

Predictions of Future HIV Infection by Subtype and Circulating Recombinant Form.

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ABSTRACT

There has been little research conducted on the global prevalence and spread of HIV subtypes. The future likelihood of infection by the various subtypes holds great importance as different subtypes are known to be more infectious than others. In turn, as some regions seem to control the rate of growth of HIV infection, the subtypes in these regions will account for a large proportion of future infections. Specific subtypes are associated with different ways of contracting HIV including heterosexual sex, homosexual sex, and intravenous drug use. The rate of change of the infections by various subtypes between the years of 2000 and 2002 was used to predict HIV infections by subtype in 2004 and 2010 using simple exponential growth models. A linear growth model was used as a comparison to the exponential models of various software programs. These models predict cases of future HIV infection globally, by region, by subtype. The output from our models will be compared to approximations of HIV infection made by individuals and groups in academia and in government organizations. Differences in the proportion of infections by subtype can be used to determine what steps must be taken in the future to control the spread of HIV infection according to subtype.

1. INTRODUCTION

Human immunodeficiency virus or HIV was first introduced into humans in the 1950's by infection by a rhesus monkey from Africa. In 2002, the cumulative number of HIV infections worldwide had reached 42 million [22]. Twenty three million people have died as a result of the onset of acquired immunodeficiency syndrome, better known as AIDS, which is caused by the HIV virus. This tells us that AIDS is one of the worst diseases in existence. It is unlikely that a HIV vaccine will be created in the near future to cure the AIDS epidemic. The current task that scientists are working on is to prolong the lives of those infected. Currently researchers are working on better ways to treat patients with the HIV virus including the use of AZT; an anti HIV drug; and the triple cocktail approach which utilizes three different drugs to drop HIV levels in the body. As anti-HIV drugs cannot cure AIDS and HIV interventions cannot prevent all HIV infections, we must focus our attention on how to control the spread of the HIV virus in the future.

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There are two types of HIV: HIV-1 and HIV-2. HIV-1 is the cause of most of the global HIV infections. HIV-2 is slower to progress to infection, causes less infection, and has a mortality rate per infection equal to one third of that of HIV-1. This type is not studied as actively as HIV-1. It is mainly found in West Africa, and cannot always be detected by tests for HIV-1, thus there is a high genetic variability between the two strains. HIV strains can be broken down into various subtypes which originated in different geographical regions around the globe. Each subtype is unique in its reaction to medication, its probability of transmission, and its transmission rate. Understanding the differences between HIV subtypes is essential to understanding HIV infection.

There are several subtypes of HIV-1, and some of the subtypes themselves are recombinants of other subtypes. The current known subtypes include types A, B, C, D E, F, G, H, I/J, NT, K, N, O, AB, AG, and AE [16]. There are also other subtypes which have not been classified as of yet and can only be referred to as 'other'. HIV-2 subtypes include types A, B, C, D, and E named such due to their similarity to HIV-1 subtypes [16]. Since the HIV-2 virus only infects a fraction of the people that HIV-1 infects, it does not have any recombinants, and thus is limited in its number of subtypes. The World Health Organization in collaboration with the UNAIDS Joint United Nations program on HIV/AIDS does not possess extensive data on HIV subtypes. Yet this information is vital to the control of future HIV infections and outbreaks as there are subtypes that infect and mutate at a greater rate than others.

In the past, subtype C has caused the majority of infections in Sub-Saharan Africa. In 2002, subtype A infections represented the majority of infections in this region [10]. Although the main subtype causing infections in Sub-Saharan Africa has changed, the region still holds the majority of global total HIV infections. According to data from the WHO-UNAIDS report in 2000 and 2002, the total cases of HIV in Sub-Saharan Africa alone account for nearly 70% of the global total HIV cases [20]. Specific attention will be given to Sub-Saharan Africa for the purpose that it accounts for the majority of total HIV infections worldwide. Sexual intercourse is the most common form of HIV transmission in Sub-Saharan Africa, and the sexual behavior of this group depends on economic circumstances, culture, and social circumstances [20]. HIV interventions including sexual education must take place to ensure a decrease in prevalence in this region.

Change in HIV Infections

The figures of HIV infection given by WHO and UNAIDS for the years 2000 and 2002 are overwhelming. Sub-Saharan Africa had an approximate total of 25 million HIV infections in 2000 and 29 million infections in 2002. Globally, the world housed a total of 36 million HIV infections in 2000 and 42 million in 2002 [20]. There lies significant importance in finding the link between the subtype infections of Sub-Saharan Africa in comparison to the rest of the world (figure 1). Sub Saharan Africa experiences nearly the same growth rate as all of the HIV infections in the world combined; being approximately a 16 percent increase over 2 years. As a result of this similar growth trend, and because Sub-Saharan Africa accounts for nearly 70 percent of all infections worldwide, the subtypes causing HIV infections in Sub-Saharan Africa will be the most common subtypes of HIV that cause HIV infection throughout the globe in the future.

