Modelling HIV Transmission and Control

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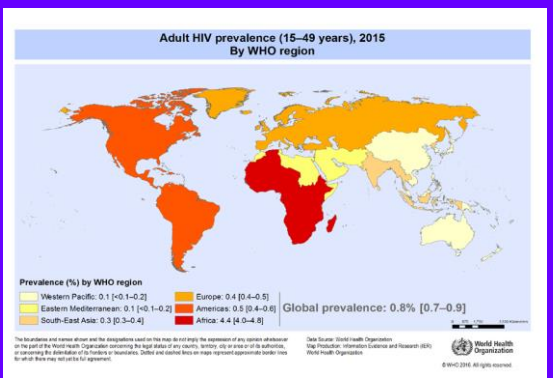
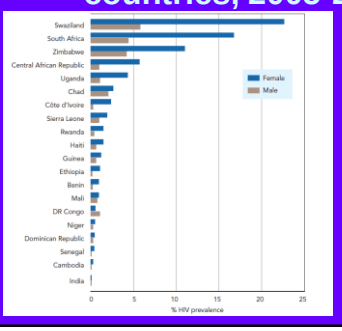
LSHTM

Aims

- Heterogeneity of HIV worldwide
- How HIV modelling studies have evolved with pandemic
- Simple HIV model can be used to estimate R_0 and to predict the shape and timing of the epidemic
- Simple models of HIV/STI co-infection can be used to predict the potential impact of cofactor STIs on the HIV epidemic
- How modelling has been used to explore changing role of STI treatment for HIV prevention
- A couple more examples: male circumcision and HAART



HIV prevalence (%) among 15-24 years old, by sex, selected countries, 2005-2007



UNAIDS/WHO, 2008

History of modelling HIV

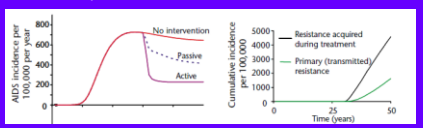
- Modelling of HIV has evolved with pandemic
- 1980s/ early 1990s models more theoretical
  - Identified importance of risk factors for HIV transmission
    - partner change rates,
    - heterogeneity in risk behaviour
    - mixing between risk groups
- Early models lacked data to validate and were presented as tools that could be used in the future
- Crucial in showing how little known => guide data collection
- Models in the early literature also presented with intention they could be used in future to estimate impact of control strategies
  - initially for HIV researchers, but later policy makers

History of modelling HIV

- Early modelling studies showed
  - impact of interventions on HIV incidence would be non-linear (as for most infectious disease control)
  - stage of the HIV epidemic would be important.
  - Impact on HIV incidence larger when near R_0=1
  - also showed intervention early and targeted at higher risk individuals would be most effective
- Focus on sub-Saharan Africa as even then apparent that this was most severely affected region.
- However as early as 1990, studies suggested that HIV was already so widespread, that large scale behaviour change in the general population and greatly increased resources, would be required to control the HIV epidemic

History of modelling HIV

- As understanding improved and more data available modelling used to
  - predict the impact of more realistic prevention strategies
  - Interpret the results on empirical trials
  - Warm of perverse outcomes



Garnett et al, Nature Med, 2002

- See more examples later…
- As most new infections occur in sub-Saharan Africa via heterosexual transmission, we will focus on this

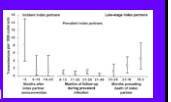
Simple model of HIV/AIDS

All STIs

- Mass action principle doesn't apply
- Importance of core groups and mixing patterns

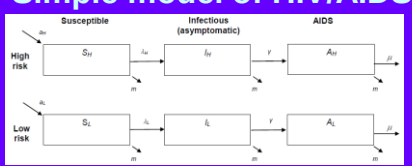
HIV

- Clinical syndrome called Acquired Immune Deficiency Syndrome (AIDS)
- AIDS caused by retrovirus human immunodeficiency virus
- Primarily targets CD4 cells
- Death without treatment
- No cure (as HSV-2)
- Less infectious that curable bacterial STIs
- But, longer duration
- Infectiousness varies by time since infection



