ASSESSING HIV/AIDS INTERVENTION STRATEGIES USING AN INTEGRATIVE MACRO-MICRO LEVEL COMPUTATIONAL EPIDEMIOLOGIC MODELING APPROACH

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Introduction: Epidemiologic research involves the study of a complex set of host, environmental and causative agent factors as they interact to impact health and diseases in any population. The most advanced of these efforts have focused on micro (cellular) or macro (human) population level studies but lacked the integrative framework as presented in this article. Modeling the cumulative impact of HIV/AIDS at the cellular, molecular, and individual behaviors at the population-level can be complex. The main objective of our research is to develop a macro-micro level computational epidemiologic model that integrates the dynamic interplay of HIV/AIDS at the cellular and molecular level (micro-epidemiologic modeling), and the dynamic interplay of multifactorial determinants: biomedical, behavioral, and socioeconomic factors at the human population level (macro-epidemiologic modeling).

Methods: The computational epidemiologic model was constructed using systems dynamics modeling methodology. The dynamics of the relationships was described by means of ordinary/partial differential equations. All state equations in the model were approximated using the Runge-Kutta 4th order numerical approximation method.

Results: Computational tools and mathematical approaches that integrate models from micro to macro levels in a seamless fashion have been developed to study the population-level effects of various intervention strategies on HIV/AIDS. The critical variables that facilitate transmission of HIV and intracellular interactions and molecular kinetics were examined to assess different interventions strategies. Such multilevel models are essential if we are to develop quantitative, predictive models of complex biological systems such as HIV/AIDS. (*Ethn Dis*. 2010;20[Suppl 1]:S1-207–S1-210)

Key Words: Computational Micro-Epidemiologic Modeling, Computational Macro-Epidemiologic Modeling, HIV/AIDS

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INTRODUCTION

This article focuses on research in computational epidemiology as applied to the study of HIV/AIDS, a health disparity disease of global concern. Even though Blacks (including African Americans) account for about 13% of the US population, they account for about half (49%) of the people who get infected by HIV annually.[1] Despite extraordinary improvements in HIV treatment, AIDS remains the leading cause of death among Black women aged 25–34 years and the second leading cause of death in Black men aged 35–44 years.[1]

Computational models and simulations are becoming central research tools in epidemiology, biology, and other fields. The most advanced of these efforts have focused on micro (cellular) or macro (human) population levels studies but lacked the integrative framework as presented in this article.[2–6] The main objective of our research is to develop a macro-micro level computational epidemiologic model that integrates the dynamic interplay of HIV/AIDS at the cellular and molecular level (micro-epidemiologic modeling), and the dynamic interplay of multifactorial determinants: biomedical, behavioral, and socioeconomic factors at the human population level (macro-epidemiologic modeling).

MATERIALS AND METHODS

The working hypothesis is that an epidemiologic model that incorporates cellular/molecular (micro level) and human population (macro level) epidemiologic dynamics can be developed for examining preventive and therapeutic strategies of HIV/AIDS in African American populations. The epidemiologic modeling steps included: a) applying the epidemiologic problem oriented approach (EPOA) to develop a conceptual systems analysis knowledgebase of the macro (human population) and micro-level (cellular) dynamics; b) developing the mathematical and computational representation of step a); and c) validating the model and using the validated model to evaluate effective anti-retroviral, education and other intervention strategies.

Epidemiologic Data Collection

Epidemiologic data was collected from five primary sources: a) CDC - Division of HIV/AIDS - Surveillance and Epidemiology databases; b) State of Alabama Health Department; c) Macon County, Alabama Health Department; d) information extracted from existing knowledge about HIV/AIDS; and e) questionnaire information gathered to capture socioeconomic and behavioral risk factors of HIV/AIDS.

Computational Epidemiologic Modeling

The HIV/AIDS model relied upon mass-action theory and state transition modeling. The dynamics of the relationships between state and rate variables were described by means of differential or difference equations. All state equations in the model were

approximated using the Runge-Kutta 4th order numerical approximation method. The major state variables in the macro-model were as described previously.[2] The micro-level modeling included: uninfected CD4+ lymphocytes, infected CD4+ cells, and replicated virions.[4,6] In each of these substates, molecular level transitions occurred consisting of the stages of: binding (between virus and CD4+ receptors), uncoating, reverse transcription, integration, transcription, translation, assembly and budding. The molecular and cellular model (micro-epidemiologic model) was nested within and integrated into the macro-epidemiologic model that represented the multifactorial epidemiology of HIV/AIDS. Interventions using various drug therapy scenarios of monotherapy vs combined drug therapies were studied.