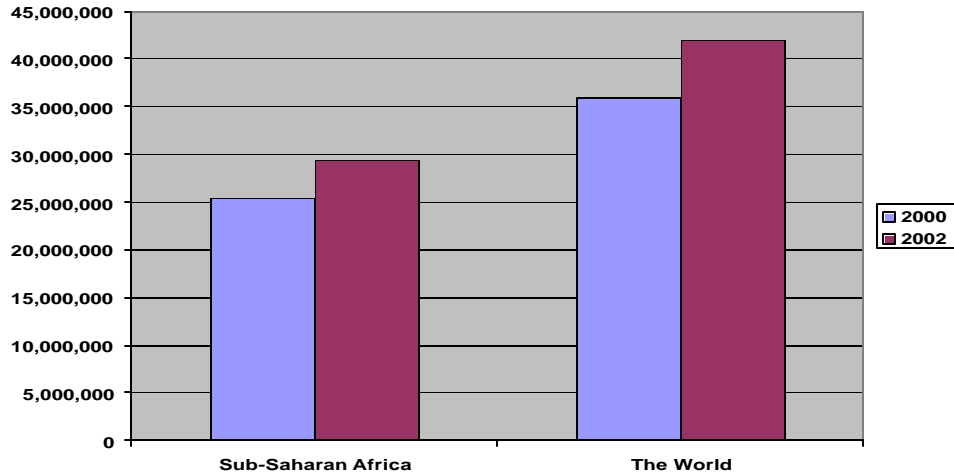


Figure 1. Change in total HIV infections in Sub-Saharan Africa and worldwide between the years 2000 and 2002.

2. HIV-1 SUBTYPE DISTINCTION AND TRANSMISSION

Phylogenetic analysis of HIV-1 strains has revealed that they could be divided into groups including M, N and O due to their genetic diversity. Group M infections cause the large majority of infections, greater than 95 percent, across the globe [16]. Group M is so genetically diverse that it is broken into subtypes including A, B, C, D, E, F, G, H, I, and J. There are also recombinant forms including the combinations of subtypes. These are known as circulating recombinant forms. Some of these recombinants include AE, AG, AB, DF, BC, CD, AEGJ, and others [16].

The different subtypes are generally geographically distinct. North and South America consist of HIV infections by subtype B, Australia with type B, Asia and Europe with types A, B, E and C, and Africa houses A, C, and E subtypes as well as all other subtypes and most recombinant forms [16].

Subtypes are not only geographically distinct but also associated with specific modes of HIV infection transmission. Subtype B is associated with homosexual intercourse and intravenous drug use while subtypes A, E, and C are associated with heterosexual transmission [7]. This finding is significant since subtype A has increased from 28 percent to nearly 35 percent of all cases. This means that AIDS is being transmitted more and more through heterosexual contact. As a result, we have both subtype A and subtype C to consider when planning HIV interventions for the majority of HIV infections.

There has been limited research on the rate of transmission of various subtypes. According to one study, subtype E was found to be more easily transmissible than subtype B [7]. Another study shows that subtype A is more easily transmissible than subtype D and C [24]. Combining this data, subtype A is most transmissible and B appears to be least transmissible with subtypes C, E, D, and others somewhere in between. Subtype A is the more easily transmissible subtype. This leads us to believe

that subtype A infections will continue to increase at a high rate in the future and possibly cause the majority of HIV infections within a ten years.

3. HIV SUBTYPE DATA

All the data for comparing numbers of total worldwide HIV infection was obtained from the WHO-UNAIDS 2000 and 2002 AIDS reports [20]. The subtype data for the year 2000 was obtained from another research study, which collected subtype data using a questionnaire asking for results from molecular epidemiology studies [15]. The questionnaire was given to 15 specialized research laboratories collaborating within the WHO-UNAIDS Network for HIV Isolation and Characterization. As the subtype data were given in proportions of HIV infections, we converted the proportions to populations using HIV infection data from the WHO-UNAIDS report. We did this in order to predict the number of people infected with each subtype of HIV at that time and to compare this data with other future approximations.

The subtype data for the year 2002 was more difficult to calculate. The Los Alamos National Laboratory (LANL) sequence database contained sample sizes and infection by subtype for most countries with significant HIV infection worldwide [10]. The database was created using data from all available published research articles on HIV subtypes. From the LANL sequence database, we took the sample size and infection per each sample for each country, and estimated the HIV prevalence of various subtypes in 13 regions.

There was some necessary manipulation to combine the data from these 2 subsequent years as data on recombinant forms was not included in the publication of subtypes in 2000. In order to deal with this problem and to account for the fact that the 2002 data included possible infection by recombinant forms, we allowed subtypes recorded in 2002 including K, N, O, AB, and AG, to combine into a NT/Other classification. We also placed the infections by recombinant form AE into the infections by subtype E for the year 2002. This was done because all subtype E infections appear to be recombinants of both subtype A and E [16]. Also, subtype E was included in the 2000 paper on HIV subtypes, for which we accommodated. The sample sizes for the 2000 and 2002 data on HIV subtypes can be viewed to show the accuracy of each years subtype approximations (table 1). Over twice the amount of samples in 2000 were used in 2002. The majority of these new samples in 2002 occurred in North America and Western Europe which began considering and recording to a great extent which subtype caused the HIV infection.

