}{\partial x_k}$ which exist and are continuous in $\mathbb{R}_+^n$ for $j, k = 1, 2, \dots, n$. Then, F is locally Lipschitz continuous in $\mathbb{R}_+^n$.*

Theorem 4.1. *Let $F : \mathbb{R}_+^n \rightarrow \mathbb{R}^n$ be locally Lipschitz continuous and for each $j = 1, 2, \dots, n$ satisfy $F_j(x) \geq 0$ whenever $x \in \mathbb{R}_+^n$, $x_j = 0$. Then, for every $x_0 \in \mathbb{R}_+^n$, there exists a unique solution of $x' = F(x)$, $x(0) = x_0$ with values in $\mathbb{R}_+^n$ which is defined in some interval $(0, b]$ with $b \in (0, \infty]$. If $b < \infty$, then $\sup \sum_{j=1}^n x_j(t) = \infty$.*

Theorem 4.2. *For all $S_N^0, S_T^0, I_N^0, I_T^0 > 0$ there exist S_N, S_T, I_N, I_T such that $(0, \infty) \rightarrow (0, \infty)$ which solve model system (4.3) with initial conditions $S_N = S_N^0, S_T = S_T^0, I_N = I_N^0, I_T = I_T^0$.*

Proof. Applying Theorem (4.1), we define

$$F_1(x) = \frac{dS_N}{dt}, \quad F_2(x) = \frac{dS_T}{dt}, \quad F_3(x) = \frac{dI_N}{dt}, \quad F_4(x) = \frac{dI_T}{dt}, \quad (4.4)$$

where $x = (S_N, S_T, I_N, I_T) = (x_1, x_2, x_3, x_4)$.

By the properties of continuity over operations, we have continuity of $F_i(x)$ for all

$i = 1, 2, 3, 4$, further

$$\begin{aligned}
\frac{\partial F_1}{\partial x_1} &= -\mu - \frac{\alpha\beta_h(I_T + (1-\eta)I_N)(S_T + I_N + I_T)}{N^2} - \frac{\beta_p(S_T + I_T)(S_T + I_N + I_T)}{N^2}, \\
\frac{\partial F_1}{\partial x_2} &= \phi + \frac{\alpha\beta_h(I_T + (1-\eta)I_N)S_N}{N^2} - \frac{\beta_p(S_N + I_N)S_N}{N^2}, \\
\frac{\partial F_1}{\partial x_3} &= \frac{\alpha\beta_h(I_T - (1-\eta)(S_N + S_T + I_N))S_N}{N^2} + \frac{\beta_p(S_T + I_T)S_N}{N^2}, \\
\frac{\partial F_1}{\partial x_4} &= \frac{\alpha\beta_h S_N((1-\eta)I_N - (S_N + I_N + I_T))}{N^2} - \frac{\beta_p(S_N + I_N)S_N}{N^2},
\end{aligned} \tag{4.5}$$

and these partial derivatives exist and are continuous. Following the same procedure it can be shown that $\frac{\partial F_j}{\partial x_i}$ exist and is continuous for $i = 1, 2, 3, 4$ and $j = 2, 3, 4$. By Lemma 4.1, F exists and locally Lipschitz continuous. Let $x_1 = S_N = 0$ and $x_2 = S_T > 0$, $x_3 = I_N > 0$, $x_4 = I_T > 0$, then

$$F_1(x) = \Lambda + \phi S_T > 0. \tag{4.6}$$

Let $x_2 = S_T = 0$ and $x_1 = S_N > 0$, $x_3 = I_N > 0$, $x_4 = I_T > 0$, then

$$\frac{\beta_p I_T S_N}{S_N + I_N + I_T} > 0. \tag{4.7}$$

Let $x_3 = I_N = 0$ and $x_1 = S_N > 0$, $x_2 = S_T > 0$, $x_4 = I_T > 0$, then

$$\frac{\alpha\beta_h I_T S_N}{S_N + S_T + I_T} + \phi I_T > 0. \tag{4.8}$$

Finally, let $x_4 = I_T = 0$ and $x_1 = S_N > 0$, $x_2 = S_T > 0$, $x_3 = I_N > 0$, then

$$\frac{\beta_h(1-\eta)I_N S_T}{S_N + S_T + I_N} + \frac{\beta_p S_T I_N}{S_N + S_T + I_N} > 0. \tag{4.9}$$

By Theorem 4.1, for every $x_0 = (S_N^0, S_T^0, I_N^0, I_T^0) \in \mathbb{R}_+^4$, there exist a unique solution of $x' = F(x)$, $x(0) = x_0$ with values in $\mathbb{R}_+^4$ which is defined in some interval $(0, b]$

with $b \in (0, \infty]$. If $b < \infty$, then

$$\sup_{0 \leq t \leq b} [N_N + N_T] = \infty. \quad (4.10)$$

Adding all the differential equations in (4.3) gives

$$\begin{aligned} \frac{dN}{dt} &= \frac{dS_N}{dt} + \frac{dS_T}{dt} + \frac{dI_N}{dt} + \frac{dI_T}{dt}, \\ &= \Lambda - \mu N. \end{aligned} \quad (4.11)$$

Applying the Gronwall lemma (Gronwall, 1919), to equation (4.11) yields

$$N(t) \leq \frac{\Lambda}{\mu} + \left(N(0) - \frac{\Lambda}{\mu} \right) e^{-\mu t}, \quad \forall t \geq 0, \quad (4.12)$$

which implies that $0 \leq N(t) \leq \frac{\Lambda}{\mu}$, for all $t \geq 0$ if $N(0) \leq \frac{\Lambda}{\mu}$, where $N(0)$ represents the value of the total population at the initial values of the respective variables.

Thus, $N(t)$ is bounded, a contradiction to Theorem 4.1. As a result $b = \infty$, implying that solutions of model system (4.3) are positive and defined on $(0, \infty)$. $\square$

Therefore, the state variables remain biologically meaningful in the set

$$\Gamma = \left\{ (S_N(t), S_T(t), I_N(t), I_T(t)) \in \mathbb{R}_+^4 : N(t) \leq \frac{\Lambda}{\mu} \right\}, \quad (4.13)$$

for all initial conditions in $\mathbb{R}_+^4$. Thus, Γ is positively invariant and it is sufficient to consider solutions of model system (4.3) in Γ . Existence, uniqueness and continuation results for model system (4.3) hold in this region, and all solutions of model system (4.3) starting in Γ remain in Γ for all (time) $t \geq 0$. All parameters and state variables for model system (4.3) are assumed to be non-negative (for biological relevance) $\forall t \geq 0$, since it monitors human population.

4.3.2. Disease-free equilibrium and its stability analysis

Disease-free equilibrium points (DFE) are steady state solutions where there is no disease. We define the *diseased* class as the human population that is infected with HSV-2. Hence in the absence of the infection we have $I_N = 0$ and $I_T = 0$. Thus, model system (4.3) is reduced to

$$\begin{aligned}\frac{dS_N}{dt} &= \Lambda - \frac{\beta_p S_T}{S_T + S_N} - \mu S_N + \phi S_T, \\ \frac{dS_T}{dt} &= \frac{\beta_p S_T}{S_T + S_N} - (\mu + \phi) S_T.\end{aligned}\tag{4.14}$$

Model system (4.3) has an evident DFE given by,

$$\begin{aligned}\mathcal{U}^0 &= (S_N^0, S_T^0, I_N^0, I_T^0) \\ &= \left(\frac{\Lambda(\mu + \phi)}{\mu\beta_p}, \frac{\Lambda}{\mu} - \frac{\Lambda(\mu + \phi)}{\mu\beta_p}, 0, 0 \right).\end{aligned}\tag{4.15}$$

Following van den Driessche and Watmough (2002), the non-negative matrix F of the new infection terms and the M matrix V , of the transition terms associated with model system (4.3), are given by

$$F = \begin{bmatrix} \frac{\alpha(1-\eta)(\mu+\phi)\beta_h}{\beta_p} & \frac{\alpha(\mu+\phi)\beta_h}{\beta_p} \\ \frac{(1-\eta)(\beta_p - (\mu+\phi))}{\beta_p} & \frac{(\beta_p - (\mu+\phi))}{\beta_p} \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \beta_p - \phi & -\phi \\ (\mu + \phi) - \beta_p & \mu + \phi \end{bmatrix},\tag{4.16}$$

and the effective reproduction number of model system (4.3), denoted by $\mathcal{R}_{HP}$, is given by

$$\mathcal{R}_{HP} = \rho(FV^{-1}) = \frac{\beta_h[\psi^2 + \alpha(1-\eta)(\mu+\phi)^2 + \psi(\mu(1+\alpha) + \phi(1-\eta) + \alpha\phi)]}{\mu\beta_p^2}.\tag{4.17}$$

$\psi = \beta_p - (\mu + \phi) > 0$, by positivity of solutions, throughout the chapter since

$$S_t = \frac{\Lambda}{\mu} \left(1 - \frac{\mu + \phi}{\beta_p} \right) > 0.$$

The reproduction number $\mathcal{R}_{HP}$ is defined as the number of secondary HSV-2 infections produced by one HSV-2 infected individual during his/her entire infectious period in a mixed population of susceptible adolescents who perform sexting and those who do not.

Theorem 4.3 follows from van den Driessche and Watmough (2002).

Theorem 4.3. *The disease free equilibrium $\mathcal{U}^0$ of model system (4.3) is locally asymptotically stable if $\mathcal{R}_{HP} < 1$ and unstable otherwise.*

Analysis of the reproduction number, $\mathcal{R}_{HP}$

The reproduction number is differentiated into categories:

Case 1: Every adolescent is joining sexting in the society.

In this case $\phi \rightarrow 0$ so that $\mathcal{R}_{HP}$ becomes $\mathcal{R}_{0P}$ which is given by

$$\mathcal{R}_{0P} = \frac{\beta_h[\psi^2 + \alpha\mu(1 + \alpha + \mu(1 - \eta))]}{\mu\beta_p^2}. \quad (4.18)$$

Here, $\mathcal{R}_{0P}$ denotes the number of secondary HSV-2 cases generated by one infected HSV-2 adolescent during his/her entire life as an adolescent in the presence of sexting, and other adolescents who are also sexting.

Case 2: No sexting in the society amongst adolescents.

In this case we set $S_T = I_T = 0$, and $\mathcal{R}_{HP}$ becomes $\mathcal{R}_{H0}$, given by

$$\mathcal{R}_{H0} = \frac{\alpha(1 - \eta)\beta_h}{\mu}. \quad (4.19)$$

Here, $\mathcal{R}_{H0}$ denotes the number of secondary HSV-2 cases generated by one infected HSV-2 adolescent during his/her entire life as an adolescent in the absence of sexting, amongst other susceptible adolescents who are also not into sexting.

Case 3: The general case.

It is given and defined in equation (4.17).

We now use numerical illustration to explore the relationship between R_{H0} , R_{0P} and R_{HP} .

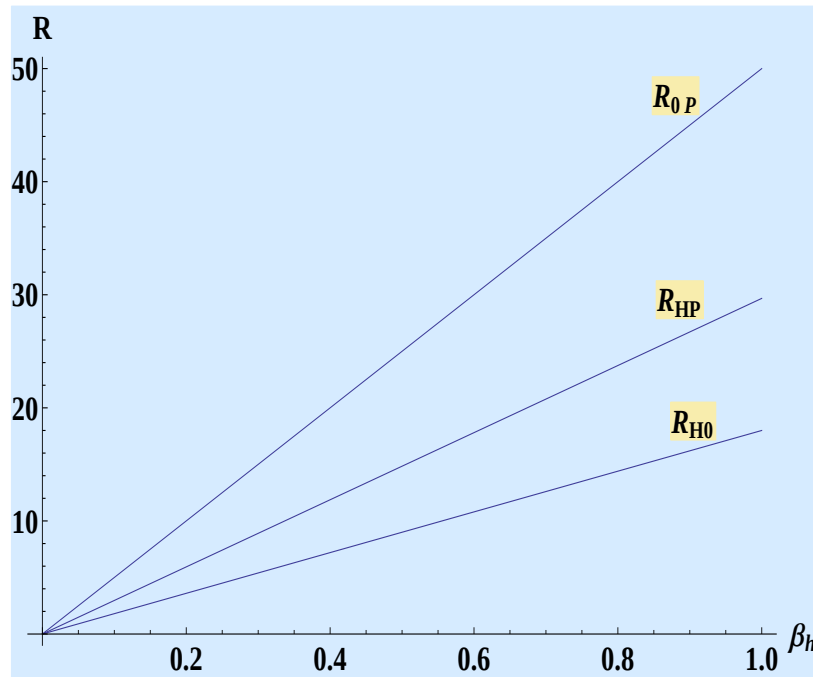


Figure 4.2: Effects of varying the effective contact rate for HSV-2 infection (β_h), on the reproduction numbers. $\mathbf{R}$ represents the reproduction number

R_i	R_{0P}	R_{H0}	R_{HP}
K_i	49.88	17.45	30.01

Table 4.1: The linear dependence of the reproduction number R_i on the constant rate β_h , for $i = 0P, H0, HP$.

Figure 4.2 depicts that in a society where all adolescents would be sexting, the prevalence of HSV-2 is higher as shown by the graph of $\mathcal{R}_{0P}$. In the absence of sexting, the reproduction number would be very low hence HSV-2 can be easier to curtail. Thus $\mathcal{R}_{0P} > \mathcal{R}_{HP} > \mathcal{R}_{H0}$, as illustrated in Figure 4.2.

Table 4.1 depicts the numerical values of the relationship of the linear equation $R_i = K_i \beta_h$, for $j = 0P, HO, HP$, with respect to each reproductive number plotted in Figure 4.2. R_i is the reproduction number, β_h the effective contact rate for HSV-2 and K_i is the respective constant of proportionality. We now explore the global stability of the disease-free equilibrium.

Global stability of the disease-free equilibrium

In order to examine the global stability of $\mathcal{U}^0$, we use the method proposed by Kamgang and Sallet (2008). By closely following Kamgang and Sallet (2008), we present model system (4.2) in the form

$$\begin{aligned} x'_1 &= A_1(x) \cdot (x_1 - x_1^*) + A_{12} \cdot (x_2), \\ x'_2 &= A_2(x)x_2, \end{aligned} \tag{4.20}$$

on the positively invariant set $\Gamma \subset \mathbb{R}_+^{n_1+n_1}$. Here $x_1 = (S_N, S_T)$ and $x_2 = (I_N, I_T)$, where $x_1 \in \mathbb{R}_+^2$ denotes (its components) the number of uninfected individuals, $x_2 \in \mathbb{R}_+^2$ denoting the number of infected components and $x_1^* = \mathcal{U}^0$. We have to prove that the following conditions hold:

(H1) The system is defined on a positively invariant set Γ of the non-negative or-

thant. The system is dissipative on Γ .

(H2) The sub-system $x'_1 = A_1 \cdot (x_1, 0) \cdot (x_1 - x_1^*)$ is globally asymptotically stable at the equilibrium x_1^* on the canonical projection of Γ on $\mathbb{R}_+^{n_1}$.

(H3) The matrix $A_2(x)$ is a Metzler and irreducible matrix for any given $x \in \Gamma$.

(H4) There exists an upper-bound matrix $\bar{A}_2$ for $\mathbb{M} = \{A_2(x) \mid x \in \Gamma\}$ with the property that either $\bar{A}_2 \notin \mathbb{M}$ or if $\bar{A}_2 \in \mathbb{M}$, (i.e., $A_2 = \max_{\Gamma} \mathbb{M}$), then for any $\bar{x} \in \Gamma$ such that $\bar{A}_2 = A_2(\bar{x})$, $\bar{x} \in \mathbb{R}_+^{n_1} \times \{0\}$ (i.e., the points where the maximum is realised are contained in the disease-free sub-manifold)

(H5) $\alpha(\bar{A}) \leq 0$,

are satisfied. If conditions $(H_1 - H_5)$ are satisfied, then $\mathcal{U}^0$ is globally asymptotically stable in Γ .