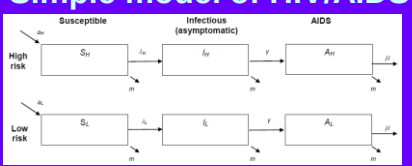
Wawer, 2005

Simple model of HIV/AIDS



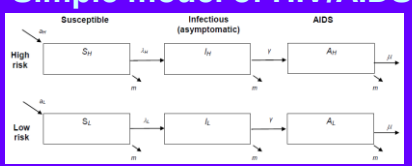
- Adapt our 2-group SIS model for gonorrhoea
  - Remove possibility of cure
  - Add AIDS compartment
  - Add AIDS-related mortality
  - As we are now modeling long term dynamics of a persistent infection that leads to death we need to model
    - rate of recruitment into sexually active age groups, 'a' otherwise we will run out of susceptibles, and
    - also the rate of non-AIDS mortality among sexually active individuals, m.

Simple model of HIV/AIDS



- Adapt our 2-group SIS model for gonorrhoea
  - Assume that the proportion of newly sexually active individuals recruited into each of the two activity groups (high and low) remains constant over time
  - Ignore all other population/bug heterogenities

Simple model of HIV/AIDS



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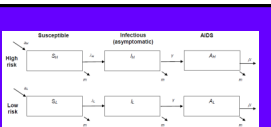


$$\frac{dS_H}{dt} = a_H N - \lambda_H S_H - mS_H$$

$$\frac{dI_H}{dt} = \lambda_H S_H - \gamma I_H - mI_H$$

$$\frac{dA_H}{dt} = \gamma I_H - \mu A_H - mA_H$$

$$a_H = a\,n_H(0)$$

$$\lambda_H = c_H \beta_p p$$

$$p = g_H i_H + g_L i_L$$

$$i_H = \frac{I_H}{U_H} \quad \text{and} \quad i_L = \frac{I_L}{U_L}$$

$$U_H = S_H + I_H, \text{ and } U_L = S_L + I_L$$

S_H is the number of individuals susceptible to HIV at time t in high-activity group
I_H is the number of individuals infectious with HIV at time t in high-activity group
A_H is the number of individuals with AIDS at time t in high-activity group
N is the total population size
λ_H is the force of HIV infection on the high-activity group at time t

a is the recruitment rate, per year
$n_H(0)$ is the proportion of individuals in the high-activity group at $t = 0$
a_H is the recruitment rate into the high-activity group, per year
m is the non-HIV mortality rate among sexually active individuals, per year
γ is progression rate to AIDS, per year
μ is the death rate due to AIDS, per year
c_H is the partner change rate per year in the high-activity group
β_p is the probability of HIV transmission probability per partnership
p is the probability a new partner is HIV infectious
g_H and g_L are the probability that a sexual partner will be a member of the high and low-activity group, respectively
$i_H(t)$ and $i_L(t)$ are the prevalences of infectious individuals in the high and low-activity groups, respectively
U_H and U_L are the numbers of sexually active individuals in the high and low-activity groups, respectively

(Equations for high activity group shown)

The R_0 of HIV infection

- Can calculate R_0 for HIV in this model using the same methods we derived for R_0 for gonorrhoea in a proportionately mixing population with two activity groups in the STI lecture
- Need to make an assumption about duration of infectious, infectiousness and contact rate

Duration of infection

- Need to adjust duration of infectiousness for non-AIDS mortality
- Assume average life expectancy (HIV uninfected) is 50 years & age at sexual debut is 15 years => average life exp. at debut is 35 years
- Assume median time HIV infection -> death is 10 years,
  = 9 years + 1 year assumed sexually inactivive AIDS year

=> HIV infected individuals will leave infectious stage at rate = sum of progression to AIDS (1/9) and non-AIDS mortality (1/35)

=> Duration of infectious stage = $\frac{1}{(1/9 + 1/35)}$ = 7.16 years

The R_0 of HIV infection

Infectiousness

- mean per-sex act HIV transmission probability over the entire period of HIV infection in low-risk HIV-discordant partnerships in rural Uganda (Wawer, Gray et al, 2005) was around 0.0016
- 30 acts (averaging over 1 off contacts…)
- per-partnership transmission probability will be around 0.05
  ie 1-(1-0.0016)^{30}