4. PAST CHANGES AND FLUCTUATIONS IN HIV SUBTYPES

Significant changes are viewed when considering the proportion of HIV infections caused by each subtype between the years 2000 and 2002 (figure 2). In comparing the proportion of total HIV infections by subtype, we can see which subtype is responsible for a large proportion of the total HIV cases, and the important changes among subtype proportions including the decrease and increase in the proportion of subtypes causing a majority of HIV infections.

<u>Region</u>	<u>Year 2000</u>	<u>Year 2002</u>
Southern Africa	744	430
West Africa	1,921	293
East Africa	1,969	498
Ethiopia	40	164
Central Africa	536	900
North Africa/Middle East	25	114
Western Europe	967	5,956
Eastern Europe and Central Asia	536	514
East Asia and Pacific	84	902
Southeast Asia	640	612
South Asia(excluding India)	52	142
Latin America and Caribbean	933	800
North America	57	8,668
Worldwide	8,504	19,993

Table 1. Sample sizes for HIV subtypes in the various regions around the world for the years 2000 and 2002.

The two leading subtypes which caused HIV infection in the past are subtypes C and A. It is significant to note that that subtype A HIV infections have increased by 7% as a proportion of total infections, and subtype C HIV infections have decreased by 15 % as a proportion of the total infections over a two year period. This tells us that the growing problem of HIV will most likely have to do with subtype A infections, and be less dependent on infections caused by subtype C, which has caused the majority of HIV infections in the past. Unfortunately, subtype A is known to be the easiest to transmit among the subtypes, and it is mainly transmitted through heterosexual intercourse. Subtype C also is transmitted in most cases through heterosexual intercourse but with a lower transmission rate than subtype A. HIV infections caused by subtype A are expected to multiply significantly in the near future.

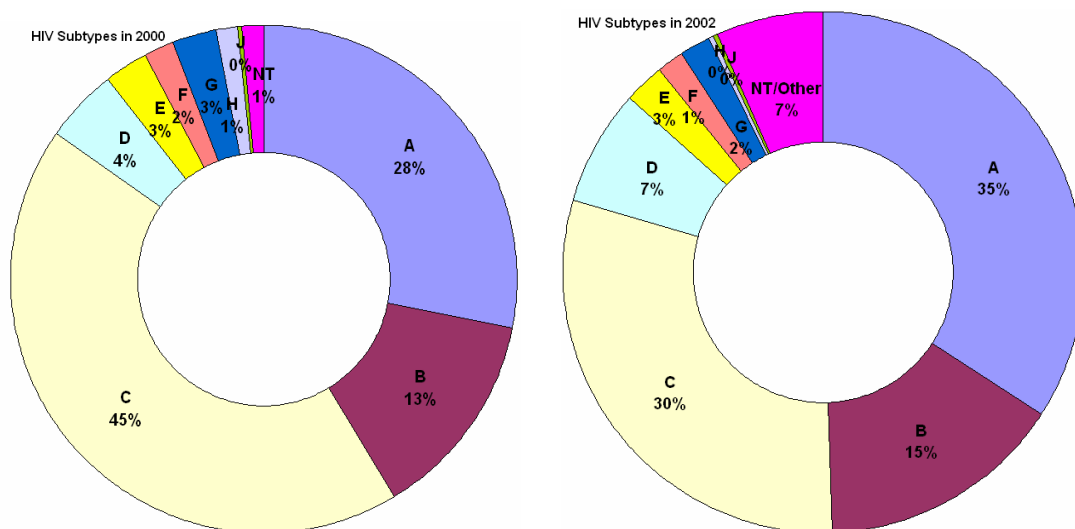


Figure 2. A comparison of the proportion of HIV infection by subtypes in 2000 (left) and 2002 (right).

The breakdown of HIV subtypes by region is also useful in determining the future likelihood of infections. The provided figures illustrate the breakdown of HIV subtypes both globally (figure 3) and also in Sub-Saharan Africa (figure 4). The graphs show the change in total HIV infections between 2000 and 2002 by subtype. We can see that what was once the dominant subtype, subtype C, has been overtaken by subtype A in total global infections and also in infections in the region of Sub-Saharan Africa. Subtype A is increasing at a greater rate than subtype B. This is a disturbing fact as subtype A is associated with heterosexual intercourse, and currently accounts for nearly 50% of all cases of HIV infection in Sub-Saharan Africa. As subtype B is associated with homosexual intercourse, HIV infections associated with homosexual intercourse fall far behind those transmitted through heterosexual sex.