By closely following Kamgang and Sallet (2008), we set

$$x_1 = (S_N, S_T) \quad \text{and} \quad x_2 = (I_N, I_T).$$

We express the sub-system $x'_1 = A_1 \cdot (x_1, 0) \cdot (x_1 - x_1^*)$ as

$$\begin{aligned} \frac{dS_N}{dt} &= \Lambda - \frac{\beta_p S_T}{S_T + S_N} - \mu S_N + \phi S_T, \\ \frac{dS_T}{dt} &= \frac{\beta_p S_T}{S_T + S_N} - (\mu + \phi) S_T. \end{aligned} \tag{4.21}$$

System (4.21) is a linear system which is globally asymptotically stable at the equi-

librium

$$\left(\frac{\Lambda(\mu + \phi)}{\mu\beta_p}, \frac{\Lambda}{\mu} - \frac{\Lambda(\mu + \phi)}{\mu\beta_p} \right)$$

corresponding to $\mathcal{U}^0$, which satisfies condition H_1 and H_2 . Then matrix $A_2(x)$, a Metzler matrix, is given by

$$A_2(x) = \begin{bmatrix} -\mu - \frac{\beta_p S_T}{S_N + S_T} + \frac{\alpha(1-\eta)\beta_h S_N}{S_N + S_T} & \phi + \frac{\alpha\beta_h S_N}{S_N + S_T} \\ \frac{\beta_p + (1-\eta)\beta_h}{S_N + S_T} & -(\mu + \phi) + \frac{\beta_h S_T}{S_N + S_T} \end{bmatrix}. \quad (4.22)$$

The upper bound for $x \in \Gamma$ is given by

$$A_2 = \begin{bmatrix} -\mu + \beta_p \left(1 - \frac{\mu + \phi}{\beta_p}\right) - \frac{\alpha(1-\eta)(\mu + \phi)\beta_h}{\beta_p} & \phi + \frac{\alpha(\mu + \phi)\beta_h}{\beta_p} \\ (\beta_p + (1-\eta)\beta_h) \left(1 - \frac{\mu + \phi}{\beta_p}\right) & -(\mu + \phi) + \left(1 - \frac{\mu + \phi}{\beta_p}\right)\beta_h \end{bmatrix}. \quad (4.23)$$

Thus, condition (H3) and (H4) are satisfied. Condition (H5) requires that $\alpha(A_2) \leq 0$. Since A_2 is a Metzler matrix, the condition $\alpha(A_2) \leq 0$ is equivalent to the condition $\alpha(A_2(x)) \leq 0$, like

$$\frac{\beta_h[\psi^2 + \alpha(1-\eta)(\mu + \phi)^2 + \psi(\mu(1+\alpha) + \phi(1-\eta) + \alpha\phi)]}{\mu\beta_p^2} \leq 1,$$

which is the reproduction number for model system (4.3). Thus $\mathcal{U}^0$ is globally asymptotically stable whenever $R_{HP} \leq 1$. We summarise the result in Theorem 4.4.

Theorem 4.4. *The disease free equilibrium ($\mathcal{U}^0$) of model system (4.3) is globally asymptotically stable if $R_{HP} \leq 1$ and unstable if $R_{HP} > 1$.*

4.3.3. Persistence

In this section we present a result which shows that, for $R_{HP} > 1$, it actually implies that model system (4.3) admits at least one endemic equilibrium and the

disease is uniformly persistent.

Theorem 4.5. *System (4.3) is uniformly persistent on Γ .*

Proof. If $\mathcal{R}_{HP} > 1$, then the disease is uniformly persistent; Where, uniform persistence of a system implies that there exists $\zeta > 0$ such that

$$\liminf_{t \rightarrow \infty} I_N(t) > \zeta, \quad \liminf_{t \rightarrow \infty} I_T(t) > \zeta, \quad (4.24)$$

for all solutions (S_N, S_T, I_N, I_T) of (4.3) with $I_N(0) > 0$ and $I_T(0) > 0$.

Let $\Delta = \{(S_N, S_T, I_N, I_T) \in \mathbb{R}_+^4 : I_N = I_T = 0\}$. Thus, Δ is the set of all disease free states of model system (4.3) and it can be verified that Δ is positively invariant. Let $M = \Delta \cap \Gamma$, then, since Δ is positively invariant and Γ is also positively invariant, thus M is also positively invariant. It is worth noting that $\mathcal{U}^0 \in M$ and $\mathcal{U}^0$ attracts all solutions in Δ , so $\Omega(M) = \{\mathcal{U}^0\}$. The equations for the infected components of model system (4.3) can be written as

$$x'(t) = Y(x)x(t), \quad (4.25)$$

where $x(t) = (I_N(t), I_T(t))^T$ and $Y(x) = [\mathcal{G} - V]$,

with

$$\mathcal{G} = \begin{bmatrix} \frac{\alpha(1-\eta)\beta_h S_N}{N} & \frac{\alpha\beta_h S_N}{N} \\ \frac{(1-\eta)\beta_h S_T}{N} & \frac{\beta_h S_T}{N} \end{bmatrix}. \quad (4.26)$$

It can be shown that $Y(\mathcal{U}^0) = F - V$, also it can be verified that $Y(\mathcal{U}^0)$ is irreducible. To show that M is a uniform weak repeller, we will apply Lemma A.4 from Ackleh et al. (2011), stated below for elucidation.

Lemma 4.2. *Assume that $\Omega(M)$ is a union of periodic orbits and the following hold:*

- 1) $\forall \mathcal{P} \subseteq \Omega(M)$ a periodic orbit of period T , $\exists x \in \mathcal{P}$ such that $P(T, x)$ is primitive.
- 2) $r(P) > 1$, for each periodic orbit $\mathcal{P} \subseteq \Omega(M)$.

Then M is a uniformly weak repeller.

Since the spectral radius of $Y(\mathcal{U}^0) = \mathcal{R}_{HP} > 1$, the spectral radius of $e^{Y(\mathcal{U}^0)} > 1$. So condition 2 of Lemma (4.2) is satisfied. Taking $x = \mathcal{U}^0$, we get $P(T, \mathcal{U}^0) = e^{Y(\mathcal{U}^0)}$ which is a primitive matrix, because $Y(\mathcal{U}^0)$ is irreducible, as mentioned in Theorem A.12(i) (Smith and Waltman, 1995). This satisfies the condition 1 of Lemma (4.2). Thus, M is a uniform weak repeller and the disease is weakly persistent. M is trivially closed and bounded relative to Γ and hence compact. Therefore, by Theorem 1.3 (Thieme, 1993), we have that M is a uniform strong repeller and the disease is uniformly persistent. $\square$

The epidemiological implication of Theorem 4.5 is that the disease will persist in the population whenever $\mathcal{R}_{HP} > 1$.

4.3.4. Endemic equilibrium

Model system (4.3) has two possible endemic equilibria: sexting free endemic equilibrium and the endemic equilibrium where the adolescents who are sexting and those who are not sexting co-exist, “interior equilibrium point”.

Sexting-free endemic equilibrium

This occurs when there are no adolescents who are involved in sexting, that is, $(S_T = 0, I_T = 0)$. Model system (4.3) reduces to

$$\frac{dS_N}{dt} = \Lambda - \alpha\lambda_h S_N - \mu S_N, \quad (4.27)$$

$$\frac{dI_N}{dt} = \alpha\lambda_h S_N - \mu I_N.$$

For model system (4.27), it can be shown that the region

$$\Gamma_1 = \left\{ (S_N(t), I_N(t)) \in \mathbb{R}_+^2 : N_N(t) \leq \frac{\Lambda}{\mu} \right\}, \quad (4.28)$$

is invariant and attracting. The basic reproduction number for model system (4.27) is

$$\mathcal{R}_{H0} = \frac{\alpha(1-\eta)\beta_H}{\mu}, \quad (4.29)$$

as given by equation (4.19). The dynamics of sexting-free endemic equilibrium will be considered in Γ_1 , and it is given by,

$$\mathcal{U}_{H0}^* = (S_N^*, 0, I_N^*, 0) = \left(\frac{\Lambda}{\mu\mathcal{R}_{H0}}, 0, \frac{\Lambda}{\mu} \left(1 - \frac{1}{\mathcal{R}_{H0}} \right), 0 \right). \quad (4.30)$$

Thus, the sexting-free endemic equilibrium point exists and is unique for $\mathcal{R}_{H0} > 1$. Now we have to explore the stability of this endemic equilibrium following an approach by Korobeinikov (2006).

Global stability of sexting-free endemic equilibrium

Let $\frac{(1-\eta)\beta I_N S_N}{S_N + I_N} = g(S_N, I_N)$ (monotonic and positive function) and define the following continuous function $V(S_N, I_N)$ in $\mathbb{R}_2^+$ (for more details, see (Korobeinikov, 2006)). If a function is such that

$$V(S_N, I_N) = S_N - \int_{\epsilon}^{S_N} \frac{g(S_N^*, I_N^*)}{g(\tau, I_N^*)} d\tau + I_N - \int_{\epsilon}^{I_N} \frac{g(S_N^*, I_N^*)}{g(S_N^*, \tau)} d\tau. \quad (4.31)$$

Given $g(S_N, I_N)$ is monotonic with respect to its variables, then the endemic equilibrium point $\mathcal{U}_{H0}^*$ is the only extremum and the global minimum of this function. Indeed

$$\frac{\partial V}{\partial S_N} = 1 - \frac{g(S_N^*, I_N^*)}{g(S_N, I_N^*)} = \frac{I_N^*(S_N - S_N^*)}{S_N(S_N^* + I_N^*)}, \quad \frac{\partial V}{\partial I_N} = 1 - \frac{g(S_N^*, I_N^*)}{g(S_N^*, I_N)} = \frac{S_N^*(I_N - I_N^*)}{I_N(S_N^* + I_N^*)}. \quad (4.32)$$

Furthermore,

$$\frac{\partial^2 V}{\partial S_N^2} = \frac{S_N^* I_N^*}{S_N^2 (S_N^* + I_N^*)}, \quad \frac{\partial^2 V}{\partial I_N^2} = \frac{S_N^* I_N^*}{I_N^2 (S_N^* + I_N^*)}, \quad (4.33)$$

are non-negative, then $\mathcal{U}_{H_0}^*$ is a minimum. That is $V(S_N, I_N) \geq V(S_N^*, I_N^*)$ and hence V is a Lyapunov function. At endemic equilibrium point, model system (4.27) have the following identities,

$$\Lambda = g(S_N^*, I_N^*) + \mu S_N^*, \quad (4.34)$$

$$\mu I_N^* = g(S_N^*, I_N^*).$$

The Lyapunov function (4.31) satisfies

$$\begin{aligned} \frac{dV}{dt} &= S'_N - S'_N \left(\frac{g(S_N^*, I_N^*)}{g(S_N, I_N^*)} \right) + I'_N - I'_N \left(\frac{g(S_N^*, I_N^*)}{g(S_N^*, I_N)} \right) \\ &= (\Lambda - g(S_N^*, I_N^*) - \mu S_N^*) \left(1 - \frac{g(S_N^*, I_N^*)}{g(S_N, I_N^*)} \right) + (g(S_N^*, I_N^*) - \mu I_N^*) \left(1 - \frac{g(S_N^*, I_N^*)}{g(S_N^*, I_N)} \right) \\ &= \mu S_N^* \left(1 - \frac{S_N}{S_N^*} \right) \left(1 - \frac{g(S_N^*, I_N^*)}{g(S_N, I_N^*)} \right) + g(S_N^*, I_N^*) \left(1 - \frac{g(S_N^*, I_N^*)}{g(S_N, I_N^*)} \right) \left(1 - \frac{g(S_N, I_N)}{g(S_N^*, I_N)} \right) \\ &\quad + g(S_N^*, I_N^*) \left(\frac{I_N}{I_N^*} - \frac{g(S_N, I_N)}{g(S_N, I_N^*)} \right) \left(\frac{g(S_N^*, I_N^*)}{g(S_N^*, I_N)} - 1 \right). \end{aligned} \quad (4.35)$$

Since $\mathcal{U}_{H_0}^* > 0$, the function $g(S_N, I_N)$ is concave with respect to I_N and $\frac{\partial^2 g(S_N, I_N)}{\partial I_N^2} \leq 0$, then $(dV/dt) \leq 0$ for all $S_N, I_N > 0$. Also, the monotonicity of $g(S_N, I_N)$ with respect to S_N and I_N ensures that

$$\left(1 - \frac{S_N}{S_N^*} \right) \left(1 - \frac{g(S_N^*, I_N^*)}{g(S_N, I_N^*)} \right) \leq 0 \quad \text{and} \quad \left(1 - \frac{g(S_N^*, I_N^*)}{g(S_N, I_N^*)} \right) \left(1 - \frac{g(S_N, I_N)}{g(S_N^*, I_N)} \right) \leq 0 \quad (4.36)$$

holds for all $S_N, I_N > 0$. Furthermore,

$$\left(\frac{I_N}{I_N^*} - \frac{g(S_N, I_N)}{g(S_N, I_N^*)} \right) \left(\frac{g(S_N^*, I_N^*)}{g(S_N^*, I_N)} - 1 \right) \leq 0 \quad (4.37)$$

if

$$\frac{g(S_N, I_N)}{g(S_N, I_N^*)} \geq \frac{I_N}{I_N^*} \quad \text{when } g(S_N^*, I_N^*) \geq g(S_N^*, I_N) \quad \text{and} \quad (4.38)$$

$$\frac{g(S_N, I_N)}{g(S_N, I_N^*)} \leq \frac{I_N}{I_N^*} \quad \text{when } g(S_N^*, I_N^*) \leq g(S_N^*, I_N)$$

holds for all $S_N, I_N > 0$. Since $g(S_N, I_N)$ is a monotonic function, then

$$g(S_N^*, I_N) \geq g(S_N^*, I_N^*) \Rightarrow I_N \geq I_N^*.$$

Inequalities (4.36 - 4.38) will hold for any concave function and sufficient to ensure that $dV/dt \leq 0$. Thus, we have established the following result.

Theorem 4.6. *The unique endemic equilibrium $\mathcal{U}_{H0}^*$ is globally asymptotically stable whenever conditions (4.38) are satisfied.*

Interior equilibrium

This equilibrium occurs when the non-sexting adolescents and the adolescents who are into sexting both exist in the presence of HSV-2, denoted by

$$\mathcal{U}_{HP}^{**} = (S_N^{**}, I_N^{**}, S_N^{**}, I_N^{**}). \quad (4.39)$$

Expressing the expressions for each variable in terms of λ_p^{**} and λ_h^{**} and solving the problem is a daunting task, but we claim a biologically feasible interior equilibrium exists. The permanence of the disease destabilises the disease-free equilibrium $\mathcal{U}^0$ since $\mathcal{R}_{HP} > 1$, and the endemic equilibrium $\mathcal{U}_{HP}^{**}$ exists.

4.4. Numerical results

In order to illustrate the results of the foregoing analysis, we have simulated model system (4.3) using the parameters in Table 4.2. Unfortunately, the scarcity of the data on HSV-2 and sexting correlation with a focus on adolescents limits our ability to calibrate, nevertheless, we assume some of the parameters in the realistic range for illustrative purposes. These parsimonious assumptions reflect the lack of information currently available on HSV-2 and sexting with a focus on adolescents. Reliable data on the risk of transmission of HSV-2 among adolescents would enhance our understanding and aid in the possible intervention strategies to be implemented.

- (i) The recruitment rate of susceptible Λ , natural death rate μ and the effective contact rate for HSV-2, β_h ; we adopt the same rates as explained in Table 2.1.
- (ii) Effective contact rate for peer influence $\beta_p = 0.04$ per year and this value was adopted from published work by Thompson et al., (2013), which was conducted among USA adolescents; and also from the work of Bhunu et al., (2011).
- (iii) The sexting quitting rate ϕ , we assume a value of $\phi = 0.02$ as our point estimate, although we let the parameter ϕ vary between 0 and 1 for illustrative purposes.

Definition	Symbol	B^* (Range)	Source
Recruitment rate	Λ	10000yr^{-1}	(Mhlanga et al., 2014)
Natural death rate	μ	$0.02(0.015-0.02)\text{yr}^{-1}$	(Bhunu and Mushayabasa, 2011)
Modification parameter	α	0.6(0-1)	Assumed
Modification parameter	η	0.6(0-1)	Assumed
Effective contact rate for HSV-2	β_h	$0.01(0.001-0.03)\text{yr}^{-1}$	(Bryson et al., 1993 Corey et al., 2004b Mertz et al., 1988 Wald et al., 2001)
Rate of quitting sexting	ϕ	variable	Assumed
Effective contact rate for peer influence	β_p	0.4	(Bhunu et al., 2011)

Table 4.2: Model parameters and their interpretations (B^* represents the Baseline Values).