Partner change rate

- high and low-activity groups are 8 and 0.2 per year

$R_H = c_H \beta_p D$
$= 8 \times 0.05 \times 7.16$
$= 2.86$

$R_L = c_L \beta_p D$
$= 0.2 \times 0.05 \times 7.16$
$= 0.07$

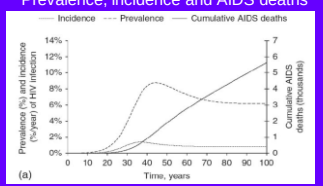
Assume 15% in high activity group and proportionate mixing =>

$R_0 = g_H R_H + g_L R_L$
$= 0.88 \times 2.86 + 0.12 \times 0.07$
$= 2.52$

Predictions for the HIV epidemic

HIV

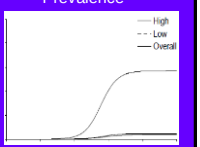
Prevalence, incidence and AIDS deaths



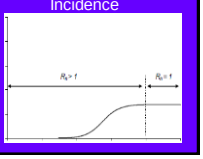
- Unlike curable STI prevalence and incidence rises and falls
- HIV preferentially kills higher risk => unless replaced at same rate, risk falls in pop.

Gonorrhoea

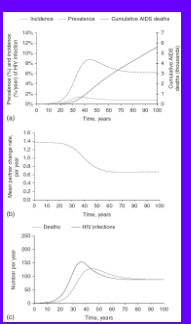
Prevalence



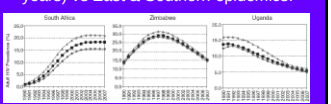
Incidence



Predictions for the HIV epidemic



- Risk falls in pop even in absence of IEC
- If nothing else changes, such as the impact of intervention efforts, HIV prevalence will level-off when the annual number of HIV deaths and new HIV infections come into equilibrium
- Note rise to peak relatively slow (45 years) vs East & Southern epidemics:



UNAIDS, 2008

Simple models of HIV/STI co-infection

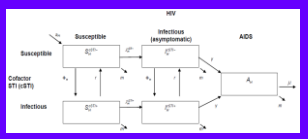
- Use simple model of HIV/STI co-infection to explore possible impact of cofactor STIs (cSTIs) on increasing rate of spread of sexually transmitted HIV
- Large body of laboratory, clinical and epidemiological studies supporting hypothesis that cSTIs facilitate the spread of HIV
- HIV-uninfected individual
  - increase susceptibility to HIV infection due to breaks in the skin caused by ulcers, or increased presence of T lymphocytes that are targets for HIV
- HIV-infected individual
  - increase transmission of HIV as STI frequently cause increased shedding of HIV
- Magnitude of a STI cofactor is defined as the multiple by which the probability of HIV transmission will be increased in the presence of the classical STI
- But, translating RRs for STIs on HIV transmission measured in epi. studies into per-partnership/act transmission probabilities, is difficult

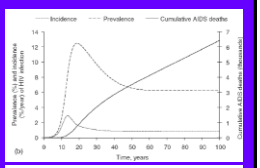
Reviews: Fleming and Wasserheit, 1999; Laga, Nzila et al, 1991; Rottingen, Cameron et al, 2001; Wasserheit, 1992

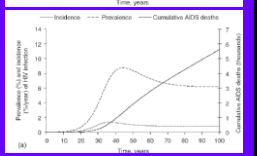
STI cofactors

- *The per-act* cofactor for genital ulcer disease (GUD) have been estimated to be in the range of 50-300 for female-to-male transmission and 10-50 for male-to-female transmission for ulcerative STI (Hayes, Schulz et al. 1995)
- If we assume the per-act cofactor is 10 and that GUD is only present in 25% of the acts within partnerships that reported ulcers then the *per-partnership* cofactor is ~3.1

Predictions from the HIV/STI co-infection model



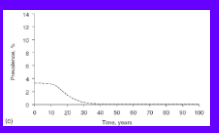




- Addition of a cofactor STI greatly increases the rate of spread of HIV
- Peak at ~20y, rather than 45y
- Doubling time of the HIV epidemic from 2.9 years to 1.1 years.