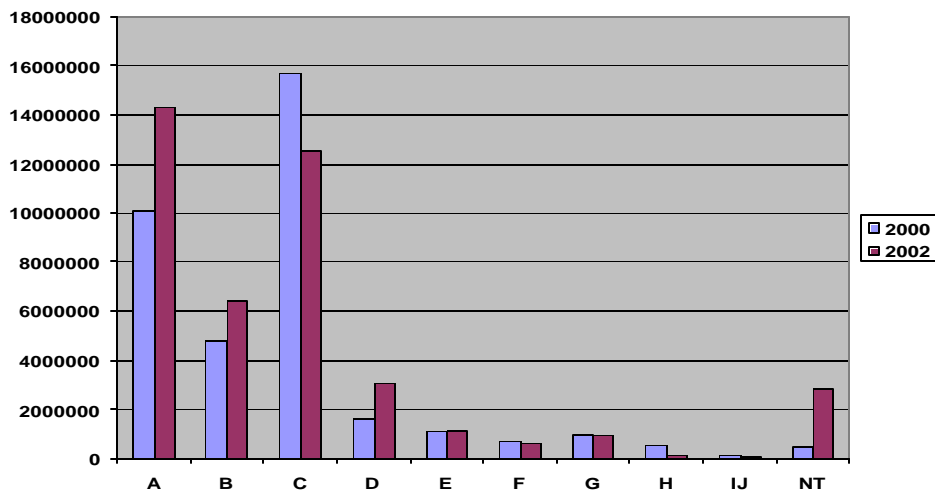


Figure 3. Breakdown of global HIV infections by subtype

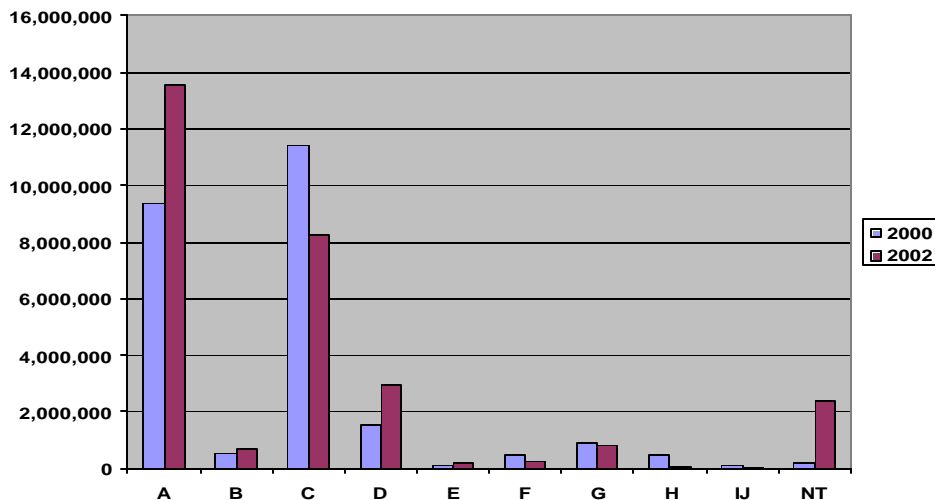


Figure 4. Breakdown of Sub-Saharan African HIV infections by subtype

As stated earlier, infections in Sub Saharan Africa represent about 70% of total global HIV infections in the year 2000 and 2002. The change in total subtype infections between Sub-Saharan Africa and the world look specifically similar when viewing subtypes A and C. In 2000, subtype C infections accounted for about 45% of all global infections while in 2002, C accounted for close to 30%. Subtype C has been overtaken by subtype A. The increase in infections by subtype A indicates greater problems of HIV infection if effective prevention programs are not implemented.

5. FUTURE APPROXIMATIONS OF HIV INFECTION

We used three software programs to create simulations of the future likelihood and proportion of HIV subtypes. Using the ratio of change in total infections between 2000 and 2002 for each subtype and region, we get rates that could be used to predict future HIV infections. The number of infections from the year 2000 served as the base case for all of our programs. Populus is one of the programs we used to create a continuous exponential growth model. The growth model utilizes continuous and consistent change in a population by way of total population growth at each time step. This model closely matches the change in infections between the years of 2000 and 2002 given by data from the World Health Organization. Biota is another program that we used to model exponential growth of HIV infections by subtype and region. The data output given by the model for this program should be a fair approximation for infections in 2004 and 2010.

The final program we used was Matlab 6.5. We used a simple exponential growth model using a built in ordinary differential equation available with matlab. Matlab was most flexible with parameterization and displaying multiple patterns of HIV infection by region and by subtype. The output from these models differs from the WHO-UNAIDS data on total global HIV infections for 2002 by less than one percent.

According to WHO-UNAIDS 2000 and 2002 data, the growth rates for both total global HIV infections and Sub-Saharan Africa HIV infections were very similar. The growth rate for global HIV infections was 16.34 percent and Sub-Saharan Africa yielded a 16.15 percent growth rate over two years. The same growth trend approximately carries through for both the total global HIV infections and the HIV infections within Sub-Saharan Africa (figure 5). The time step is organized in periods of one year each starting from 2000 and ending in the year 2010. Total global infections reach a number of approximately 50 million in 2004 and a frightening 81.7 million by 2010. Sub-Saharan African infections reach 35 million in 2004 and 56 million by 2010. In both cases, the number of HIV infections in 2010 becomes nearly twice what it was in 2000.