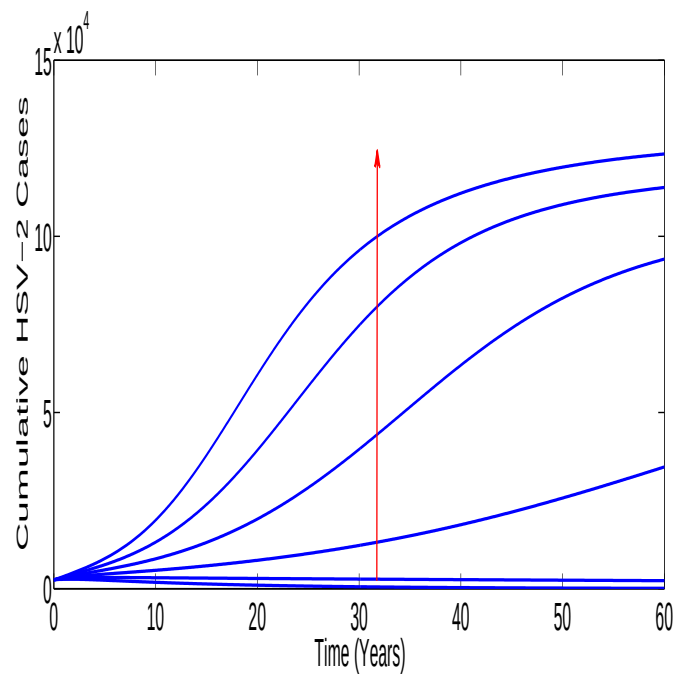


Figure 4.3: Figure 4.3 shows the influence of β_p on cumulative HSV-2 cases over a period of 60 years, with β_p varying from 0 to 1 with a step size of 0.2 and the rest of the parameters being fixed on their baseline values from Table 4.2. The direction of the arrow shows an increase of β_p .

From Figure 4.3 we observe that increasing the effective contact rate for peer influence, results in an increase of the cumulative HSV-2 cases. It is worth noting that

the disease can be reduced to very low levels after 20 years, if the effective contact rate for sexting is zero ($\beta_p \simeq 0$). Furthermore, we note that the impact of β_p begins to be very significant from around 6-7 years. Thus, implementing some measures which are capable of reducing the contact rate would be vital in the reduction of the cumulative HSV-2 cases.

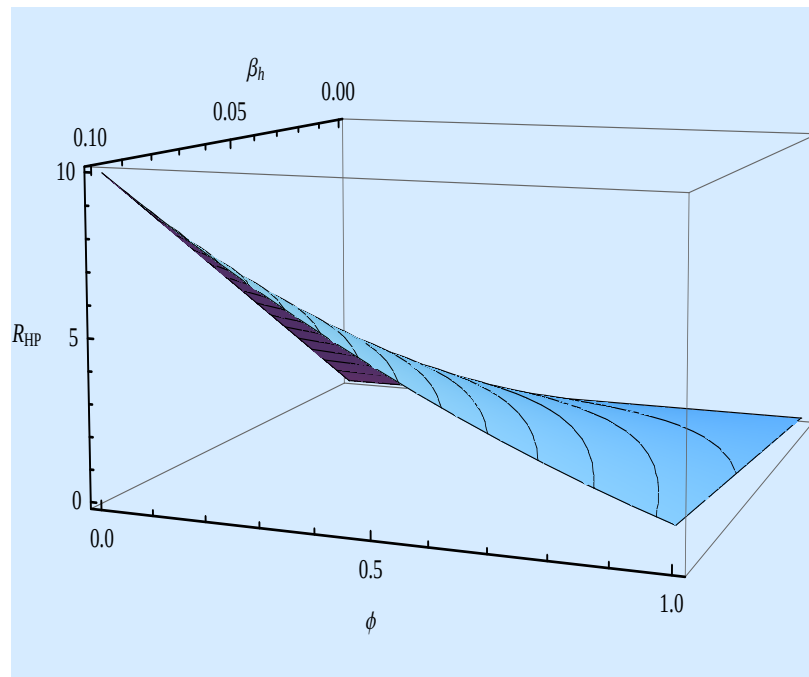


Figure 4.4: Figure 4.4 shows the effects of the effective contact rate for HSV-2 infection β_h , and the sexting quitting rate ϕ , on $\mathcal{R}_{HP}$.

Figure 4.4 shows that, when the sexting quitting rate is significantly high, the reproduction number reduces significantly. The same scenario happens when we have low values of the sexting quitting rate, the reproduction number becomes significantly very high. Thus, it would be very crucial for us to have high sexting quitting rate coupled with low peer influence for us to be able to curtail the prevalence of the STI amongst adolescents.

Sensitivity analysis investigates the type of change and the amount inherent in the model as captured by the terms that define the reproduction number. If the

reproduction number is very sensitive to a particular parameter, then a perturbation of the conditions that connect the dynamics to such a parameter may prove useful in identifying policies or intervention strategies that reduce the epidemic prevalence. In this section the Partial rank correlation coefficients (PRCCs) were calculated to estimate the correlation between values of the reproduction number and the six model parameters across 1000 random draws from the empirical distribution of $\mathcal{R}_{HP}$ and its associated parameters.

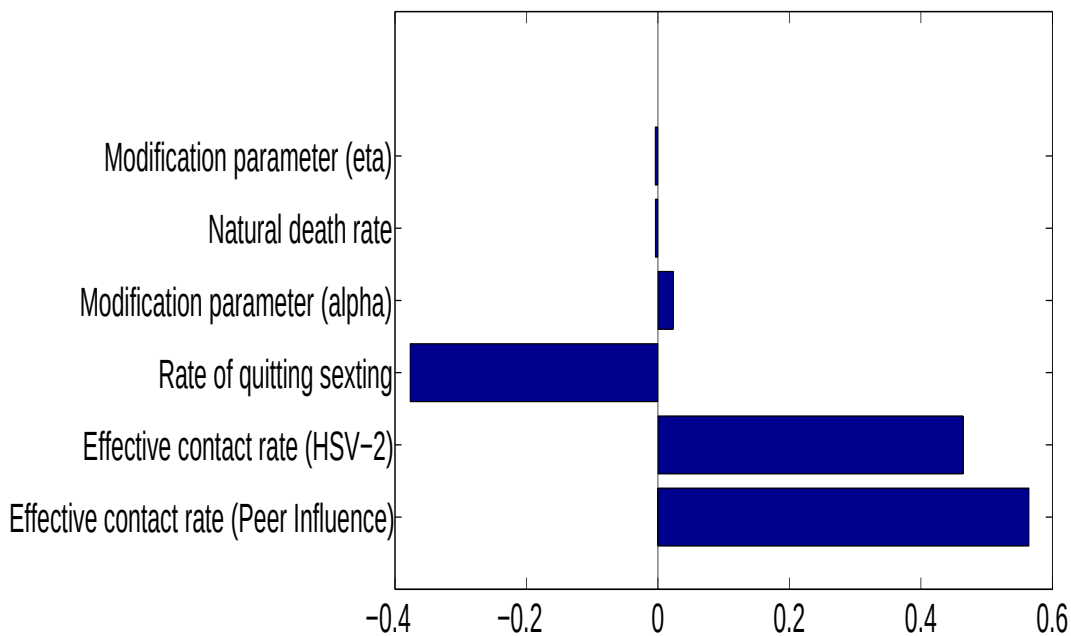


Figure 4.5: Partial rank correlation coefficients showing the effects of parameter variation on $\mathcal{R}_{HP}$ using ranges from Table 4.2. Parameters with positive PRCCs will increase $\mathcal{R}_{HP}$ when they are increased, whereas parameters with negative PRCCs will decrease $\mathcal{R}_{HP}$ when they are increased.

Figure 4.5 illustrates the PRCCs using $\mathcal{R}_{HP}$ as an output variable. Results here suggest that peer influence effective contact rate is the most sensitive parameter in increasing the magnitude of the reproduction number, followed by the effective contact rate for HSV-2. The rate of quitting sexting is the most sensitive in reducing the magnitude of the reproduction number. Thus, it would be very advisable to

find ways of increasing the number of adolescents quitting sexting and at the same time, finding ways of reducing the number of adolescents who are falling into the behaviour of sexting. Introducing methods such as filtering, with the help of the parents, may be very helpful in reducing the number of adolescents who would be joining sexting, and at the same time minimising sexting.

Since peer influence effective contact rate and the rate of quitting sexting have a significant impact on $\mathcal{R}_{HP}$, we examined their dependence in more detail. We used Latin Hypercube Sampling and Monte Carlo simulations to run 1000 simulations, where all parameters were simultaneously drawn from across their ranges.

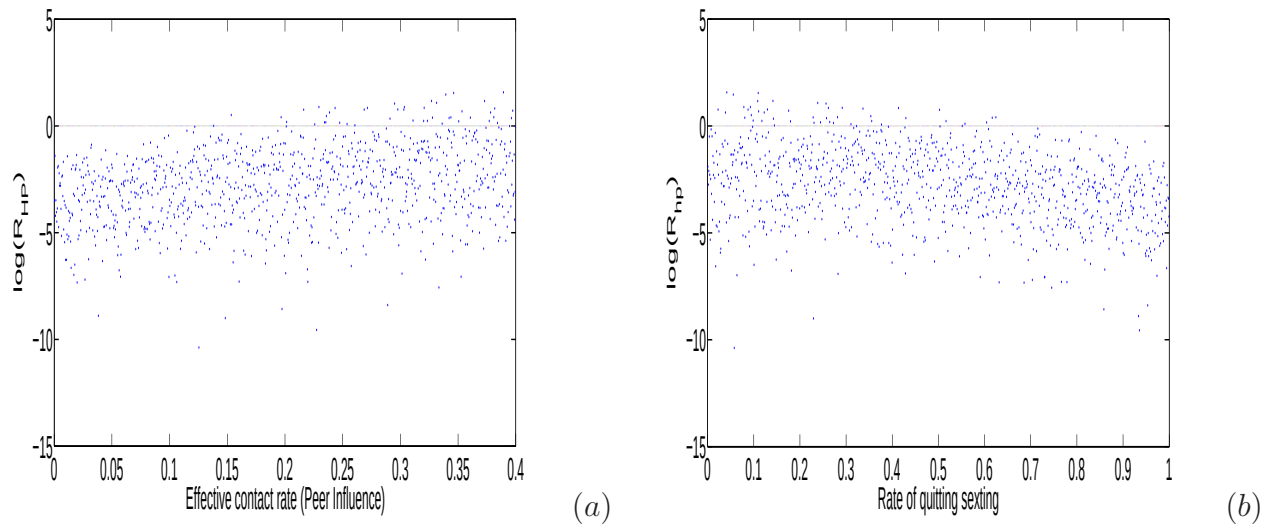


Figure 4.6: Latin Hypercube Sampling for varying of (a) peer influence effective contact rate and (b) the rate of quitting sexting.

Figure 4.6 illustrates that varying two sample parameters will have on $\mathcal{R}_{HP}$. If the rate at which the adolescents quit sexting is sufficiently high, then $\mathcal{R}_{HP} < 1$ and the disease can be controlled. However, if the rate of quitting sexting is low, then $\mathcal{R}_{HP} > 1$ and the disease will persist. We can also see that, the disease persists for higher values of the effective contact rate for peer influence, and may be controlled for lower values of the peer influence effective contact rate. Figure 4.6 results are

in agreement with our earlier findings that suggested low peer influence effective contact rate and high sexting quitting rate are crucial in reducing the prevalence of HSV-2.

4.5. Optimal control problem

In order to assess an effective campaign to control sexting and HSV-2 in a society which pursue the goals of minimising the HSV-2 infected adolescents and sexting adolescents, and having more susceptible non-sexting and non HSV-2 infected adolescents. To achieve this goal we will reconsider model system (4.3) and introduce two control variables $u_1(t)$ and $u_2(t)$, so as to try and reduce the number of HSV-2 infected adolescents and the sexting adolescents. The control variable $u_1(t)$ is used to control the number of adolescents who are joining the trade of sexting, usually through peer influence (Carter, 2009). Internet service providers and mobile phone operators with the help of the parents, can protect adolescents by installing filters on their devices and networks. These filters that would be fitted to deal with all explicit material, can be at network or device level (Carter, 2009). The control variable $u_2(t)$, is used to control the number of adolescents who can become infected with HSV-2, usually through unsafe sex. Measures such as counselling and awareness campaigns can be employed to fulfil control $u_2(t)$. However, there will be a lot of costs generated during the control process. So, it would be advisable to balance between the costs and the effects of HSV-2 prevalence and sexting. In view of this, our optimal control problem is to minimise the objective functional given by

$$J(u_1, u_2) = \int_0^{t_f} [\Phi_1 S_T + \Phi_2 I_N + \Phi_3 I_T + \frac{1}{2}(\Psi_1 u_1^2(t) + \Psi_2 u_2^2(t))] dt, \quad (4.40)$$

subject to

$$\begin{aligned}
\frac{dS_N}{dt} &= \Lambda - (1 - u_2(t))\alpha\lambda_h S_N - (1 - u_1(t))\lambda_p S_N - \mu S_N + \phi S_T, \\
\frac{dS_T}{dt} &= (1 - u_1(t))\lambda_p S_N - (1 - u_2(t))\lambda_h S_T - (\mu + \phi)S_T, \\
\frac{dI_N}{dt} &= (1 - u_2(t))\alpha\lambda_h S_N + \phi I_T - (1 - u_1(t))\lambda_p I_N - \mu I_N, \\
\frac{dI_T}{dt} &= (1 - u_2(t))\lambda_h S_T + (1 - u_1(t))\lambda_p I_N - (\mu + \phi)I_T,
\end{aligned} \tag{4.41}$$

with initial conditions

$$S_N(0) = S_N^0, \quad S_T(0) = S_T^0, \quad I_N(0) = I_N^0, \quad I_T(0) = I_T^0. \tag{4.42}$$

Here, $u_i(t) \in U \triangleq \{(u_1, u_2) | u_i(t) \text{ is measurable and } 0 \leq u_i(t) \leq 1, \text{ for all } t \in [0, t_f]\}$, t_f is the end time to be controlled, U is an admissible control set, Ψ_i , for $i = 1, 2$, are the weights and cost of awareness campaigns and filtering that adjust the intensity of the two different control measures, (Ψ_1 and Ψ_2 are positive constants). Also, Φ_1 , Φ_2 and Φ_3 represent the weight constants of the susceptible adolescents who are into sexting, infected adolescents who are not into sexting and the infected adolescents who are into sexting respectively. The terms u_1^2 and u_2^2 reflect the effectiveness of filtering and awareness campaigns in the control of the disease. The values $u_1 = u_2 = 1$, represent maximum effectiveness of filtering and awareness campaigns.

4.5.1. Existence of the optimal control

Now we investigate the existence of the optimal control of the above-mentioned problem.

Theorem 4.7. *There exists an optimal control pair $u^* = (u_1^*, u_2^*) \in U$ such that*

$$J(u_1^*, u_2^*) = \min J(u_1, u_2), \quad u_1, u_2 \in U \quad (4.43)$$

subjects to the control system (4.41) with initial conditions (4.42).