RESULTS

In our research we have extended the classical epidemiologic triad into two dimensions by adding macro (M) and micro (m) resulting in three pillars: host (*M*,*m*) = Host (*human*, *CD4+ lymphocytes*); agent (*M*,*m*) = agent (*HIV*, *HIV viral population*); and environment (*M*, *m*) =environment (blood(f), cellular and intracellular/ molecular ecosystem).

A Macro-epidemiologic Model of HIV Transmission

The dynamic epidemiologic model developed in the macro level of the transmission of HIV and its progression to AIDS relies on a set of multiple determinants that affect the epidemiology of HIV/AIDS in populations. At the macro level, the population is divided into three sub-populations based on their health status. These include those who are susceptible (*S*), infected with HIV (*I*), advanced state of HIV infection or AIDS)(*A*). The transitions between the states of health are regulated by the respective rates such as birth rate, infection rate, progression rate to AIDS and death rate. The macro model considers five ethnic populations: White (not Hispanic), African Americans, Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native. Within each ethnic group, each individual has demographic characteristics (eg, age, sex) and HIV/AIDS risk behaviors: male to male sexual contact (MSM); injection drug use (IDU); male to male sexual contact and injection drug use (MSM/IDU); high risk heterosexual contact; and others (include hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or identified). The HIV/AIDS infection rate in a given susceptible population directly depends on the proportion of the risk behaviors listed above. Manipulation of one or several of these variables changes the behavior of the system and results in an increase or decrease of the incidence of HIV/AIDS; thus allowing critical evaluation of alternative disease control strategies.

Micro-epidemiologic Modeling

Cellular Level Modeling (CD4+ lymphocyte/HIV viral population dynamics)

The host populations are CD4+ lymphocytes, the agent is HIV viral population and the environment is the cellular and intracellular/molecular ecosystem. The new state that represents infected CD4+ lymphocytes, referred to as HIV infected CD4+ cell subpopulation, is further subdivided into four substates: productively infected, latently infected, defectively infected, and chronically infected.

Molecular Level Modeling

The CD4+ lymphocyte cell is assumed infected as soon as the virion enters the host cell.[7] Ordinary differential equations were used to mathematically represent the viral kinetics as they move from reverse transcription through progeny formation and maturation.

The Mathematical Model

The framework for representing the integrated components of the HIV/AIDS epidemiologic model including macro level population dynamics as well as micro level population cellular/molecular level biological dynamics is shown in figure 1.

The dynamics of the model is described using a system of partial differential equations.

$$\frac{\partial \overline{S}(S_{ijk}(a,\,t,\,\overline{u}))}{\partial t}+\frac{\partial \overline{S}(S_{ijk}(a,\,t,\,\overline{u}))}{\partial a}=\{\sigma_{ijk}(\overline{u}(t),a)[1-\gamma_{ijk}(\overline{u}(t),a)]-1\}\ \overline{S}(S_{ijk}(a,\,t,\,\overline{u})) \quad (1)$$

where S_{ijk} denotes the number of susceptible individuals of drug use status k, sex related status j, ethnic group i, age a at time t; $\sigma_{ijk}(\overline{u}(t),a)$ is the age-group specific survival rate of individuals of drug use status k, sex related status j in ethnic group i; $\gamma_{ijk}(\overline{u}(t),a)$ is the HIV infection rate of individuals of age a at time t, drug use status k, sex related status j in ethnic group i, which depends on time of infection and the number of CD4+ count and the viral load at time t and cellular level dynamics of CD4+, $(\overline{u}(t),\tau)$, with $\overline{u}=(C_i(t,\tau),V_i(t,\tau))$ (C_i's are infected cells and V_i is the viral population), and age a of the individual.

$$\frac{\partial C_i(t,a,[dNTP])}{\partial t}+\frac{\partial C_i(t,a,[dNTP])}{\partial a}=-d_iC_i(t,a,[dNTP])\quad with\ C_i(t,0,[dNTP])=\beta C_i(t,[dNTP])V(t,[RNA_{cor}])\ for\ i\in\{L,P,C,D\},\ and\ \frac{\partial V(t,[RNA_{cor}])}{\partial t}=\sum_{i\in\{L,P,C\}}\int_{a_{iP}}^{a_{\max}}\gamma_i(a)C_i(t,a,[dNTP])\,da-uV(t,[RNA_{cor}]) \quad (2)$$

where for $i=D$, defectively infected CD4+ cells, for $i=L$, latently infected CD4+ cells, for $i=P$, productively