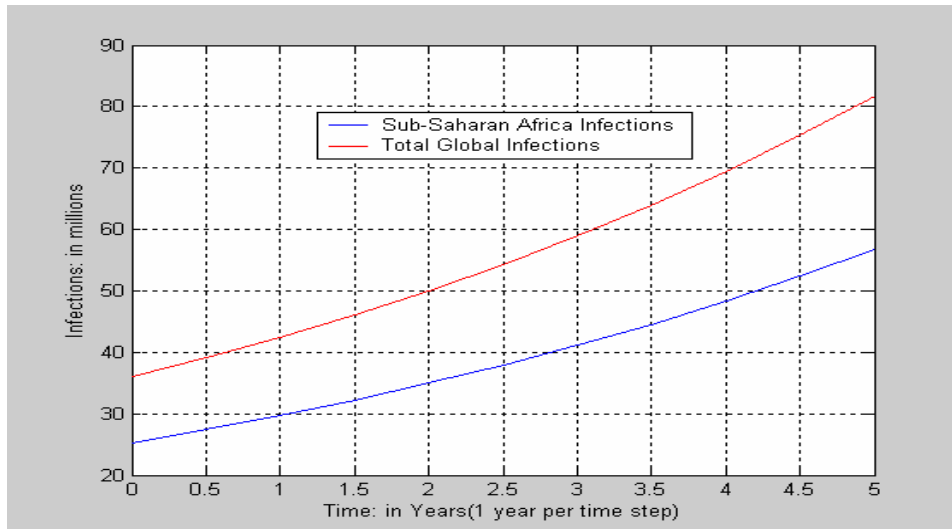


Figure 5. A comparison of future likelihood of HIV infections in Sub-Saharan Africa and on a global scale.

Subtypes A, B, C, and D all have a similar base number of total HIV infections in 2000 (figure 6). The exponential model illustrates that subtype D seems to be at the root of a future problem ahead. The subtype D infections rise above all other infections. Our model predicts that it will be the most prevalent of all subtypes in 2010. Subtype B is also increasing but not close to the rate of increase of A and D. The increase in subtype A is highly likely since it is more easily transmissible than other subtypes paired with the fact that it causes the majority of HIV infections in Sub-Saharan Africa and worldwide. Experts working on minimizing the infections caused by HIV virus should now focus on subtypes A and D as well as C. Subtype C has caused the bulk of the infections in the past but subtype's A and D are likely to cause the greater proportion of HIV infections in the future.

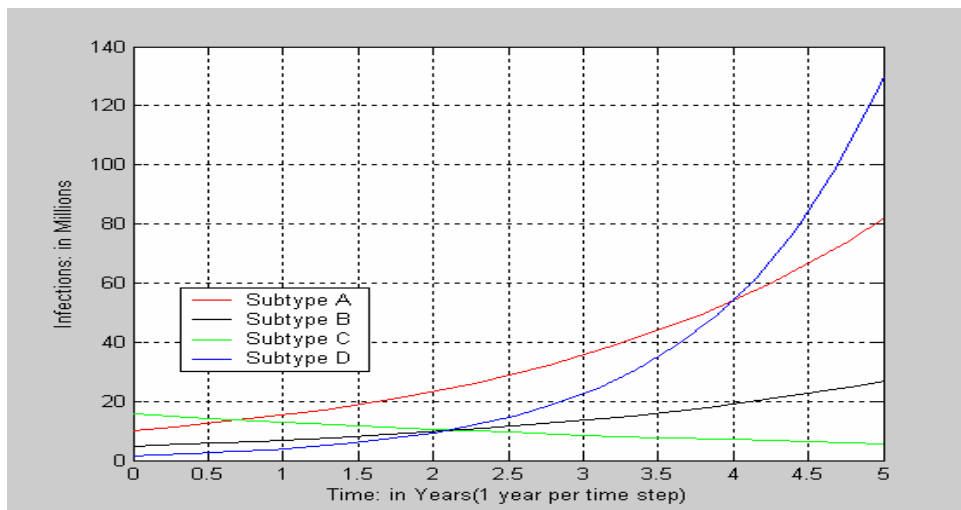


Figure 6. Future subtype approximations for A, B, C, D.

Infection by subtypes E, F, G, H, and I/J seem to be stabilized in terms of their rate of increase and their relationship to the increase of subtypes A, B, and D. According to the exponential model, these subtypes are not likely to cause many HIV infections in the future. All of these subtypes are decreasing in their total number of HIV infections aside from subtype E (figure 7). This in itself is a disturbing fact since the HIV infections in Thailand are predominantly of type E. Fortunately, drastic prevention efforts in Thailand have considerably reduced HIV infection in this area, and what was once one of the most HIV infected countries of the world has become an example for other countries to halt the spread of HIV infection.