Proof. To prove the existence of an optimal control, we shall make use of some results from Fleming and Rishel (1975), and we have to show the following;

1. The control state variables are non-negative values.
2. The control set U is convex and closed.
3. The right side of the state system is bounded by linear function in the state and control variables.
4. The integrand of the objective functional is concave on U .
5. There exists constants $\kappa_1, \kappa_2 > 0$ and $\alpha > 1$ such that the integrand $L(t, u_1, u_2) \triangleq \Phi_1 S_T + \Phi_2 I_N + \Phi_3 I_T + \frac{1}{2}(\Psi_1 u_1^2 + \Psi_2 u_2^2)$ of the objective functional satisfies

$$L(t, u_1, u_2) \geq \kappa_1(|u_1| + |u_2|)^{\alpha/2} - \kappa_2 \quad (4.44)$$

Statements 1, 2 and 3 are obviously satisfied, we only need to verify and check the last two. Since the four state variables have all been proved to be bounded above by Λ/μ , we will get the following inequalities:

$$\begin{aligned} \frac{dS_N}{dt} &\leq \Lambda + \phi S_T, \\ \frac{dS_T}{dt} &\leq (1 - u_2(t))\lambda_h S_T, \\ \frac{dI_N}{dt} &\leq (1 - u_2(t))\alpha\lambda_h S_N + \phi I_T, \\ \frac{dI_T}{dt} &\leq (1 - u_2(t))\lambda_h S_T + (1 - u_1(t))\lambda_p I_N, \end{aligned} \quad (4.45)$$

so the fourth condition is set up. As for the last condition,

$$L(t, u_1, u_2) \geq \kappa_1(|u_1| + |u_2|)^{\alpha/2} - \kappa_2 \quad (4.46)$$

is also true, when we choose $\kappa_1 = \min(\Psi_1/2, \Psi_2/2)$ and for all $\kappa_2 \in \mathbb{R}^+$, $\alpha = 2$ and that completes the proof. $\square$

4.5.2. The characterisation of the optimal control

We use Pontryagin's Maximum Principle (Pontryagin et al., 1985) to derive the necessary conditions for this optimal control, since there exist an optimal control for minimising the functional (4.47) subject to the equations (4.41). This is done by first defining an augmented Hamiltonian H , with penalty terms for the control constraints as follows

$$\begin{aligned} H = & \Phi_1 S_T + \Phi_2 I_N + \Phi_3 I_T + \frac{\Psi_1}{2} u_1^2(t) + \frac{\Psi_2}{2} u_2^2(t) + \sum_{i=1}^4 \lambda_i g_i \\ & - w_{11} u_1(t) - w_{12}(1 - u_1(t)) \\ & - w_{21} u_2(t) - w_{22}(1 - u_2(t)), \end{aligned} \quad (4.47)$$

where $w_{ij}(t) \geq 0$, $i = 1, 2$, $j = 1, 2$ are penalty multipliers, satisfying

$$\begin{aligned} w_{11}(t)u_1(t) &= w_{12}(t)(1 - u_1(t)) = 0 \text{ at optimal control } u_1^*, \\ w_{21}(t)u_2(t) &= w_{22}(t)(1 - u_2(t)) = 0 \text{ at optimal control } u_2^*. \end{aligned} \quad (4.48)$$

Also, where g_i is the right hand side of the differential equation of the i th state variable. By applying Pontryagin's Maximum Principle (Pontryagin et al., 1985) and the optimal control existence result from Fleming and Rishel (1975), we obtain

Theorem 4.8. *Given optimal control pairs (u_1^*, u_2^*) and solutions $S_N(t), S_T(t), I_N(t), I_T(t)$ of the corresponding state system (4.41), there exist adjoint variables λ_i , $i = 1, 2, 3, 4$, satisfying*

$$\begin{aligned}\frac{\partial \lambda_1}{\partial t} &= \frac{\alpha \beta_h (I_N(1 - \eta) + I_T)}{N} (1 - u_2(t)) [\lambda_1 - \lambda_3] + \frac{\beta_p (S_T + I_T)}{N} (1 - u_1(t)) [\lambda_1 - \lambda_2] + \mu \lambda_1, \\ \frac{\partial \lambda_2}{\partial t} &= -\Phi_1 + \frac{\beta_h (I_N(1 - \eta) + I_T)}{N} (1 - u_2(t)) [\lambda_2 - \lambda_4] + \frac{\beta_p I_N}{N} (1 - u_1(t)) [\lambda_1 - \lambda_2] \\ &\quad + \frac{\beta_p (S_T + I_T) I_N}{N} (1 - u_1(t)) [\lambda_3 - \lambda_4] + \phi [\lambda_2 - \lambda_1] + \mu \lambda_2, \\ &\hspace{15em} (4.49)\end{aligned}$$

$$\begin{aligned}\frac{\partial \lambda_3}{\partial t} &= -\Phi_2 + \frac{\beta_p (S_T + I_T)}{N} (1 - u_1(t)) [\lambda_3 - \lambda_4] + \frac{(1 - \eta) \beta_h S_T}{N} (1 - u_2(t)) [\lambda_2 - \lambda_4] \\ &\quad + \frac{\alpha (1 - \eta) \beta_h S_N}{N} (1 - u_2(t)) [\lambda_1 - \lambda_3] + \mu \lambda_3,\end{aligned}$$

$$\begin{aligned}\frac{\partial \lambda_4}{\partial t} &= -\Phi_3 + \frac{\alpha S_N \beta_h}{N} (1 - u_2(t)) [\lambda_1 - \lambda_3] + \frac{\beta_p S_N}{N} (1 - u_1(t)) [\lambda_1 - \lambda_2] \\ &\quad + \frac{\beta_h S_T}{N} (1 - u_2(t)) [\lambda_2 - \lambda_4] + \frac{\beta_p I_N}{N} (1 - u_1(t)) [\lambda_3 - \lambda_4] + \phi [\lambda_4 - \lambda_3] + \mu \lambda_4,\end{aligned}$$

with the terminal conditions

$$\lambda_i = 0, \quad i = 1, 2, 3, 4. \quad (4.50)$$

Furthermore, (u_1^*, u_2^*) are represented by

$$u_1^* = \min \left(1, \max \left(0, \frac{\beta_p (S_T + I_T) S_N}{N \Psi_1} [\lambda_2 - \lambda_1] + \frac{\beta_p (S_T + I_T) S_N}{N \Psi_1} [\lambda_4 - \lambda_3] \right) \right), \quad (4.51)$$

$$u_2^* = \min \left(1, \max \left(0, \frac{\alpha\beta_h(I_N(1-\eta) + I_T)S_N}{N\Psi_2}[\lambda_3 - \lambda_1] + \frac{\alpha\beta_h(I_N(1-\eta) + I_T)S_T}{N\Psi_2}[\lambda_4 - \lambda_2] \right) \right). \quad (4.52)$$

Proof. According to Pontryagin's Maximum Principle (Pontryagin et al., 1985; Fleming and Rishel, 1975; Lukes, 1982), we first differentiate the Hamiltonian operator H , with respect to states. Then the adjoint system can be written as,

$$\frac{\partial \lambda_1}{\partial t} = -\frac{\partial H}{\partial S_N}, \quad \frac{\partial \lambda_2}{\partial t} = -\frac{\partial H}{\partial S_T}, \quad \frac{\partial \lambda_3}{\partial t} = -\frac{\partial H}{\partial I_N}, \quad \frac{\partial \lambda_4}{\partial t} = -\frac{\partial H}{\partial I_T}. \quad (4.53)$$

The terminal condition of the adjoint equations is given by $\lambda_i(t_f) = 0$, $i = 1, 2, 3, 4$.

To obtain the necessary conditions of optimality, we differentiate the Hamiltonian operator H , with respect to $u_1(t)$ and $u_2(t)$ and set them equal to zero. Thus,

making $u_1^*(t)$ subject of formulae

$$u_1^*(t) = \frac{\beta_p(S_T + I_T)S_N}{N\Psi_1}[\lambda_2 - \lambda_1] + \frac{\beta_p(S_T + I_T)I_N}{N\Psi_1}[\lambda_4 - \lambda_3] + \left(\frac{w_{12} - w_{11}}{\Psi_1} \right); \quad (4.54)$$

making $u_2^*(t)$ subject of formulae

$$u_2^*(t) = \frac{(\alpha\beta_h(I_N(1-\eta) + I_T))S_N}{N\Psi_2}[\lambda_3 - \lambda_1] + \frac{(\beta_h(I_N(1-\eta) + I_T))S_T}{N\Psi_2}[\lambda_4 - \lambda_2] + \left(\frac{w_{22} - w_{21}}{\Psi_2} \right). \quad (4.55)$$

To determine the explicit expression for the optimal control without $w_{11}(t)$, $w_{12}(t)$, $w_{21}(t)$ and $w_{22}(t)$, a standard optimality system is utilised (Fleming and Rishel, 1975).

The specific characterisation of the optimal controls $u_1^*(t)$ and $u_2^*(t)$.

$$u_1^*(t) = \min \left\{ 1, \max \left\{ 0, \frac{\beta_p(S_T + I_T)S_N}{N\Psi_1}[\lambda_2 - \lambda_1] + \frac{\beta_p(S_T + I_T)I_N}{N\Psi_1}[\lambda_4 - \lambda_3] \right\} \right\}.$$

$$u_2^*(t) = \min \left\{ 1, \max \left\{ 0, \mathcal{D} \right\} \right\}, \quad (4.56)$$

with

$$\mathcal{D} = \frac{(\alpha\beta_h(I_N(1-\eta) + I_T))S_N}{N\Psi_2}[\lambda_3 - \lambda_1] + \frac{(\beta_h(I_N(1-\eta) + I_T))S_T}{N\Psi_2}[\lambda_4 - \lambda_2].$$

The optimality system consists of the state system coupled with the adjoint system with the initial conditions, the transversality conditions and the characterisation of the optimal control. Substituting $u_1^*(t)$ and $u_2^*(t)$ for $u_1(t)$ and $u_2(t)$, in equations (4.49) gives the optimality system. The state system and adjoint system have finite upper bounds. These bounds are needed in the uniqueness proof of the optimality system. Due to a *priori* boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ordinary differential equations, we obtain the uniqueness of the optimal control for small t_f (Magombedze et al., 2011). The uniqueness of the optimal control follows from the uniqueness of the optimality system. $\square$

4.5.3. Numerical simulations

The optimality system is solved using an iterative method with Runge-Kutta fourth order scheme. Starting with a guess for the adjoint variables, the state equations are solved forward in time. Then these state values are used to solve the adjoint equations backward in time, and the iterations continue until convergence. The simulations were carried out using parameter values in Table 4.2 and the following values $\Phi_1 = 1.5$, $\Phi_2 = 0.35$, $\Phi_3 = 0.01$, $\Psi_1 = 0.0002$, $\Psi_2 = 0.00005$. The assumed initial conditions for the differential equations are $S_N = 0.4$, $S_T = 0.3$, $I_N = 0.2$ and $I_T = 0.1$.

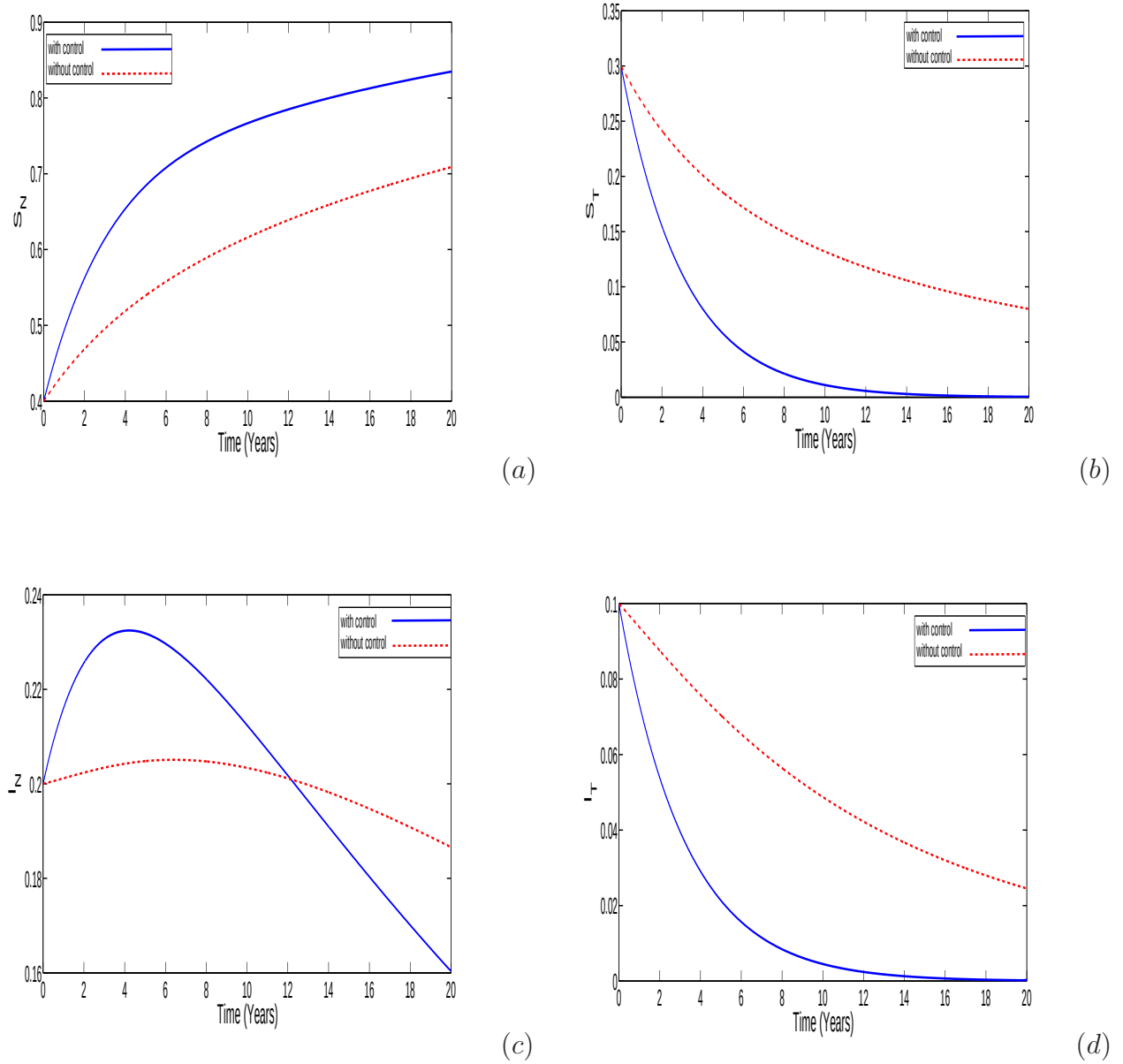


Figure 4.7: Dynamics of model system (4.41) showing the impact of filtering and awareness campaigns on HSV-2 dynamics and sexting.

Figure 4.7(a) represents the population of the susceptible non-sexting adolescents, in the presence and absence of controls over a period of 20 years. The susceptible non-sexting adolescents have a slightly sharp increase on the interval 0-6 years, for both cases (with or without the control). Further, we note that the population of the susceptible non-sexting adolescents is higher when there is a control, compared to a situation when there is no control.

In Figure 4.7(b), the population of the susceptible sexting adolescents in the presence and absence of the controls, over a period of 20 years is presented. The susceptible sexting adolescents have a slightly sharp decrease over a period of 0-6 years, for both cases (with or without the control). Further we note that the population of the susceptible sexting adolescents is higher when there is no control, compared to a situation where there is a control. It is also worth noting that the population of the sexting susceptible adolescents goes to zero after 17 years of implementation of the controls.

Figure 4.7(c) represents the population of the infected non-sexting adolescents, in the presence and absence of controls over a period of 20 years. The infected non-sexting adolescents have a sharp increase for the first 4 years for the case when there are controls, and then have a sharp decrease for the remaining period, that is 4-20 years. The infected non-sexting adolescents have a moderate increase for the first 7 years for the case where there are no controls, then also have a slight decrease for the remaining period under review, that is 7-20 years. Further, we note that the population of the infected non-sexting adolescents is higher when there is a control, compared to a situation where there is no control for the period 0-12 years. After 12 years, the population of the non-sexting adolescents in the presence of the controls begins to decrease sharply and also being less than the case where there are no controls. Thus, change becomes to be significant in the society after 12 years amongst the adolescents who are infected yet not into sexting.

In Figure 4.7(d), the population of the infected sexting adolescents in the presence and absence of the controls, over a period of 20 years is presented. The infected sexting adolescents have a slightly sharp decrease over a period of 0-6 years, for both cases (with or without the control). Further we note that the population of the infected sexting adolescents is higher when there is no control, compared to a situation where there is a control, showing the effectiveness of the controls. It is also worth noting that the population of the sexting infected adolescents goes to zero after 18 years of implementation of the controls.