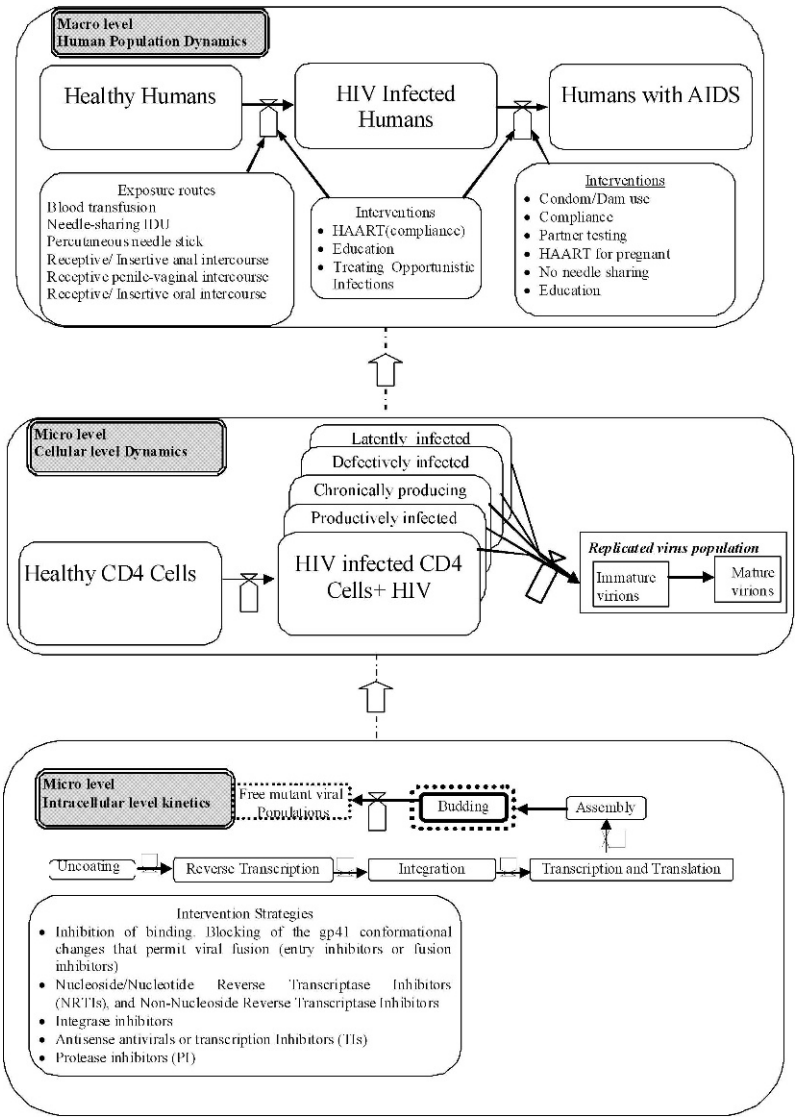

Fig 1. An epidemiologic systems model of macro-micro (human-cellular) population dynamics

infected CD4+ cells, and for $i=C$, chronically infected CD4+ cells and a is the age of the CD4 cell. A selected equation representing the molecular kinetic level interactions is shown below.

$$\frac{d[RNA_{cor}]}{dt} = -\frac{V_m[RNA_{cor}]}{K_{m(RNA_{cor})}+[RNA_{cor}]}\cdot \frac{[dNTP]}{K_{m(dNTP)}+[dNTP]} - (k_{RNA_{cor}}+\varphi_{RT})[RNA_{cor}] \quad (3)$$

where $[RNA_{cor}]$ is the concentration of genomic RNA present in the viral core and [dNTP] is the concentration of the dNTP pool of the host cell. $K_{m(RNA_{cor})}$ *and* $K_{m(dNTP)}$ are the Michaelis constants for reverse transcriptase with the substrates $RNA_{cor} = 2*[V_E]$ and the dNTP (Deoxyribonucleoside triphosphate) pool, respectively. $k_{RNA_{cor}}$ is the degradation rate constant of the genomic RNA and φ_{RT} is the efficacy of the drug for reverse transcription inhibitor.