What was previously described as NT/other subtypes including types NT, K, N, O, AB, AG, and AE had increased a great deal in the time period between 2000 and 2002. The emergence of these recombinants and new subtypes has not caused many problems with HIV testing and there has not been much data recorded on these. However, as can be seen with the HIV infection data of these subtypes between 2000 and 2002, the number of recorded cases of recombinants has increased a great deal. In 2000, there were 480,541 recorded cases of recombinant HIV infections. In 2002, this number jumped to 2,829,630 HIV infections by recombinants [15]. HIV infected individuals are becoming more and more likely to be infected by a recombinant form of HIV which was formed by the merging of various HIV subtypes.

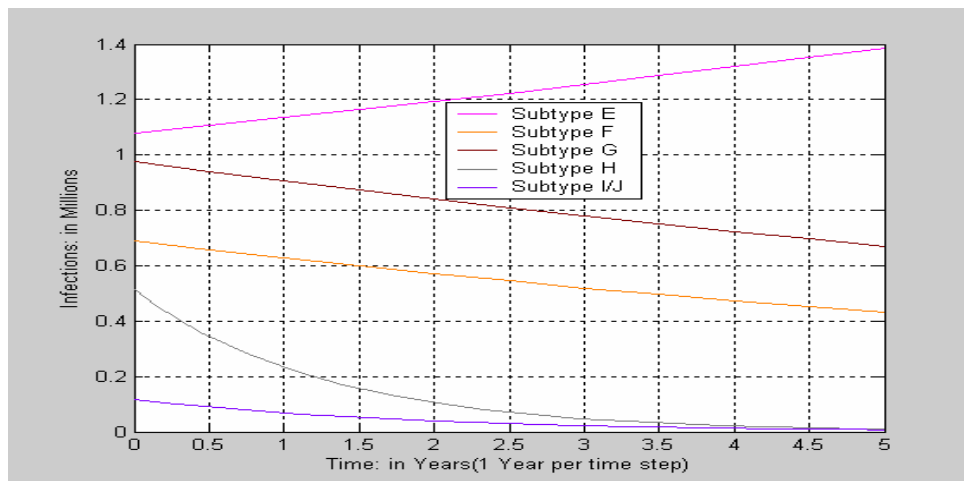


Figure 7. Future subtype approximations of E, F, G, H, I/J

Linear Growth Projections of HIV-1 Group M subtypes

In order to make a further comparison between all our sources of data and models, we chose to make a linear growth model using the rates of change between the subtypes in the years of 2000 and 2002 and using the year 2000 as the base case. Utilizing this model, we can see precisely what we can expect with HIV infections in the future if all trends for subtype and total HIV infection growth continue to increase exactly as they did between the years of 2000 and 2002.

First, the growth of total HIV infections along with infections in Sub-Saharan Africa was considered in order to predict the possible future number of infections and to

compare this with the exponential models (figure 8). Next, each HIV subtype was projected for the time period from 2000-2010 using 2000 data as the base case. The same trend follows for the various HIV subtypes as was seen in the exponential models, and this is acceptable since both project subtype growth using rates of growth from 2000 and 2002 (figure 9 and 10). As expected, the output for the various subtypes (aside from subtype D) and also for the global total number of infections according to this linear growth model is under-estimated compared to the other growth models. The reason for this is the fact that linear growth allows for only a proportion of the entire previous HIV infected population to contribute to future infection, creating smooth growth. The exponential model allows for an increase in HIV infections in proportion to the population that already exists. The whole HIV infected population increases at a certain rate, depending on regions and subtype, at each time step. Comparison of the output from the linear growth model to the exponential model shows that the linear model falls short in terms of predicting future HIV infections in both Sub-Saharan Africa and globally, and also with the breakdown of infection by subtypes.

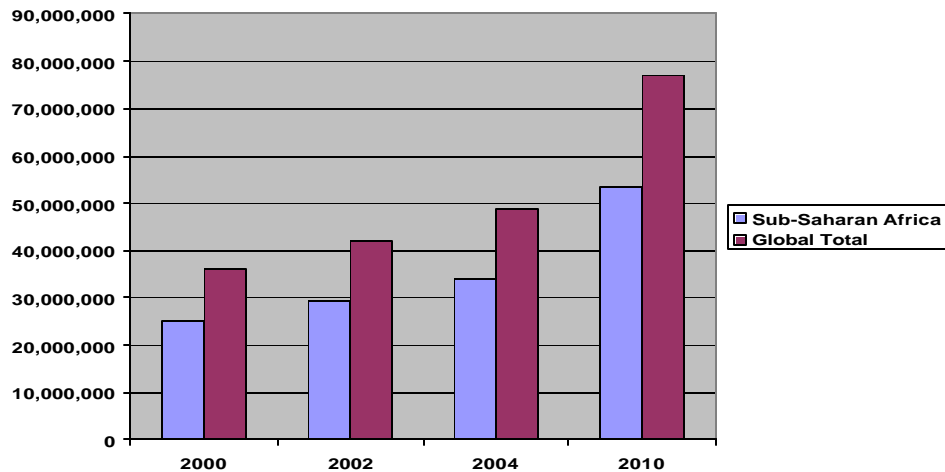


Figure 8. Linear projection of HIV infections in Sub-Saharan Africa and worldwide.