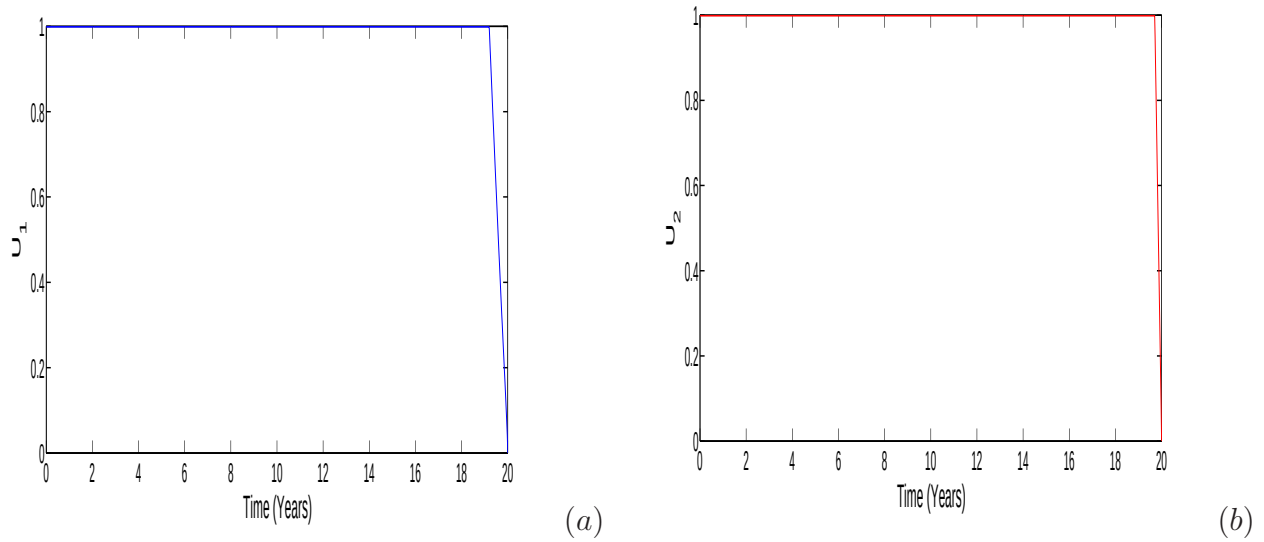


Figure 4.8: Control profiles for control functions (a) $u_1(t)$ and (b) $u_2(t)$.

Figure 4.8 represents the controls u_1 and u_2 . These results suggest that more effort should be devoted to both strategies “filtering” control u_1 , and “awareness campaigns” u_2 .

4.6. Concluding remarks

Sexting is associated with health jeopardising behaviours including sex with multiple partners, unprotected sex and STIs. Prior studies have found that adolescents are amongst the groups who are heavily involved in sexting, and they mostly join this bad behaviour due to peer influence. A mathematical model for assessing the effects of sexting and peer influence on the spread of HSV-2 amongst adolescents is developed. Comprehensive and robust mathematical techniques have been used to analyse the model steady states. It has been established that the model has a disease-free equilibrium which is locally asymptotically stable when the associated reproduction number is less than unity. Sensitivity analysis of the reproduction number has been carried out. Results from the sensitivity analysis of the repro-

duction number suggest that an increase on the effective contact rate for HSV-2 infection and an increase on the effective contact rate for peer influence will have a very large influence on increasing the magnitude of the associated reproduction number. We also noted that quitting sexting by the adolescents would be very crucial in reducing the magnitude of the reproduction number. Numerical results have suggested that an increase on the effective contact rate for sexting results in an increase of the cumulative HSV-2 cases. Furthermore, the numerical simulations suggest that for us to be able to curtail the prevalence of HSV-2, we need to have a combination of high sexting quitting rate and low peer influence effective contact rate for at least 6 to 7 years.

Our optimal control results show the effectiveness of the combination of filtering and awareness campaigns within a population, may influence HSV-2 infected and sexting cases of adolescents over a period of 20 years. Pontryagin's Maximum Principle is used to characterise the optimal levels of the 2 controls, then numerically solved them. Overall, the application of the optimal control theory suggests that more effort should be devoted to both controls, filtering and awareness campaigns.

Chapter 5

Exploring the association between gender and HSV-2 treatment adherence

5.1. Introduction

The lack of focus on treatment adherence is a shame given the clear relationships between health behaviour and outcomes (Bosworth, 2010). In the USA, more than 90% of their health budget is spent on treating diseases and their complications, of which many are preventable (Satcher and Higginbotham, 2008; Woolf, 2009). Without a system that addresses the determinants of poor treatment adherence behaviour, advances in biomedical technology will fail to realise their potential to reduce the burden of chronic illness (Bosworth, 2010).

Some studies have provided some evidence supporting gender differences in coping with treatment adherence to prescribed medications (Goldstein, 2010). Men attribute their illness to behavioural factors like smoking and alcohol drinking where

as women view illness as their fault and punishment (Klonoff and Landrine, 1994, Yau et al., 2011). Various authors have suggested that men have better treatment adherence than women (Wong et al., 2013; Chilcot et al., 2010; Tapp et al., 2011), and some other researchers have found no differences in between gender groups and adherence (Kyngas and Lahdenperg, 1999; Ross et al., 2004; Victor et al., 2008). Women may need family support, including redistribution of household responsibilities, to enable them to adhere to treatment. Even if drugs are for free or subsidised, women may not be able to afford the time or money required to travel to a clinic. A qualitative study of women living with HIV in Colombia found that women prioritised the needs of their HIV-positive children over their own adherence needs (Arrivillaga et al., 2011). An improved understanding of gender differences in treatment adherence may contribute to the development of more effective gender-based interventions that can potentially reduce therapy failure during follow-up (Bonolo et al., 2013).

This chapter aims to investigate the prevalence of HSV-2 in relation to gender of infected individuals, to identify the gender group responsible for fuelling HSV-2 infection and also to identify the gender group to target with more intervention strategies.

5.2. Model Formulation

In this chapter we propose a deterministic model to explore the association between gender and HSV-2 treatment adherence. We subdivide the total population into four classes per gender at times t ; susceptibles ($S_i(t)$), individuals infected with acute HSV-2 and under anti-viral treatment ($A_i(t)$), individuals infected with acute HSV-2 and not under anti-viral treatment ($H_i(t)$) and the quiescent individuals ($Q_i(t)$), for $i = m, f$, with f representing females and m , males. Thus the total population is given by $N = N_m(t) + N_f(t)$, where $N_i(t) = S_i(t) + A_i(t) + H_i(t) + Q_i(t)$, for $i = m, f$. It is worth noting that the population under consideration is the sexually

active population, hence entry into the system represents an individual becoming sexually active at a rate Λ_i . μ_i , represents cessation of sexual activity, which may or may not be due to natural death and is assumed to be constant in all classes. Assuming homogeneous mixing of the population, the susceptible individuals in group i acquire infection with HSV-2 at the rate λ_i , given by

$$\lambda_i(t) = \frac{\beta_j c_i (H_j(t) + (1 - \eta_j) A_j(t))}{N_j(t)}, \quad i = m, f, \quad j = m, f, \quad i \neq j. \quad (5.1)$$

where β_j , is the probability per partner of HSV-2 transmission by an HSV-2 infectious individual of group j to a partner in group i . c_i being the rate of sexual contacts of group i . $\eta_j \in (0, 1)$ is a modification factor accounting for the assumed reduced likelihood for individuals in class A_j to pass on the infection compared to individuals in class H_j . This is due to the fact that individuals in treatment have reduced viral load compared to those who have failed to adhere to anti-viral treatment guidelines. Upon being infected with HSV-2, people in group i enter the class A_i (infected with acute HSV-2). They then become latent at a rate κ_i . Reactivation may occur following an appropriate stimulus in individuals with latent HSV-2 (Blower et al., 1998). The antiviral treatment rate for individuals with acute HSV-2 is denoted by ψ_i per individual of group i . Since the antiviral medication will also suppress reactivation of latent HSV-2, we assume that the reactivation rate of people with latent HSV-2 is at rate $\gamma_i(\psi_i)$, where $\gamma_i(\psi_i)$ is a decreasing function of ψ_i (Feng et al., 2013). Thus,

$$\gamma_i(\psi_i) = \gamma_i(0) \frac{\alpha}{\alpha + \psi_i}, \quad i = m, f, \quad (5.2)$$

in which the factor $\frac{\alpha}{\alpha + \psi_i}$ represents reduced reactivation to class A_i . In the case where there is no treatment, we have $\psi_i = 0$; and it follows that $\gamma_i(\psi_0) = \gamma_i(0) = \gamma_i^0$. A proportion $(1 - \theta_i)$ of individuals on treatment fail to adhere to treatment at a rate δ_i , and they move to class H_i . For simplicity, we shall refer to $\gamma_i(\psi_i)$ and $\gamma_i(0)$ as γ_i and γ_i^0 respectively, throughout the chapter.

The system of differential equations summarising the aforementioned assumptions and description is:

$$\left\{ \begin{array}{l} \frac{dS_i}{dt} = \Lambda_i - \lambda_i S_i - \mu_i S_i, \\ \frac{dA_i}{dt} = \lambda_i S_i + \gamma_i Q_i - (\mu_i + \kappa_i + \psi_i + \delta_i(1 - \theta_i)) A_i, \\ \frac{dH_i}{dt} = \delta_i(1 - \theta_i) A_i + \gamma_i^0 Q_i - (\kappa_i + \mu_i) H_i, \\ \frac{dQ_i}{dt} = (\kappa_i + \psi_i) A_i + \kappa_i H_i - (\gamma_i + \mu_i + \gamma_i^0) Q_i, \quad i = m, f, \quad j = m, f, \quad i \neq j. \end{array} \right. \quad (5.3)$$

The model flow diagram is depicted in Figure 5.1

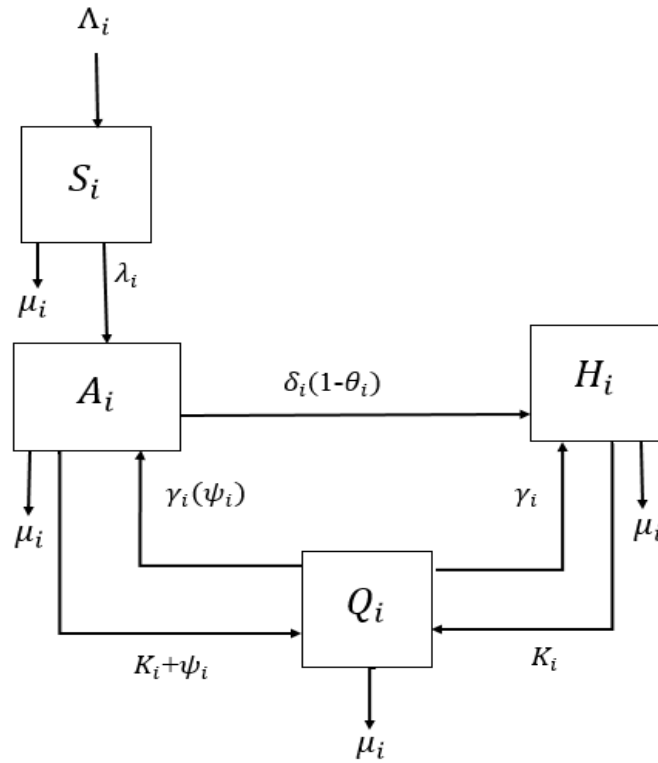


Figure 5.1: Structure of the model.

5.3. Model Analysis

5.3.1. Basic properties of the model

In this section, we study the basic results of solutions for model system (5.3), which are essential in the proofs of stability.

Theorem 5.1. *The feasible region $\mathcal{G}$ defined by*

$$\mathcal{G} = \left\{ (S_i(t), A_i(t), H_i(t), Q_i(t)) \in \mathbb{R}_+^8 : N_i(t) \leq \frac{\Lambda_i}{\mu_i}, i = m, f \right\}, \quad (5.4)$$

with initial conditions $S_i(0) \geq 0$, $A_i(0) \geq 0$, $H_i(0) \geq 0$, $Q_i(0) \geq 0$ is positively invariant and attracting with respect to model system (5.3) for all $t > 0$.

Proof. Adding all the equations of model system (5.3), we have

$$\begin{aligned} \frac{dN_i}{dt} &= \frac{dS_i}{dt} + \frac{dA_i}{dt} + \frac{dH_i}{dt} + \frac{dQ_i}{dt} \\ &= \Lambda_i - \mu_i N_i. \end{aligned} \quad (5.5)$$

Applying a theorem by Birkhoff and Rota (1982), on differential inequalities, we have that

$$0 \leq N_i(t) \leq \frac{\Lambda_i}{\mu_i} + N_i(0)e^{-\mu_i t}, \quad (5.6)$$

where $N_i(0) = S_i(0) + A_i(0) + H_i(0) + Q_i(0)$, at the initial values of the respective variables. Taking the limit as $t \rightarrow \infty$, we have that $0 \leq N_i \leq \frac{\Lambda_i}{\mu_i}$. Thus, the state variables remain biologically feasible in the set

$$\mathcal{G} = \left\{ (S_i(t), A_i(t), H_i(t), Q_i(t)) \in \mathbb{R}_+^8 : N_i(t) \leq \frac{\Lambda_i}{\mu_i}, i = m, f \right\},$$

for all positive initial conditions in $\mathbb{R}_+^4$. Existence, uniqueness and continuation results for model system (5.3) hold in this region and all the solutions of model system (5.3) starting in $\mathcal{G}$ remain in $\mathcal{G}$ for all $t \geq 0$. All parameters and state variables for

model system (5.3) are assumed to be non-negative (for biological relevance, $\forall t \geq 0$) since it monitors the human population. $\square$

5.3.2. Disease-free equilibrium and its stability analysis

The disease-free equilibrium point of model system (5.3) represents the state at which there is no infection in the whole population, that is, $A_i = H_i = Q_i = 0$. We substitute these values into model system (5.3) and this reduces to

$$0 = \Lambda_i - \mu_i S_i \Rightarrow S_i^0 = \frac{\Lambda_i}{\mu_i}.$$

Thus, the disease-free equilibrium of model system (5.3) is given by

$$\mathcal{E}^0 = (S_i^0, A_i^0, H_i^0, Q_i^0) = \left(\frac{\Lambda_i}{\mu_i}, 0, 0, 0 \right), \quad i = m, f. \quad (5.7)$$

The basic reproduction number; a threshold value representing how many secondary infections result from the introduction of one infected individual into a population of susceptibles (van den Driessche and Watmough, 2002). Using the notation in van den Driessche and Watmough (2002) on the model system (5.3), the matrices F and V , for the new infection terms and the remaining transfer terms

are respectively given by

$$F = \begin{bmatrix} 0 & 0 & 0 & \beta_f(1 - \eta_f)\frac{\mu_f\Lambda_m}{\mu_m\Lambda_f} & \beta_f\frac{\mu_f\Lambda_m}{\mu_m\Lambda_f} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_m(1 - \eta_m)\frac{\mu_m\Lambda_f}{\mu_f\Lambda_m} & \beta_m\frac{\mu_m\Lambda_f}{\mu_f\Lambda_m} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

and

(5.8)

$$V = \begin{bmatrix} k_1 & 0 & -\gamma_m & 0 & 0 & 0 \\ -\delta_m(1 - \theta_m) & k_2 & -\gamma_m^0 & 0 & 0 & 0 \\ -(\kappa_m + \psi_m) & -\kappa_m & k_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_4 & 0 & -\gamma_f \\ 0 & 0 & 0 & -\delta_f(1 - \theta_f) & k_5 & -\gamma_f^0 \\ 0 & 0 & 0 & -(\kappa_f + \psi_f) & -\kappa_f & k_6 \end{bmatrix},$$

$$\text{with } k_1 = \mu_m + \kappa_m + \psi_m + \delta_m(1 - \theta_m),$$

$$k_2 = \kappa_m + \mu_m,$$

$$k_3 = \gamma_m + \mu_m + \gamma_m^0,$$

$$k_4 = \mu_f + \kappa_f + \psi_f + \delta_f(1 - \theta_f),$$

$$k_5 = \kappa_f + \mu_f,$$

$$k_6 = \gamma_f + \mu_f + \gamma_f^0.$$

It follows from (5.8) that the reproduction number for model system (5.3) is the spectral radius of FV^{-1} given by

$$R_{mf} = \sqrt{R_m R_f}, \quad (5.9)$$

where

$$R_m = \frac{\beta_m \mu_m c_f \Lambda_f [V_{m_1} + V_{m_2}]}{\Lambda_m \mu_f [V_{m_3} + V_{m_4}]}, \quad R_f = \frac{\beta_f \mu_f c_m \Lambda_m [V_{f_1} + V_{f_2}]}{\Lambda_f \mu_m [V_{f_3} + V_{f_4}]}, \quad (5.10)$$

with

$$\begin{aligned} V_{m_1} &= (1 - \eta_m)(\mu_m \gamma_m^0 + (\mu_m + \kappa_m)(\mu_m + \gamma_m)), \\ V_{m_2} &= \gamma_m^0(\kappa_m + \psi_m) + \delta_m(1 - \theta_m)(\gamma_m + \gamma_m^0 + \mu_m), \\ V_{m_3} &= \mu_m(\mu_m + \kappa_m + \psi_m + \delta_m(1 - \theta_m))(\mu_m + \kappa_m)(\mu_m + \kappa_m + \gamma_m^0), \\ V_{m_4} &= \mu_m \gamma_m(\mu_m + \kappa_m) + \gamma_m \kappa_m \delta_m(1 - \theta_m), \\ V_{f_1} &= (1 - \eta_f)(\mu_f \gamma_f^0 + (\mu_f + \kappa_f)(\mu_f + \gamma_f)), \\ V_{f_2} &= \gamma_f^0(\kappa_f + \psi_f) + \delta_f(1 - \theta_f)(\gamma_f + \gamma_f^0 + \mu_f), \\ V_{f_3} &= \mu_f(\mu_f + \kappa_f + \psi_f + \delta_f(1 - \theta_f))(\mu_f + \kappa_f)(\mu_f + \kappa_f + \gamma_f^0), \\ V_{f_4} &= \mu_f \gamma_f(\mu_f + \kappa_f) + \gamma_f \kappa_f \delta_f(1 - \theta_f). \end{aligned} \quad (5.11)$$

Using Theorem 2 in Diekmann and Heesterbeek (2000), the following result is established.

