Use of agent-based simulations to design and interpret HIV clinical trials

Diego F. Cuadros, Laith J. Abu-Raddad, Susanne F. Awad, Gisela García-Ramos

Abstract

In this study, we illustrate the utility of an agent-based simulation to inform a trial design and how this supports outcome interpretation of randomized controlled trials (RCTs). We developed agent-based Monte Carlo models to simulate existing landmark HIV RCTs, such as the Partners in Prevention HSV/HIV Transmission Study. We simulated a variation of this study using valacyclovir therapy as the intervention, and we used a male circumcision RCT based on the Rakai Male Circumcision Trial. Our results indicate that a small fraction (20%) of the simulated Partners in Prevention HSV/HIV Transmission Study realizations rejected the null hypothesis, which has no effect from the intervention. Our results also suggest that an RCT designed to evaluate the effectiveness of a more potent drug regimen for HSV-2 suppression (valacyclovir therapy) is more likely to identify the efficacy of the intervention. For the male circumcision RCT simulation, the greater biological effect of the male circumcision yielded a major fraction (81%) of RCT realizations that rejects the null hypothesis, which has no effect from the intervention. Our study highlights how agent-based simulations synthesize individual variation in the epidemiological context of the RCT. This methodology will be particularly useful for designing RCTs aimed at evaluating combination prevention interventions in community-based RCTs, wherein an intervention’s effectiveness is challenging to predict.

1. Introduction

HIV infection remains a major public health challenge, especially in sub-Saharan Africa [1]. Nearly 30 years of HIV research has improved our understanding of the determinants for HIV transmission and identified key candidate interventions to prevent HIV infection. More than 40 randomized controlled trials (RCTs) were designed to measure the effectiveness of interventions on HIV incidence. These RCTs include HIV vaccines, pre-exposure prophylaxis, antiretroviral therapy, male circumcision, and behavioral interventions [2]. Regrettably, almost 90% of the RCTs failed to demonstrate statistically significant effectiveness against HIV incidence [2,3]. Despite the outstanding scientific evidence supporting intervention, it remains unclear why most RCTs fail to demonstrate effectiveness [2,4–6]. However, several factors, such as treatment adherence and retention, condom use frequency, HIV testing, sero-disclosure, and counseling, have been proposed as important trial components that could substantially impact RCT results [7].

HIV transmission dynamics is a complex phenomenon. As such, any intervention that attempts to change an aspect of these dynamics may have unpredictable effects due to the nonlinear interplay between factors and confounders in infection transmission dynamics [8]. This complexity may frustrate accurate estimates for the magnitude of an effect from an intervention and, thus, preclude an optimal trial design. This challenge is compounded by a growing need to design RCTs and intricate multi-component prevention intervention packages [9,10].

RCT simulation is a growing area of interest in different fields, including HIV prevention [11–16]. In drug development, RCT simulation is a well-established procedure to evaluate alternative trial designs, test hypotheses, and interpret trial outcomes [11,15–17]. Individual variations can be determined through an agent-based RCT simulation. The intervention’s action and interaction components can also be assessed to understand and predict the range of possible outcomes.

The greatest benefit of an agent-based RCT simulation is the ability to directly incorporate intervention action mechanisms in an RCT design. An RCT’s particular design and outcome depend on
the intervention’s epidemiological context. As such, the intervention outcome is influenced by the HIV transmission drivers in a given population, such as behavioral factors or biological cofactors. Therefore, an intervention’s impact could differ among populations. As a formative stage of trial design, an agent-based RCT simulation could include empirical data associated with the infection drivers to assess an intervention’s impact on a specific population. As a result, agent-based simulations would provide a range for the likely effectiveness of the intervention within a specific epidemiological context; it would also estimate HIV incidence projections for both control and intervention groups. Hence, agent-based RCT simulation of HIV clinical trials could be used during the formative stage of trial planning to both complement and validate conventional sample sizes and power calculations (Fig. 1). Furthermore, the trial can be conducted thousands of times in silico under a variety of assumptions at a limited cost compared with implementing a single trial in the field, which is more expensive and demanding.

In this article, we argue that agent-based HIV RCT simulation could be an integral step in planning and designing RCTs for HIV interventions by assisting with the multiple challenges confronted during HIV RCT design. Furthermore, agent-based RCT simulations could play an integral role in interpreting the trial results (Fig. 1). Here, we show the utility of agent-based RCT simulations by illustrating this approach using existing landmark HIV RCTs.

2. Methods

We constructed agent-based Monte Carlo models using the MATLAB® computing language version R2013a [18] to simulate the HIV prevention RCT, the Partners in Prevention Study, which was used to test the effectiveness of acyclovir (400 mg twice daily) [19]. The Partners in Prevention Study aimed to examine the therapeutic benefits of controlling herpes simplex virus type 2 (HSV-2) reactivation and shedding on reducing HIV transmission. Despite a significant reduction in the mean plasma HIV viral load and genital ulceration episodes in the treatment group, the study demonstrated that acyclovir did not significantly affect HIV incidence. As a result, this field study concluded that acyclovir treatment in dually HIV/HSV-2-infected individuals does not reduce the risk of HIV transmission [19]. Our study implemented RCT simulations to examine this trial and to assess recent findings on a potent HSV-2 suppressive therapy [20].

For comparison, we examined the drivers of success for the RCT that assessed the effectiveness of male circumcision on reducing HIV acquisition in Rakai, Uganda [21]. Our simulation results were then compared with the standard power calculation results using the original assumptions from the actual trials. In all of our simulations, the replication unit was an individual RCT.