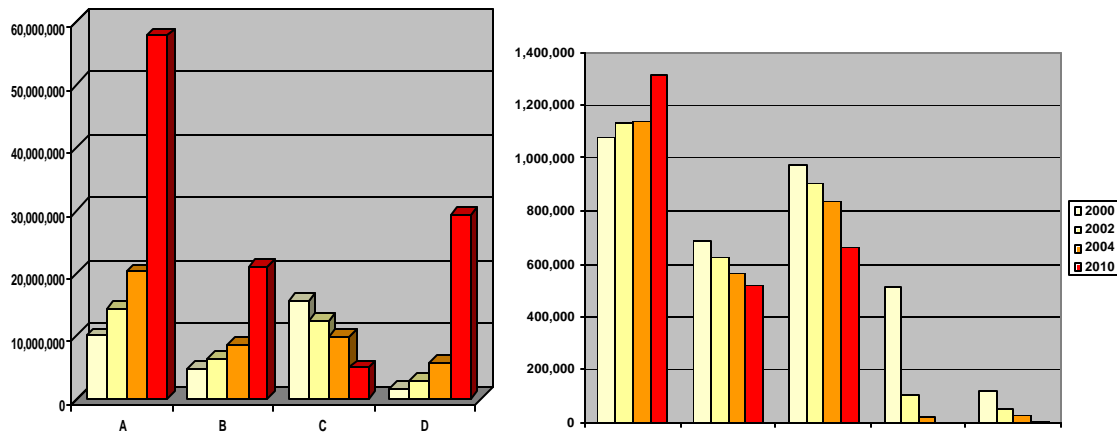


Figure 9, 10. Linear growth of subtypes A,B,C,D, E, F, G, H, I/J from 2000 to 2010.

This linear growth model shows us that subtype A infections overcome all other subtypes in number although not in rate of increase. Subtype D has a greater rate of increase at the onset of the program of 87.53 percent over 2 years compared to subtype A with a rate of increase of 41.8 percent.

The subtypes NT/Other do not lead to the creation of an accurate model using exponential and linear growth. According to linear growth, subtype NT grows to 3.5 billion by 2010 which is far larger than the global cumulative total HIV infections of 76.9 million. This large number generated by using the growth rate of NT/Other subtypes is due to the emergence of new subtypes that were not included in the subtypes counted in 2000 including NT, K, N, O, AB, and AG.

6. A COMPARISON OF HIV GROWTH MODELS

There is a significant difference between the linear growth models and the exponential models. The linear growth model yields subtype A as the major subtype causing HIV infections in 2010. The exponential models yield subtype D as the major subtype causing infection with subtype A causing less HIV infections. Due to the epidemiology of HIV-1 subtype A, coupled with the fact that it is more easily transmitted than subtype D, it is likely that subtype A will cause the majority of HIV infections in 2010.

The numerical data produced by our models show that all 4 programs give similar output for the total change in infections in Sub-Saharan Africa (figure 11). Specific attention is given to Sub-Saharan Africa since it is responsible for nearly 70% of all infections in both 2000 and 2002. The growth rate of HIV infections between 2000 and 2002 in Sub-Saharan Africa matches closely to the global rate.

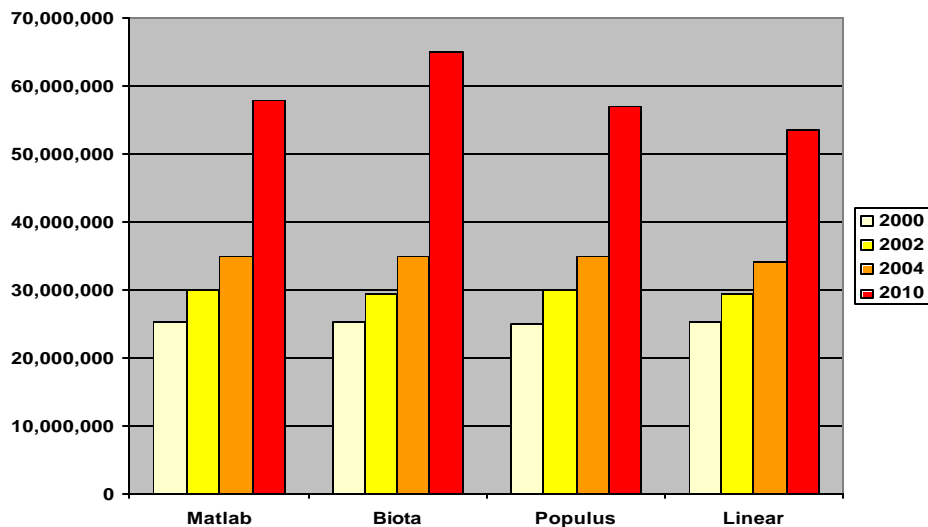


Figure 11. A comparison of models and modeling programs for the approximation of future HIV infections in Sub-Saharan Africa.