Theorem 5.2. *The disease free equilibrium $\mathcal{E}^0$ of model system (5.3) is locally asymptotically stable (LAS) if $R_{mf} < 1$ and unstable if $R_{mf} > 1$.*

In the following, we will present the globally stability of the disease-free equilibrium $\mathcal{E}^0$.

We now list two conditions that if met, also guarantee the global asymptotic stability of the disease-free state. Following Castillo-Chavez et al., (2002), we write system (5.3) in the form

$$\frac{dX}{dt} = F(X, Z), \quad (5.12)$$

$$\frac{dZ}{dt} = G(X, Z), \quad G(X, \mathbf{0}),$$

where $X = (S_m, S_f)$ and $Z = (A_m, H_m, Q_m, A_f, H_f, Q_f)$, with

$X \in \mathbb{R}_+^2$ denoting (its components) the number of uninfected individuals and

$Z \in \mathbb{R}_+^6$ denoting (its components) the number of infected individuals including the

quiescent class.

The disease-free equilibrium is now denoted by

$$\mathcal{E}^0 = (X^*, \mathbf{0}), \text{ where } X^* = \left(\frac{\Lambda_m}{\mu_m}, \frac{\Lambda_f}{\mu_f} \right). \quad (5.13)$$

We have to prove that the two conditions hold

$$\begin{aligned} \text{(M1)} : & \text{ For } \frac{dX}{dt} = F(X, \mathbf{0}), X^* \text{ is globally asymptotically stable} \\ \text{(M2)} : & G(X, Z) = BZ - \widehat{G}(X, Z), \widehat{G}(X, Z) \geq 0 \text{ for } (X, Z) \in \mathcal{G}, \end{aligned} \quad (5.14)$$

are satisfied where $\mathcal{G}$ is a positively invariant attracting domain and $B = D_Z G(X^*, \mathbf{0})$ is an M-matrix. If model system (5.12) satisfies the conditions in (5.14), then, Theorem (5.3) holds.

Theorem 5.3. *The fixed point $\mathcal{E}^0 = (X^*, \mathbf{0})$ is a globally asymptotically stable equilibrium of model system (5.3) provided that $R_{mf} \leq 1$ and unstable otherwise.*

Proof. From Theorem 5.2, it follows that the disease free equilibrium $\mathcal{E}^0$ is locally asymptotically stable if $R_{mf} < 1$ and unstable if $R_{mf} > 1$. Consider

$$F(X, \mathbf{0}) = \begin{bmatrix} \Lambda_m - \mu_m S_m \\ \Lambda_f - \mu_f S_f \end{bmatrix} \quad (5.15)$$

and

$$B = \begin{bmatrix} -k_1 & 0 & \gamma_m & \beta_f(1 - \eta_f) \frac{\mu_f \Lambda_m}{\mu_m \Lambda_m} & \beta_f \frac{\mu_f \Lambda_m}{\mu_m \Lambda_m} & 0 \\ \delta_m(1 - \theta_m) & -k_2 & \gamma_m^0 & 0 & 0 & 0 \\ (\kappa_m + \psi_m) & \kappa_m & -k_3 & 0 & 0 & 0 \\ \beta_m(1 - \eta_m) \frac{\mu_m \Lambda_f}{\mu_f \Lambda_f} & \beta_m \frac{\mu_m \Lambda_f}{\mu_f \Lambda_f} & 0 & -k_4 & 0 & \gamma_f \\ 0 & 0 & 0 & \delta_f(1 - \theta_f) & -k_5 & \gamma_f^0 \\ 0 & 0 & 0 & (\kappa_f + \psi_f) & \kappa_f & -k_6 \end{bmatrix}. \quad (5.16)$$

Then,

$$\begin{aligned}
 \widehat{G}(X, Z) &= BZ - G(X, Z) \\
 &= \begin{bmatrix} \widehat{G}_1(X, Z) \\ \widehat{G}_2(X, Z) \\ \widehat{G}_3(X, Z) \\ \widehat{G}_4(X, Z) \\ \widehat{G}_5(X, Z) \\ \widehat{G}_6(X, Z) \end{bmatrix} \\
 &= \begin{bmatrix} \frac{\beta_f c_m (H_f + (1 - \eta_f) A_f)}{N_f} (N_m - S_m) \\ 0 \\ 0 \\ \frac{\beta_m c_f (H_m + (1 - \eta_m) A_m)}{N_m} (N_f - S_f) \\ 0 \\ 0 \end{bmatrix}. \tag{5.17}
 \end{aligned}$$

Since $S_m \leq N_m$ and $S_f \leq N_f$ at the disease free equilibrium, $\mathcal{E}^0$, it follows that $\widehat{G}(X, Z) \geq 0$. The proof is complete. $\square$

5.3.3. Endemic equilibrium and its stability analysis

In this section we study the stability of the endemic equilibrium point. An equilibrium point which exists when $R_{mf} > 1$. Since the disease-free equilibrium is globally asymptotically stable, it implies that model system (5.3) admits a unique endemic equilibrium point. Thus, the endemic equilibrium point is given by $\mathcal{E}^* =$

$(S_i^*, A_i^*, H_i^*, Q_i^*)$, $i = m, f$, where

$$\mathcal{E}^* = \begin{cases} S_i^* = \frac{\Lambda_i}{\mu_i + \Lambda_i}, \\ A_i^* = \frac{\lambda_i \Lambda_i [\delta_i \kappa_i (1 - \theta_i) + (\mu_i + \kappa_i)(\psi_i + \kappa_i)]}{\mu_i (\mu_i + \lambda_i) \Delta_i}, \\ H_i^* = \frac{\lambda_i \Lambda_i [\delta_i (1 - \theta_i)(\mu_i + \gamma_i + \gamma_i^0) + \gamma_0 (\kappa_i + \psi_i)]}{\mu_i (\mu_i + \lambda_i) \Delta_i}, \\ Q_i^* = \frac{\lambda_i \Lambda_i [\mu_i \gamma_i^0 + (\mu_i + \gamma_i)(\mu_i + \kappa_i)]}{\mu_i (\mu_i + \lambda_i) \Delta_i}, \\ \text{for } i = m, f, \quad j = m, f, \quad i \neq j. \end{cases} \quad (5.18)$$

with

$$\Delta_i = [\gamma_i (\delta_i (1 - \theta_i) + \mu_i + \kappa_i) + (\mu_i + \kappa_i) (\delta_i (1 - \theta_i) + \kappa_i + \mu_i + \psi_i) + \gamma_i^0 (\delta_i (1 - \theta_i) + \kappa_i + \mu_i + \psi_i)].$$

To study the local stability of the endemic equilibrium point, we will utilise the Centre Manifold Theory (Chavez and Song, 2004).

Employing the Centre Manifold Theory (Chavez and Song, 2004) to analyse the stability of this equilibrium point as described in Theorem 4.1 (Chavez and Song, 2004), to establish the local asymptotic stability of the endemic equilibrium. Let us make the following change of variables in order to apply the Centre Manifold Theory, $S_m = x_1$, $A_m = x_2$, $H_m = x_3$, $Q_m = x_4$, $S_f = x_5$, $A_f = x_6$, $H_f = x_7$ and $Q_f = x_8$. We now use the vector notation $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8)^T$. Then, model system (5.3) can be written in the form $\frac{dX}{dt} = F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8)^T$, such that

$$\begin{aligned}
x'_1 = f_1 &= \Lambda_m - \frac{\beta_f c_m (x_6(1 - \eta_f) + x_7)x_1}{x_5 + x_6 + x_7 + x_8} - \mu_m x_1, \\
x'_2 = f_2 &= \frac{\beta_f c_m (x_6(1 - \eta_f) + x_7)x_1}{x_5 + x_6 + x_7 + x_8} + \gamma_m x_4 - (\mu_m + \kappa_m + \psi_m + \delta_m(1 - \theta_m))x_2, \\
x'_3 = f_3 &= \delta_m(1 - \theta_m)x_2 + \gamma_m^0 x_4 - (\mu_m + \kappa_m)x_3, \\
x'_4 = f_4 &= (\kappa_m + \psi_m)x_2 + \kappa_m x_3 - (\gamma_m + \mu_m + \gamma_m^0)x_4, \\
x'_5 = f_5 &= \Lambda_f - \frac{\beta_m c_f (x_2(1 - \eta_m) + x_3)x_5}{x_1 + x_2 + x_3 + x_4} - \mu_m x_5, \\
x'_6 = f_6 &= \frac{\beta_m c_f (x_2(1 - \eta_m) + x_3)x_5}{x_1 + x_2 + x_3 + x_4} + \gamma_m x_8 - (\mu_m + \kappa_m + \psi_m + \delta_m(1 - \theta_m))x_6, \\
x'_7 = f_7 &= \delta_f(1 - \theta_f)x_6 + \gamma_f^0 x_8 - (\mu_f + \kappa_f)x_7, \\
x'_8 = f_8 &= (\kappa_f + \psi_f)x_6 + \kappa_f x_7 - (\gamma_f + \mu_f + \gamma_f^0)x_8.
\end{aligned} \tag{5.19}$$

The method entails evaluating the Jacobian of system (5.19) at $\mathcal{E}^0$, with

$S_m^0 = x_1^0$, $A_m^0 = x_2^0$, $H_m^0 = x_3^0$, $Q_m^0 = x_4^0$, $S_y^0 = x_5^0$, $A_y^0 = x_6^0$, $H_y^0 = x_7^0$ and $Q_y^0 = x_8^0$. Thus,

$$J(\mathcal{E}^0) = \begin{bmatrix} \mathcal{M}_1 & \mathcal{M}_2 \\ \mathcal{M}_3 & \mathcal{M}_4 \end{bmatrix} \tag{5.20}$$

where

$$\mathcal{M}_1 = \begin{bmatrix} -\mu_m & 0 & 0 & 0 \\ 0 & -k_1 & 0 & \gamma_m \\ 0 & \delta_m(1 - \theta_m) & -k_2 & \gamma_m^0 \\ 0 & (\mu_m + \kappa_m) & \kappa_m & -k_3 \end{bmatrix}, \tag{5.21}$$

$$\mathcal{M}_2 = \begin{bmatrix} 0 & -\frac{\beta_f(1-\eta_f)\Lambda_m\mu_f}{\mu_m\Lambda_f} & -\frac{\beta_f\Lambda_m\mu_f}{\mu_m\Lambda_f} & 0 \\ 0 & \frac{\beta_f(1-\eta_f)\Lambda_m\mu_f}{\mu_m\Lambda_f} & \frac{\beta_f\Lambda_m\mu_f}{\mu_m\Lambda_f} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$\mathcal{M}_3 = \begin{bmatrix} 0 & -\frac{\beta_m(1-\eta_m)\Lambda_f\mu_m}{\mu_f\Lambda_m} & -\frac{\beta_m\Lambda_f\mu_m}{\mu_f\Lambda_m} & 0 \\ 0 & \frac{\beta_m(1-\eta_m)\Lambda_f\mu_m}{\mu_f\Lambda_m} & \frac{\beta_m\Lambda_f\mu_m}{\mu_f\Lambda_m} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$\mathcal{M}_4 = \begin{bmatrix} -\mu_f & 0 & 0 & 0 \\ 0 & -k_4 & 0 & \gamma_f \\ 0 & \delta_f(1-\theta_f) & -k_5 & \gamma_f^0 \\ 0 & \kappa_f + \mu_f & \kappa_f & -k_6 \end{bmatrix}.$$

from which it can be shown that

$$R_{mf} = \sqrt{R_m R_f}, \quad (5.22)$$

where

$$R_m = \frac{\beta_m \mu_m c_f \Lambda_f [V_{m_1} + V_{m_2}]}{\Lambda_m \mu_f [V_{m_3} + V_{m_4}]}, \quad R_f = \frac{\beta_f \mu_f c_m \Lambda_m [V_{f_1} + V_{f_2}]}{\Lambda_f \mu_m [V_{f_3} + V_{f_4}]}, \quad (5.23)$$

with V_{m_1} , V_{m_2} , V_{m_3} , V_{m_4} , V_{f_1} , V_{f_2} , V_{f_3} , V_{f_4} as defined in equation (5.11).

Now let us consider $\beta_f = \rho\beta_m$, regardless of whether $\rho \in (0, 1)$ or $\rho \geq 1$. Taking β_f as a bifurcation parameter and considering the case $R_{mf} = 1$ and solve for β_m , we obtain

$$\beta_m = \beta^* = \sqrt{H_m H_f}, \quad (5.24)$$

where,

$$H_m = \frac{\Lambda_m \mu_f [V_{m3} + V_{m4}]}{\mu_m c_f \Lambda_f [V_{m1} + V_{m2}]}, \quad H_f = \frac{\Lambda_f \mu_m [V_{f3} + V_{f4}]}{\rho \beta_f \mu_f c_m \Lambda_m [V_{f1} + V_{f2}]}, \quad (5.25)$$

with V_{m1} , V_{m2} , V_{m3} , V_{m4} , V_{f1} , V_{f2} , V_{f3} , V_{f4} as defined in equation 5.11.