Predictions from the HIV/STI co-infection model

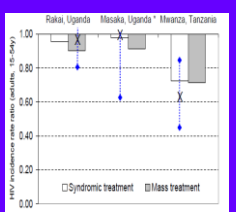
- STI/HIV interaction complex
- Predicted STI prevalence fell



- Because HIV will tend to preferentially kill the more sexually active members of the population, and these individuals are also more likely to be infected with other STIs because of the common risk-behaviour
- Uganda, a historically high HIV prevalence population, empirical analysis suggests cSTI rates have fallen during the HIV epidemic.
- But difficult to disentangle the effects of
  - HIV-attributable mortality,
  - reduction in social disruption caused by the civil war,
  - volitional behaviour change due to safer-sex campaigns,
  - improvements in STI treatment services,
- on STI trends

The changing role of STI treatment for HIV prevention

- Numerous modelling studies sparked off by
  - Hypothesis – STI control may control HIV
  - Data:
    - First HIV RCT to show impact (syndromic curable STI treatment in Tanzania) (Grosskurth, 1995)
    - Failure of 2nd (mass curable STI treatment in Uganda) RCT to show impact (Wawer, 1999)
  - A puzzle …. perfect for modelling!

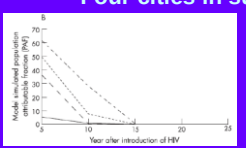


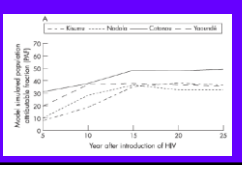
- Modelling suggested impact of either higher in Tanzania
- And population differences in sexual behaviour, curable STI rates, and HIV epidemic stage could explain most of the contrast in HIV impact observed between the three trials

Adapted from (White, Orroth et al, 2004).

Proportion of adult HIV incidence due to HSV-2 and chancroid by time since the introduction of HIV

Four cities in sub-Saharan Africa



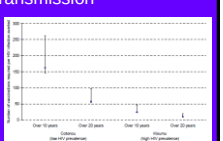


- Proportion of HIV incidence due to curable STIs was likely to fall as the HIV epidemic matures, because
- AIDS mortality and behaviour change (if it had occurred) reduced curable STI rates
- As HIV prevalence increases, a larger proportion of HIV transmission occurs outside higher-risk groups, in groups with lower rates of curable STIs
- Proportion due to HSV2 may rise?

(Cohen, Science 2005; Freeman, Orroth et al, 2007)

HSV2 control

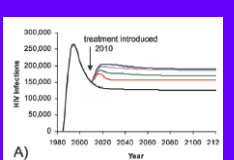
- If HSV2 PAF for HIVi increases => contol HSV2?
- RCTs disappointing
- and all 3 RCTs of herpes suppressive therapy failed to show an impact on the HIV transmission
- Because?
  - impact may be because any STI cofactor effect is small,
  - there was insufficient herpes suppression due to inadequate drug dosage or adherence
  - mechanism of action of acyclovir does not adequately control the effect of HSV-2 on HIV transmission
- Hopes for a vaccine?
  Initial modelling results showing it may have a substantial impact on HIV inci if developed

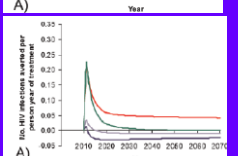


(Freeman 2009)

Models of ART

- Also used to explore impact of ART
  - Early work showed that without a reduction in infectiousness and in risk behaviour, ART would tend to increase HIV incidence
  - But ART does reduce infectiousness and transmission
    - HPTN 052 RCT,1750 couples
    - 96% reduction in HIV-1 transmission
  - So more recent work on critical importance of behavioural disinhibition and integration of treatment and prevention

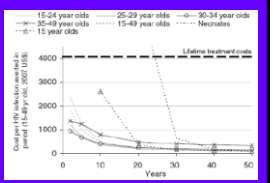




Baggaley, PloS, 2006

Models of the male circumcision

- MC likely to have been important in explaining the heterogeneous spread of HIV in sub-Saharan Africa
- 3 individual level RCTs showing impact on 50-60% HIV incidence over ~ 2 years
- Many modelling studies
- Useful in predicting population level impact from individual level RCTs
- Could prevent 6 million infections over 20 years in sub-Saharan Africa if (!) scaled up
- Predictions of impact of scale up very consistent (Expert group, Plos Med, 2009)
- Age prioritisation does determine when you will get population level impact…



White, AIDs, 2009

Summary

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- Simple HIV model can be used to estimate R_0 and to predict the shape and timing of the epidemic
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- How modelling has been used to explore changing role of STI treatment for HIV prevention
- A couple more examples: male circumcision and HAART