Other equations representing the various other states were developed in a similar fashion. The equations that describe the dynamics in HIV infected populations of drug use status k, ethnic group i, age a at time t are defined as follows

$$\frac{\partial \overline{I}(I_{ijk}(a,\,t,\,\overline{u}))}{\partial t}+\frac{\partial \overline{I}(I_{ijk}(a,\,t,\,\overline{u}))}{\partial a}+\frac{\partial \overline{I}(I_{ijk}(a,\,t,\,\overline{u}))}{\partial \overline{u}}=\{\sigma_{ijk}(\overline{u}(t),a) [1-tr(\overline{u})]-1\}I_{ijk}(a,\,t,\,\overline{u}) \quad (4)$$

where $tr\ (\overline{u}(t,\tau)))$ is the probability that an individual infected by HIV at time t- becomes an AIDS patient at time t, which is assumed to be the same for all ethnic groups. A similar equation can be given for the dynamics of AIDS patients populations.

$$\frac{\partial \overline{A}(A_{ijk}(a,\,t,\,\overline{u}))}{\partial t}+\frac{\partial \overline{A}(A_{ijk}(a,\,t,\,\overline{u}))}{\partial a}+\frac{\partial \overline{A}(A_{ijk}(a,\,t,\,\overline{u}))}{\partial \overline{u}}=\{\mu(\overline{u}(t),a)-1] A_{ijk}(a,\,t,\,\overline{u}) \quad (5)$$

The role of individual characteristics from macro (age, sex and race), socio-economic status (level of education, level of income and employment status), and psychosocial factors to the cellular level CD4+ count, HIV viral load, and the kinetics inside the cell are also incorporated in this model.

We let $F_{ijk}(t)$ denote the events that an individual of drug use status k, sex related status j, in ethnic group i is infected by HIV during *(t, t+dt)* due to sexual contact. An individual may have sexual contacts with partners from different ethnic groups. The probability of HIV transmission due to sexual contacts is formulated in terms of the number of partners, number of sexual contacts with each partner, the probability that a partner is infected, the HIV viral load of the infected and the probability that one contact with an infected partner will result in infection. In this study, since we consider six ethnic groups, each consisting of five risk behaviors related sub groups, the HIV prevalence differs from group to

group. The probability that an individual of drug use status k, risk behaviors related status j in ethnic group i is infected by HIV at time t due to sexual contacts is given by:

$$P[F_{ijk}(a, t, \overline{u})] = 1 - \prod_{e=1}^{3} \{1 - q_e(t)\} \quad (6)$$

where:

- $q_e(t) = 1 - \{1 - p_e(t)[1 - (1 - r)^{m_{ijk,e}}]\}^{n_{ijk,e}}$ is the probability that an individual of drug use status k, risk behaviors related status j in ethnic group i is infected by HIV during $(t, t+dt)$ due to sexual contacts with partners from ethnic group e,
- r is the probability of HIV transmission associated with a single sexual contact,
- $n_{ijk,e}$ is the number of sexual partners from ethnic group e,
- $m_{ijk,e}$ is the number of sexual contacts with a partner from ethnic group e, and
- $p_e(t)$ is the probability that a partner from ethnic group e is infected at time t.

Experimentation Using the Models

Once the development and integration of the computer modeling methodologies were completed, several simulations were conducted with varying initial conditions to test the validity of the model. Based on these results, enhancements and modifications were made until the model exhibited outputs which were biologically and mathematically reasonable. Sensitivity analysis was performed to examine model stability.

The computational model developed three integrated stochastic and dynamic sub-models: one to represent AIDS at the human level; the second to represent CD4+ population dynamics at the cellular level; and the third to represent the kinetics at the intracellular viral kinetics level. Computational models were developed to examine the epidemiology and pharmacoepidemiology of HIV/AIDS. Using the integrated model as the experimental medium, computer simulations were conducted to examine and answer specific scientific questions. The results of computational experiments showed that the prevalence of infection will be decreased if: a) the number of sexual partners per person is decreased; b) injection drug use is decreased; c) condom use is increased; d) the number of sexual contacts per partner is decreased; and e) if injection drug needles are not shared.

DISCUSSION

These epidemiologic models, if complemented by multimedia and scientific visualization resources, can now be used as tools to visually show how targeted prevention and therapeutic strategies in high-risk populations such as African Americans can be effective. These could also serve as powerful tools to effectively communicate and promote effective disease control and prevention practices and reduction of risk factors. Furthermore, the results from this study may be extrapolated to assist in public health policy planning, decision making, and in education to prevent and/or reduce the HIV/AIDS pandemic. In addition, the integration of the macro and micro modeling will help to see the effect of mitigation measures from individual level to the population level and ultimately to the national and international levels.

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