Note that the linearised system of the transformed equation (5.19) with the bifurcation point β^* has a simple zero eigenvalue. Hence the centre manifold theory (Chavez and Song, 2004) can be used to analyse the dynamics of system (5.19) near $\beta_m = \beta^*$. It can be shown that the Jacobian of model system (5.19) has a right eigenvector associated with the following zero eigenvalue given by $u = (u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8)^T$, where

$$\begin{aligned} u_1 &= -\beta_f c_m \frac{\Lambda_m \mu_f}{\mu_m^2 \Lambda_f} (u_6(1 - \eta_f) + u_7) < 0, \quad u_4 = u_4 > 0, \\ u_2 &= \frac{[\kappa_m(\gamma_m + \mu_m) + \mu_m(\gamma_m + \mu_m + \gamma_m^0)]}{\delta_m(1 - \theta_m)[(\kappa_m + \mu_m)(\mu_m + \kappa_m) + \kappa_m \delta_m(1 - \theta_m)]} u_4 > 0, \\ u_3 &= \frac{[\gamma_m^0(\mu_m + \kappa_m) + (\gamma_m + \mu_m + \gamma_m^0)\delta_m(1 - \theta_m)]}{(\kappa_m + \mu_m)(\mu_m + \kappa_m) + \kappa_m \delta_m(1 - \theta_m)} u_4 > 0, \\ u_5 &= -\beta_m c_f \frac{\Lambda_f \mu_m}{\mu_f^2 \Lambda_m} (u_2(1 - \eta_m) + u_3) < 0, \quad u_8 = u_8 > 0, \\ u_6 &= \frac{[\kappa_f(\gamma_f + \mu_f) + \mu_f(\gamma_f + \mu_f + \gamma_f^0)]}{\delta_f(1 - \theta_f)[(\kappa_f + \mu_f)(\mu_f + \kappa_f) + \kappa_f \delta_f(1 - \theta_f)]} u_8 > 0, \\ u_7 &= \frac{[\gamma_f^0(\mu_f + \kappa_f) + (\gamma_f + \mu_f + \gamma_f^0)\delta_f(1 - \theta_f)]}{(\kappa_f + \mu_f)(\mu_f + \kappa_f) + \kappa_f \delta_f(1 - \theta_f)} u_8 > 0. \end{aligned} \quad (5.26)$$

The left eigenvector of $J(\mathcal{E}^0)$ associated with the zero eigenvalue at $\beta_m = \beta^*$ is given

by

$v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8)^T$, where

$$\begin{aligned}
 v_1 = v_5 = 0, \quad v_3 = \frac{\kappa_m v_4 + \mathcal{H}_1 v_6}{k_2} > 0, \quad v_4 = v_4 > 0, \\
 v_2 = \left(\frac{\delta_m(1 - \theta_m)\kappa_m}{k_1 k_2} + \frac{\mu_m + \kappa_m}{k_1} \right) v_4 + \left(\frac{\delta_m(1 - \theta_m)\mathcal{H}_2}{k_1 k_2} + \frac{\mathcal{H}_1}{k_1} \right) v_6 > 0, \quad v_6 = v_6 > 0, \\
 v_7 = \left(\frac{\delta_m(1 - \theta_m)\kappa_m}{k_1 k_2} + \frac{\mu_m + \kappa_m}{k_1} \right) \frac{k_2 \mathcal{H}_3 v_4}{M} \\
 + \left(\gamma_f \kappa_f + \frac{k_2 \mathcal{H}_1 \mathcal{H}_3}{k_1} + \frac{k_2 \delta_m(1 - \theta_m) \mathcal{H}_2 \mathcal{H}_3}{k_1 k_2} \right) \frac{v_6}{M} > 0, \\
 v_8 = \left(\frac{k_2 \delta_m(1 - \theta_m) \kappa_m \mathcal{H}_3}{k_1 k_2} + \frac{k_2(\mu_m + \kappa_m) \mathcal{H}_3}{k_1} \right) \frac{\gamma_f^0 v_4}{M} \\
 + \left(\frac{\gamma_f M}{\gamma_f^0} + \gamma_f \kappa_f + \frac{\mathcal{H}_1 \mathcal{H}_3}{k_1} + \frac{k_2 \delta_m(1 - \theta_m) \mathcal{H}_2 \mathcal{H}_3}{k_1 k_2} \right) \frac{\gamma_f^0 v_6}{M} > 0,
 \end{aligned} \tag{5.27}$$

with

$$\begin{aligned}
 M &= \kappa_f(\gamma_f + \mu_f) + \mu_f k_6, \\
 \mathcal{H}_1 &= \frac{\beta_m(1 - \eta_m)\Lambda_f \mu_m}{\mu_f \Lambda_m}, \\
 \mathcal{H}_2 &= \frac{\beta_m \Lambda_f \mu_m}{\mu_f \Lambda_m}, \\
 \mathcal{H}_3 &= \frac{\beta_f(1 - \eta_f)\Lambda_m \mu_f}{\mu_m \Lambda_f}, \\
 \mathcal{H}_4 &= \frac{\beta_f(1 - \eta_f)\Lambda_m \mu_f}{\mu_m \Lambda_f}.
 \end{aligned}$$

Then we use Theorem (4.1) from Castillo Chavez and Song (2004), stated below for elucidation.

Theorem 5.4. *Consider the following general system of ordinary differential equations with parameter ϕ*

$$\frac{dx}{dt} = f(x, \phi) \quad f : \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R}, \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}^n) \quad (5.28)$$

where 0 is an equilibrium of the system, that is $f(0, \phi) = 0 \quad \forall \phi$, and assume

A1) $A = D_x f(0, 0) = \left(\frac{\partial f_i}{\partial x_j}(0, 0) \right)$ is the linearisation of system (5.3) around the equilibrium 0 and ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts

A2) Matrix A has the right eigenvector u and a left eigenvector v corresponding to the zero eigenvalue let f_k be the k^{th} component of f and

$$\begin{aligned} a &= \sum_{k,i,j=1}^n v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0), \\ b &= \sum_{k,i=1}^n v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0). \end{aligned} \quad (5.29)$$

The local dynamics of (5.28) around zero are totally governed by a and b .

i. $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, and there exists a positive unstable equilibrium, when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;

ii. $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;

iii. $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exist a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears;

iv. $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Corresponding a negative unstable equilibrium becomes positive and locally asymptotically stable.

Computation of the bifurcation parameters a and b

For model system (5.19), the associated non-zero partial derivatives of F at the disease-free are given by

$$\begin{aligned}
\frac{\partial^2 f_2}{\partial x_1 \partial x_6} &= \frac{\partial^2 f_2}{\partial x_6 \partial x_1} = -\beta_f c_m (1 - \eta_f) \frac{\mu_f}{\Lambda_f}, \quad \frac{\partial^2 f_2}{\partial x_5 \partial x_6} = \frac{\partial^2 f_2}{\partial x_6 \partial x_5} = -\frac{\beta_f c_m (1 - \eta_f) \Lambda_m \mu_f^2}{\mu_m \Lambda_f^2}, \\
\frac{\partial^2 f_2}{\partial x_6^2} &= \frac{-2\beta_f c_m (1 - \eta_f) \Lambda_m \mu_f^2}{\mu_m \Lambda_f^2}, \quad \frac{\partial^2 f_2}{\partial x_6 \partial x_7} = \frac{\partial^2 f_2}{\partial x_7 \partial x_6} = -\frac{\beta_f c_m \Lambda_m \mu_f^2}{\mu_m \Lambda_f^2} - \frac{\beta_f c_m (1 - \eta_f) \Lambda_m \mu_f^2}{\mu_m \Lambda_f^2}, \\
\frac{\partial^2 f_2}{\partial x_6 \partial x_8} &= \frac{\partial^2 f_2}{\partial x_8 \partial x_6} = -\frac{\beta_f c_m (1 - \eta_f) \Lambda_m \mu_f^2}{\mu_m \Lambda_f^2}, \quad \frac{\partial^2 f_2}{\partial x_1 \partial x_7} = \frac{\partial^2 f_2}{\partial x_7 \partial x_1} = -\beta_f c_m \frac{\mu_f}{\Lambda_f}, \\
\frac{\partial^2 f_2}{\partial x_5 \partial x_7} &= \frac{\partial^2 f_2}{\partial x_7 \partial x_5} = \frac{\partial^2 f_2}{\partial x_7 \partial x_8} = \frac{\partial^2 f_2}{\partial x_8 \partial x_7} = -\frac{\beta_f c_m \Lambda_m \mu_f^2}{\mu_m \Lambda_f^2}, \\
\frac{\partial^2 f_2}{\partial x_7^2} &= \frac{-2\beta_f c_m \mu_f^2 \Lambda_m}{\Lambda_f^2 \mu_m}, \quad \frac{\partial^2 f_2}{\partial x_6 \partial x_7} = \frac{\partial^2 f_2}{\partial x_7 \partial x_6} = -\frac{\beta_f c_m \mu_f^2 \Lambda_m}{\Lambda_f^2 \mu_m} - \frac{\beta_f c_m (1 - \eta_f) \mu_f^2 \Lambda_m}{\Lambda_f^2 \mu_m}, \\
\frac{\partial^2 f_6}{\partial x_1 \partial x_2} &= \frac{\partial^2 f_6}{\partial x_2 \partial x_1} = -\frac{\beta_m c_f (1 - \eta_m) \Lambda_f \mu_m^2}{\mu_f \Lambda_m^2}, \quad \frac{\partial^2 f_6}{\partial x_1 \partial x_3} = \frac{\partial^2 f_6}{\partial x_3 \partial x_1} = -\frac{\beta_m c_f \Lambda_f \mu_m^2}{\mu_f \Lambda_m^2}, \\
\frac{\partial^2 f_6}{\partial x_2 \partial x_3} &= \frac{\partial^2 f_6}{\partial x_3 \partial x_2} = -\frac{\beta_m c_f (1 - \eta_m) \Lambda_f \mu_m^2}{\mu_f \Lambda_m^2} - \frac{\beta_m c_f \Lambda_f \mu_m^2}{\mu_f \Lambda_m^2}, \\
\frac{\partial^2 f_6}{\partial x_2 \partial x_4} &= \frac{\partial^2 f_6}{\partial x_4 \partial x_2} = -\frac{\beta_m c_f (1 - \eta_m) \Lambda_f \mu_m^2}{\mu_f \Lambda_m^2}, \\
\frac{\partial^2 f_6}{\partial x_2 \partial x_5} &= \frac{\partial^2 f_6}{\partial x_5 \partial x_2} = -\frac{\beta_m c_f (1 - \eta_m) \mu_m}{\Lambda_m}, \quad \frac{\partial^2 f_6}{\partial x_3 \partial x_4} = \frac{\partial^2 f_6}{\partial x_4 \partial x_3} = -\frac{\beta_m c_f \Lambda_f \mu_m^2}{\mu_f \Lambda_m^2}, \\
\frac{\partial^2 f_6}{\partial x_3 \partial x_5} &= \frac{\partial^2 f_6}{\partial x_5 \partial x_3} = -\frac{\beta_m c_f \mu^2}{\Lambda_m}, \quad \frac{\partial^2 f_6}{\partial x_3^2} = -\frac{2\beta_m c_f \Lambda_f \mu_m^2}{\mu_f \Lambda_m^2}, \quad \frac{\partial^2 f_6}{\partial x_2^2} = -\frac{2\beta_m c_f (1 - \eta_m) \Lambda_f \mu_m^2}{\mu_f \Lambda_m^2}.
\end{aligned}$$

(5.30)

From (5.30), it follows that

$$\begin{aligned}
a &= -2\beta_m c_f (1 - \eta_m) \frac{\mu_m^2 \Lambda_f v_6}{\Lambda_m^2 \mu_f} (u_2(1 - \eta_m) + u_3)(u_1 + u_2 + u_3 + u_4) \\
&\quad + 2\beta_m c_f v_2 u_5 \frac{\mu_m^2}{\Lambda_m^2} (u_2(1 - \eta_m) + u_3) \\
&\quad - 2\beta_f c_m (1 - \eta_f) \frac{\mu_f^6 \Lambda_m v_2}{\Lambda_f^2 \mu_m} (u_6(1 - \eta_f) + u_7)(u_5 + u_6 + u_7 + u_8) \\
&\quad + 2\beta_f c_m v_6 u_1 \frac{\mu_f^2}{\Lambda_f^2} (u_6(1 - \eta_f) + u_7) \\
&< 0.
\end{aligned} \tag{5.31}$$

For the sign of b , it is associated with the following non-vanishing partial derivatives of F ,

$$\begin{aligned}
\frac{\partial^2 f_6}{\partial x_2 \partial \beta^*} &= \frac{c_f (1 - \eta_m) \mu_m \Lambda_f}{\Lambda_m \mu_f}, \quad \frac{\partial^2 f_6}{\partial x_3 \partial \beta^*} = \frac{c_f \mu_m \Lambda_f}{\Lambda_m \mu_f}, \\
\frac{\partial^2 f_2}{\partial x_6 \partial \beta^*} &= \frac{\rho c_m (1 - \eta_f) \mu_f \Lambda_m}{\Lambda_f \mu_m}, \quad \frac{\partial^2 f_2}{\partial x_7 \partial \beta^*} = \frac{\rho c_m \mu_f \Lambda_m}{\Lambda_f \mu_m}.
\end{aligned} \tag{5.32}$$

It follows from the expressions in (5.32) that

$$b = \frac{\Lambda_f \mu_m}{\mu_f \Lambda_m} c_m v_2 (u_2(1 - \eta_m) + u_3) + \frac{\Lambda_m \mu_f}{\mu_m \Lambda_f} c_f v_6 (u_6(1 - \eta_f) + u_7) > 0. \tag{5.33}$$

Since $a < 0$ and $b > 0$, according to Theorem 5.4 we have the following result.

Theorem 5.5. *The unique endemic equilibrium $\mathcal{E}^*$ guaranteed by Theorem 5.4 is locally asymptotically stable for $R_{mf} > 1$, but close to 1.*

5.4. Numerical Simulations

In order to illustrate the results of the foregoing analysis, we have simulated model system (5.3) using the parameters in Table 5.1. Unfortunately, the scarcity of the data on HSV-2 with a focus on treatment adherence with respect to gender differences limits our ability to calibrate. Nevertheless, we assume some of the

parameters in the realistic range for illustrative purposes. These parsimonious assumptions reflect the lack of information currently available on HSV-2 with a focus on HSV-2 treatment adherence. Reliable data on HSV-2 and poor treatment adherence would enhance our understanding and aid in the possible intervention strategies to be implemented.

- (i) In this section, we assume the populations for both the males (N_m) and females (N_f) to be the same. We set the population at $N_m = N_f = 500000$ per month and this value was adopted from the work of Alvey et al., (2015).
- (ii) The world's average rate of exiting sexual activity is around 35 years (420 months), the 15-49 years of age (Abu-Raddad, 2008). Thus, we set $\mu_m = \mu_f = \frac{1}{420}$ per month.
- (iii) We adopt the HSV-2 transmission probability of HSV-2 infection per female contact with HSV-2 infected males (β_m) of 0.3 and the HSV-2 transmission probability of HSV-2 infection per male contact with HSV-2 infected females (β_f) of 0.2 as estimated by Blower et al., (1998) and Abu-Raddad et al., (2008).
- (iv) We set the rate of sexual contacts for both the males (c_m) and the females (c_f) at 0.33 per month, based on the published results of Abu-Raddad et al., (2008).
- (v) Both the proportions of adherence for males (θ_m) and females (θ_f) are given by $\theta_m = 0.6$ and $\theta_f = 0.55$ respectively. These values were estimated through a study in Tanzania within a randomised, double blinded, placebo-controlled trial of HSV-2 therapy (Watson-Jones, 2009).
- (vi) We set the treatment quitting rate for both the males (δ_m) and the females (δ_f) at 0.3 per month and this value was adopted from the work of Bangsberg (2001) and Golin (2002).
- (vii) For the rate of acute becoming latent for the males (κ_m) and females (κ_f), we adopt the following rates as derived by Abu-Raddad et al., (2008), $\kappa_m = 2.678$ and $\kappa_f = 2.083$.

- (viii) For the baseline reactivation rate of latent HSV-2 males (γ_m^0) and females (γ_f^0), we adopt the following rates as derived by Abu-Raddad et al., (2008), $\gamma_m^0 = 0.436$ and $\gamma_f^0 = 0.339$.
- (ix) We adopt the treatment rate for both males (ψ_m) and females (ψ_f) which is varied without any point estimate, from the work of Feng et al., (2013).

Table 5.1: Model parameters and their baseline values. The time unit is in months

Definition	Symbol	Baseline values	Source
Males, Females	m, f		
Total number of males	N_m	500000	b*
Total number of females	N_f	500000	b*
Rate of exiting sexual activity	μ_m, μ_f	1/420, 1/420	a*
Recruitment rate	Λ_m, Λ_f	$N_m\mu_m, N_f\mu_f$	b*
Probability of HSV-2 infection per female contact with HSV-2 infected males	β_m	0.3	a*,e*
Probability of HSV-2 infection per male contact with HSV-2 infected females	β_f	0.2	a*,e*
Rate of sexual contacts	c_m, c_f	0.33, 0.33	a*
Rate of acute HSV-2 becoming latent	κ_m, κ_f	2.678, 2.083	a*
Treatment rate of acute HSV-2	ψ_m, ψ_f	Varied	f*
Baseline reactivation rate of latent HSV-2	γ_m^0, γ_f^0	0.436, 0.339	a*
Rate of sexual contacts of the respective groups	c_m, c_f	Varies	b*
Treatment quitting rate	δ_m, δ_f	0.3, 0.3	c*
Proportion of adherence	θ_m, θ_f	0.6, 0.55	d*
Modification factor	η_m, η_f	Varies $\in (0, 1)$	Assumed

In the Table 5.1 above, a* denotes parameter values from (Abu-Raddad et al., 2008); b* denotes parameter values from (Alvey et al., 2015); c* denotes parameter values from (Bangsberg, 2001 and Golin, 2002); d* parameter values from (Watson-Jones et al., 2009), e* parameter values from (Blower et al., 1998) and f* parameter values from (Feng et al., 2013).