Comparison to Professional Predictions of HIV Infections in 2010

In order to validate the results obtained from our models, we compared a number of our results with those given by the National Intelligence Council, which is a United States government organization responsible for making estimates of the likely course of future events. In September 2002, they estimated the future likelihood of total HIV infections worldwide using data provided from UNAIDS, non-governmental organizations, academics, in consensus with the National Institutes of Health, the American Enterprise Institute, the University of Maryland Biotechnology Institute, and the Global AIDS program at the CDC. They give an estimate of 80 million total cumulative HIV infections for 2010 [13]. The XIV International AIDS Conference also made a prediction of total infections for 2010 at 87 million total infections [25]. This is very comparable to our predictions using the various models. Our results for 2010 include 81.7 million HIV infections using Matlab with exponential growth, 86.9 million HIV infections using Biota with exponential growth, 82 million infections using Populus, and 76.9 million infections using the linear growth model (figure 12).

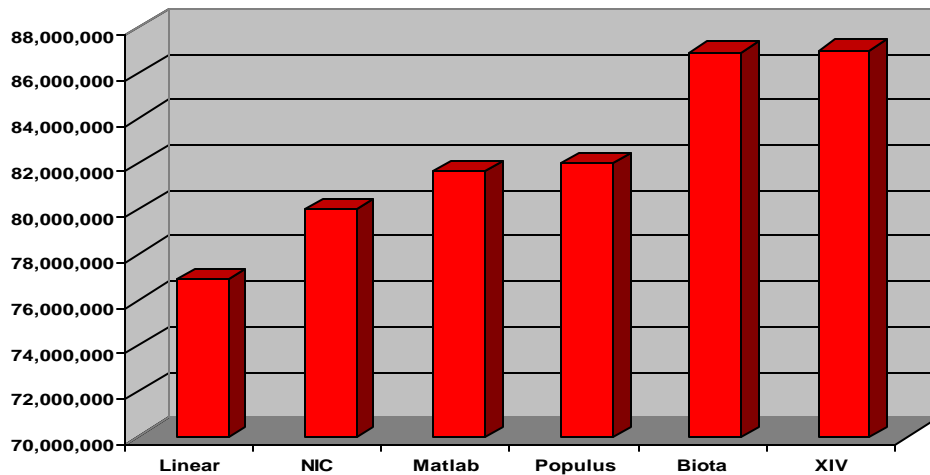


Figure 12. A comparison of projections of total HIV infections in 2010. NIC is the National Intelligence Council and XIV is the Barcelona 2002 International AIDS Conference.

There are also similarities in the growth models with respect to regional infections. In our models, Sub-Saharan Africa controls not only the current trend but also the future spread of HIV infections. The National Intelligence Council makes a similar prediction for the future. They estimate that Nigeria and Ethiopia, two of the worlds most populous countries that are in the early to mid stages of infection, are two of the next wave countries which will cause most of the HIV infections in 2010 [13]. These countries lie within Sub-Saharan Africa which we predicted to control future HIV infections. Our models give a close match to that of the National Intelligence Council for the time period of 10 years to predict the global total cumulative HIV infections.

7. DISCUSSION

This study has emphasized the importance of identifying and predicting HIV infections specifically in terms of the different subtypes. Comparing our results on future global HIV infection and infection in sub-Saharan Africa with other sources, we found that simple exponential and linear models can be used for a complex purpose. Our models use the growth rate of subtypes between 2000 and 2002 to obtain predictions of infection similar to organizations that used several other factors in their analysis.

HIV infections by subtype A are predicted to cause the majority of HIV infections in the future. As this subtype currently causes the majority of infections in Sub-Saharan Africa and it has a transmission rate higher than other subtypes, it is likely to make the situation in Africa even worse than it is today. The previous subtype causing the majority of infections in this region, subtype C, is likely to be overtaken by subtype A. It is also very likely that subtype A will form recombinants with a great deal more other subtypes in the future because of its high transmission rate. As a result, more people are likely to be infected by more than one virus as well with subtype A. As Sub-Saharan Africa contains 70 percent of the cases of HIV infection globally, subtype A will be the subtype that plagues the world with HIV infection in the future.

Subtype D is predicted to cause the many HIV infections in the future. The prevalence of this subtype increased 87.53 percent over the time period of 2000 to 2002. As subtype D infections are for the most part geographically restricted to the region of Sub-Saharan Africa, this region is likely to have a high frequency of infection by this subtype as well as by subtype A.

The linear model gives the lowest projection of future HIV infection. There are a projected 76.9 million total cases of HIV infection for 2010. Subtype A is responsible for 74.9 percent of these infections in the model giving 57.6 million HIV infections by this subtype alone. An immediate response to the HIV epidemic is necessary to stop HIV spread by subtype A.

Future work includes predicting the spread of HIV infections by utilizing more current subtype data to better approximate future infections. Prediction and estimation of recombinant forms of subtypes is an important task as the recorded cases of recombinants in 2002 increased by 400 percent compared to the recombinants of the year 2000.

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