Sensitivity analysis tells us how important each parameter is to disease transmission. Such information is crucial not only for experimental design, but also to data assimilation and reduction of complex nonlinear models. Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter

values, since there are usually errors in data collection and presumed parameter values. It is used to discover parameters that have a high impact on reproduction number and should be targeted by intervention strategies.

Sensitivity indices allow us to measure the relative change in a variable when a parameter changes. The normalised forward sensitivity index of a variable with respect to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives.

Definition 5.1. *The normalised forward sensitivity index of a variable, τ , that depends on a parameter ρ , is defined as*

$$\Upsilon_{\rho}^{\tau} = \frac{\partial \tau}{\partial \rho} \times \frac{\rho}{\tau}. \quad (5.34)$$

Symbol	Definition	Sensitivity Index
β_m	Probability of HSV-2 infection per female contact with HSV-2 infected males	0.5
β_f	Probability of HSV-2 infection per male contact with HSV-2 infected females	0.5
c_m	Sexual contacts (males)	0.5
c_f	Sexual contacts (females)	0.5
μ_m	Average sexual lifespan (males)	-0.484698
μ_f	Average sexual lifespan (females)	-0.489547
κ_m	Rate of acute becoming latent (males)	-0.311966
κ_f	Rate of acute becoming latent (females)	-0.259511
ψ_m	Treatment rate of acute HSV-2 (males)	-0.0263061
ψ_f	Treatment rate of acute HSV-2 (females)	-0.044094
γ_m^0	Baseline reactivation rate of latent males	0.0607543
γ_f^0	Baseline reactivation rate of latent females	0.0570082
δ_m	Treatment quitting rate (males)	0.0179823
δ_f	Treatment quitting rate (females)	0.0293579
θ_m	Proportion of adherence (males)	-0.233902
θ_f	Proportion of adherence (females)	-0.252119
η_m	Modification factor (males)	-0.0269734
η_f	Modification factor (females)	-0.0358819
γ_m	Reactivation rate of latent HSV-2 with an effect of treatment (males)	0.206712
γ_f	Reactivation rate of latent HSV-2 with an effect of treatment (females)	0.224233

Table 5.2: Sensitivity indices of model parameters to R_{mf}

The results in Table 5.2 suggest that, whenever the contact rates and the reactivation of the latent HSV-2 with an effect of treatment are increased, then the reproduction number would also increase. It is worth noting that the reactivation of the latent HSV-2 with an effect of treatment is inversely proportional to treatment, thus increasing treatment reduces the reactivation of the latent HSV-2, and decreasing treatment increases the reactivation of the latent HSV-2. Hence it would be important to increase the treatment rate of the latent HSV-2 individuals. Of all the parameters responsible for decreasing the size of the reproduction number, the rate of the acute becoming latent and the proportion of treatment adherence are the most vital. If the proportion for males who adhere to treatment is increased by 23%, then the reproduction number would also decrease by 23% and if the proportion of females who adhere to treatment is increased by 25%, then the

reproduction number would also decrease by 25%.

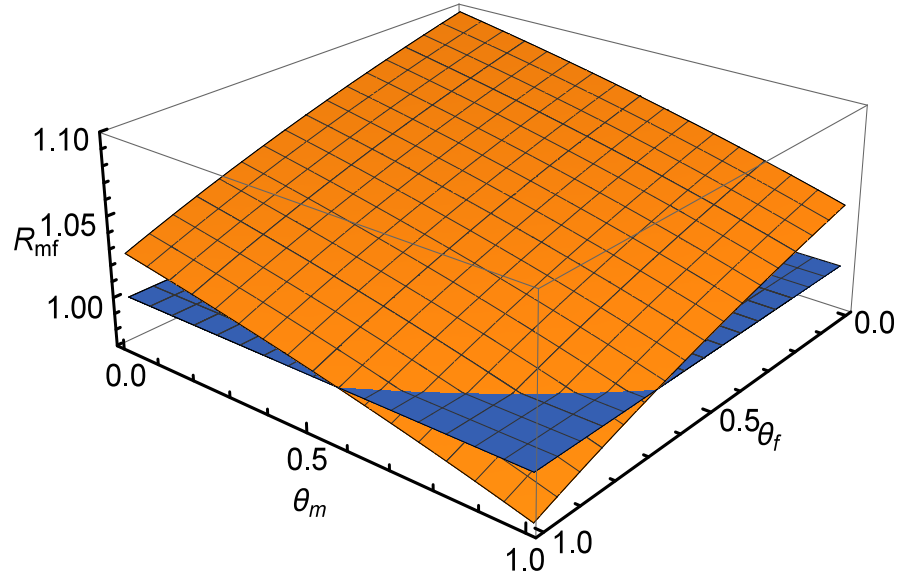


Figure 5.2: Figure 3(a) shows the effects of varying the male and female treatment adherence on the reproduction number R_{mf} .

Figure 3(a) depicts that the reproduction number can be reduced by fairly high levels of HSV-2 treatment adherence among both, the males and females. We note that if $\theta_m > 0.6$ and $\theta_f > 0.65$, then the reproduction number will always be below unity and this implies that the disease dies out as guaranteed by Theorem (5.3). Patient education within health care facilities is key to improving patient treatment adherence and should be focused more towards females for HSV-2.

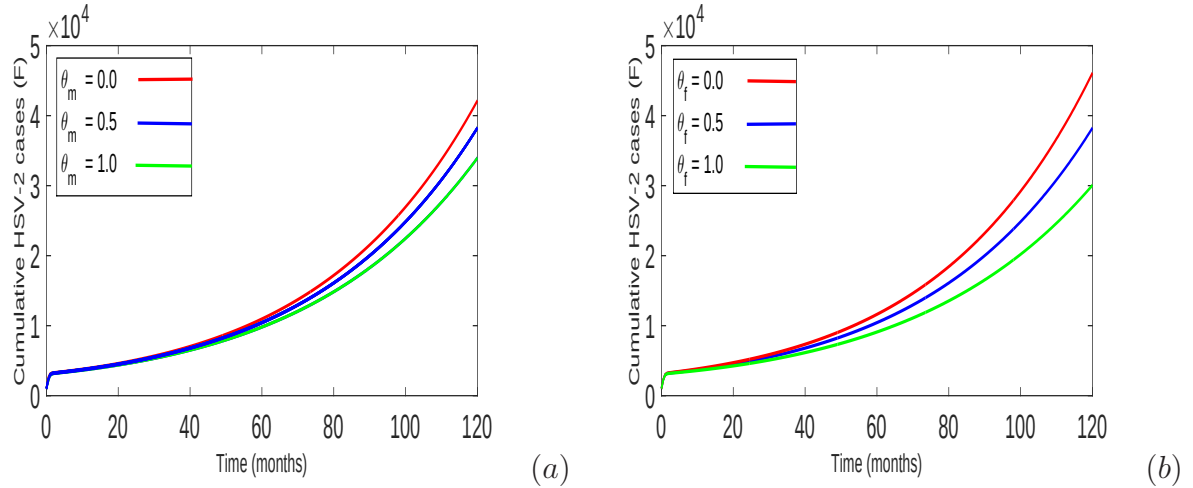


Figure 5.3: Figure 5.3(a) shows the effects of varying the proportion of males adherence (θ_m) and 5.3(b) shows the effects of varying the proportion of female adherence (θ_f) both on the female population, while all other parameters are at their baseline values.

Results in Figure 5.3(a) demonstrates that if there is low treatment adherence among females then, the cumulative HSV-2 cases increases significantly. However, an increase in adherence leads to reduction in HSV-2 prevalence especially if adherence level is 60% and above. Comparing Figure 5.3(a) and (b), we note that poor treatment adherence by the females results in more cumulative HSV-2 cases of the females compared to poor treatment adherence by the males. It is worth noting that, total adherence by the females results in cumulative HSV-2 cases of the females dropping to lower levels, as compared to the same levels of adherence by the males. Thus, female treatment adherence is more vital in reducing HSV-2 cases among females as compared to males treatment adherence.

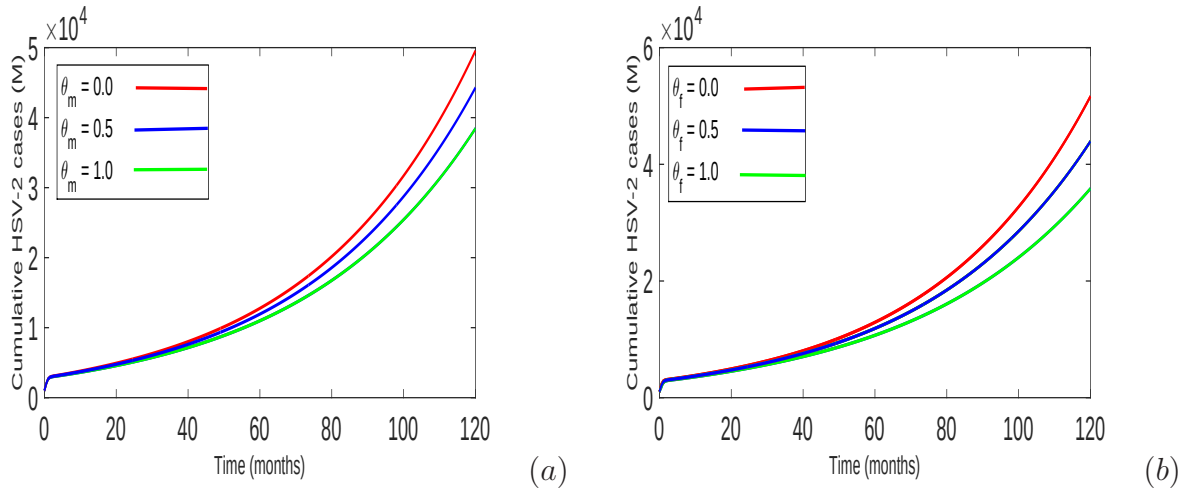


Figure 5.4: Figure 5.4(a) shows the effects of varying the proportion of males adherence (θ_m) and 5.4(b) shows the effects of varying the proportion of female adherence (θ_f) both on the female population, while all other parameters are at their baseline values.

Results in Figure 5.4(a) demonstrates that if there is low treatment adherence among males then, the cumulative HSV-2 cases increases significantly. However, an increase in adherence leads to reduction in HSV-2 prevalence especially if adherence level is 50% and above. Comparing Figure 5.4(a) and (b), we note that it is better to encourage female treatment adherence more than male treatment adherence in controlling HSV-2 prevalence among the males, although they are both crucial. In the absence of females treatment adherence, we observe far greater numbers of the cumulative HSV-2 cases for males in comparison to males absence of treatment adherence. Also, in the presence of females treatment adherence, we observe that HSV-2 infected males level, drops to lower levels in comparison to the presence of the same levels of male treatment adherence.

Overall, our simulation results show that if adherence level is above 50% among both females and males then HSV-2 prevalence will be significantly reduced. Furthermore, we noted that female's treatment adherence is more crucial in the reduction of HSV-2.

5.5. Concluding remarks

A mathematical model for the transmission of HSV-2 is developed and analysed. In this model, we seek to understand the effect of poor treatment adherence with respect to gender, between sexually active males and females. Analysis of the model has shown that the disease-free equilibrium is globally asymptotically stable when the corresponding reproduction number is less than unity. With the aid of centre manifold theory, the endemic equilibrium point is shown to be locally asymptotically stable when its corresponding reproduction number is less than unity. A sensitivity analysis of the reproduction number to the level of adherence is carried out showing that both, the proportion of treatment adherence for the males and females has the effect of reducing the transmission of HSV-2 in a community. Further, we noted that the proportion of females treatment adherence is more sensitive than the males proportion of treatment adherence, hence targeting more females and improving their adherence levels would be crucial in reducing the prevalence of HSV-2. Results from the numerical simulations illustrates that for us to keep the levels of HSV-2 cases as low as possible it is vital to keep the level of female adherence as high as possible compared to the one for males.

Chapter 6

Conclusions and future directions

6.1. Introduction

In this thesis, a number of mathematical models to investigate the effects of behavioural change on the transmission dynamics of HSV-2 were presented and analysed. The models looked at different types of behaviour by adolescents and also by the general population. Stability analysis was investigated on our developed mathematical models, and we also managed to determine their properties (positivity, boundedness, equilibria and reproduction numbers). Both analytic and numerical schemes were used to assess the effects of various intervention strategies. Optimal control theory was also applied, with the objective of assessing the impact of some time dependent controls.

6.2. Summary and concluding remarks

In Chapter 2, a mathematical model for the spread of HSV-2 within a community with substance abusing adolescents was developed and analysed. The impacts of condom use and educational campaigns were examined. The study suggested that

condom use is highly effective among adolescents, when we have more of them quitting than becoming substance abusers. Measures such as educational campaigns can be put in place to try and reduce adolescents from becoming substance abusers, by changing their behaviour. Applying the optimal control theory to the proposed model, with the controls representing condom use and educational campaigns. The objective was based on maximising the susceptible non-substance abusing adolescents, while minimising the susceptible substance abusing adolescents, the infectious non-substance abusing adolescents and the infectious substance abusing adolescents. We used Pontryagins maximum principle to characterise the optimal levels of the two controls and the resulting optimality system solved numerically. Overall, the application of the optimal control theory suggested that, more effort should be devoted to condom use as compared to educational campaigns.

A basic mathematical model for the spread of HSV-2 incorporating all the relevant biological detail and poor treatment adherence was proposed and analysed in Chapter 3. Equilibrium states of the model were determined and their stabilities investigated. The basic model was then extended to incorporate a time dependent intervention strategy. The aim of the control was tied on reducing the rate at which HSV-2 patients in treatment quit therapy before completion. Practically, this control can be implemented through monitoring and counselling all HSV-2 patients in treatment. The Pontryagins maximum principle was used to characterise the optimal level of the control, and the resulting optimality system was solved numerically. Overall, the study demonstrated that, though the time dependent control will be effective on controlling new HSV-2 cases it may not be sustainable for certain time intervals.

We formulated and qualitatively analysed a mathematical model to assess the impact of sexting and peer influence on the spread of HSV-2 among adolescents in Chapter 4. The threshold parameters of the model were determined and stabilities analysed. The impact of filtering and awareness campaigns were explored. Results from the study suggested that HSV-2 prevalence is high among adolescents

who are into sexting as compared to those who do not. Further, we applied the optimal control theory to the proposed model, with the controls representing filtering and awareness campaigns. The objective was based on minimising the susceptible sexting adolescents, infected non sexting adolescents and the infected sexting adolescents. The optimal control was characterised and numerically solved and the results suggested that more effort should be devoted to both controls, filtering and awareness campaigns.

In Chapter 5, we formulated a mathematical model to explore the association between gender and HSV-2 treatment adherence. The reproduction number and the disease free equilibrium were determined and stability analysed. The endemic equilibrium was determined and shown to be locally asymptotically stable using the Centre Manifold Theory approach. Sensitivity analysis of the reproduction number suggested that, females have more impact on reducing the reproduction as compared to the males, hence more focus should be given towards them. Analytic results also suggested that there is need for higher treatment adherence among the females as compared to the males in keeping the reproduction number as low as possible. Numerical results showed that poor treatment adherence by the females results in more HSV-2 cases than the same levels of poor treatment adherence by males.

6.3. Future research directions

The results of this thesis leave room for possible future research. We propose the following extensions.

- Having investigated various risky behaviours by the populations with regards to HSV-2, a possible extension would be to assess the effects of early sexual debut on the transmission dynamics of HSV-2. An age structured mathematical model can be formulated which would contain partial differential equations

and non-linear ordinary differential equations.

- It has been noted that HSV-2 is responsible for the spread of HIV. A further extension from this thesis would be to investigate the co-infection of HSV-2 and HIV, and it would be vital to couple this mathematical model with statistical models and real demographic data.
- In this thesis we looked at the effects of HSV-2 poor treatment adherence on the prevalence of HSV-2. A possible extension would be to look at the effects of HSV-2 treatment adherence on the prevalence of HIV, since prior studies have suggested that HSV-2 amplifies the spread of HIV.

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