2.1. Scenario 1: partners in prevention study with a 0.27 log10 HIV plasma viral load reduction

As in the clinical trial [19], we generated an agent-based Monte Carlo simulation to replicate the Partners in Prevention trial, wherein acyclovir suppressive therapy was administered as an intervention. The total number of HIV sero-discordant couples simulated in each realization (which corresponded to an individual RCT) was 3400 (1700 in the control group and 1700 in the acyclovir intervention group).

The 2-year follow-up for the study was simulated using monthly time steps. For each time step (equivalent to one month), each HIV sero-discordant couple from both groups (control and treatment) had a specific number of coital acts, c, calculated from a normal distribution with the mean μc = 9 coital acts per month and standard error SEc = 0.62 [22]. The number of unprotected coital acts was estimated from a binomial distribution assuming condom use at a 50% frequency [21,23].

The HIV-positive individual was assumed to remain in the chronic infection stage during the entire simulation. This assumption presumes that the HIV-positive partner of the stable sero-discordant couple was infected some time before the trial began. Thus, it was highly unlikely that the trial included HIV-positive individuals during the acute stage of infection. The probability of HIV transmission for each unprotected coital act without treatment, puntreated, was calculated from a normal distribution with the mean μc = 0.0015 and SEc = 0.0001 [24,25]. For each unprotected coital act, the simulation draws a random number from a uniform distribution, ranging from 0 to 1, to determine whether a HIV seronegative individual in the control group remains uninfected or becomes HIV-positive. If this number is smaller than puntreated, a transmission occurs, and the time is recorded to perform a log-rank survival analysis.

Acyclovir reduced the HIV plasma viral load and, by extension, the probability of HIV transmission per coital act [19]. In the treatment group, we assumed that this effect on reducing HIV infectiousness was consonant with the empirical relationship between HIV plasma viral load and HIV transmission probability per coital act, as initially observed by Quinn and colleagues [26].

\[
\text{p}\text{treat} = \frac{p\text{untreated}}{\exp(2.45 \log_{10}(\text{VL})} \tag{1}
\]

Here, ptreat represents the probability of HIV transmission per coital act with the intervention, and log10(VL) represents the logarithmic (base 10) reduction in HIV plasma viral load with the intervention. Previous RCTs conducted to measure the effect of acyclovir 400 mg twice daily (the treatment implemented in the Partners in Prevention trial) reported that the HIV plasma viral load was reduced by 0.27 log10 copies/mL (i.e. log10(VL) = −0.27) [19]. Therefore, for this simulation, puntreated = 0.0012. For this calculation, the viral load was assumed stable during the chronic stage of the infection [26]. After ptreat was calculated, the same procedure described for HIV transmission per unprotected coital act in the control group was performed to determine whether a HIV seronegative individual in the treatment group remains uninfected or becomes HIV-positive. If a transmission occurs, the time is recorded to perform a log-rank survival analysis. Table 1 summarizes the values of the key parameters used in this simulation. A flow diagram and MATLAB code for this simulation are included in the Supplementary material.
2.2. Scenario 2: valacyclovir therapy with a $1 \log_{10}$ HIV plasma viral load reduction

For this scenario, we implemented the same simulation used during the Partners in Prevention trial (Scenario 1). For this scenario, however, we used valacyclovir as the suppressive therapy. Recent findings on this potent HSV-2 suppressive therapy in a randomized crossover trial indicated a $1 \log_{10}$ plasma viral load reduction [29]. Therefore, for this scenario, $f_{\text{treat}} = 0.00061$.

2.3. Scenario 3: male circumcision

2.3.1. Agent-based sexual network module

To simulate a male circumcision RCT as conducted in Rakai, Uganda [21], we constructed an agent-based Monte Carlo simulation based on a previous model [27]. The model consisted of a stochastic agent-based sexual network model in which partnership acquisition and dynamic processes were simulated.

In the model, equal numbers of male individuals were allocated to the control and treatment groups (2500 in each group, as reported in the Rakai Male Circumcision trial [21]) and assigned a node degree (maximum number of female partners per year). We adopted a likelihood framework to estimate the annual degree node distribution using data from “The Malawi Social Network Project,” which is a study on sexual networks in Malawi conducted by the University of Pennsylvania Population Study Center [28]. For males, the reported number of sexual partners follows a gamma distribution:

$$f(n) = \frac{n^{k-1} e^{-n/\theta}}{\Gamma(k)\theta^k}$$

where the annual degree distribution is defined as the frequency of node degrees $n$ in the network with the shape parameter $k=1.9$ and scale parameter $\theta=1.1$, which were calculated from the Malawi Social Network Project data [27,28].

We allowed two types of relationships: casual relationships that were assumed to last 6 months on an average [29] and marriages (long-term relationships) that were assumed to last the entire RCT study period (24 months). Partnership formation occurs in two steps. First, marriages are generated until reaching the assumed percentage of marriages in the population (50%) [27]. Second, casual partnerships are then formed with the remaining available individuals (married or single) according to the node degree of each male individual. To introduce dynamics into the network, these casual partnerships were allowed to end and re-form each month.

2.3.2. Epidemiological module

HIV prevalence in the female population was assumed at 15% [29]. The HIV sero-status of each female connected with a male in the trial was randomly assigned with a 15% probability of being HIV-positive. We did not include male to female transmission in the simulation, and we only simulated female to male transmission. HIV incidence in females was not considered. Thus, if a female was uninfected, she remained uninfected during the duration of the connection with her partner. The 2-year follow-up of the study was simulated in monthly time steps [21]. For each time step (month), each male from both groups (control and treatment) had a specific number of coital acts each female partner calculated from a normal distribution with the same parameters ($\mu$, and $\sigma$) used in the Partners in Prevention trial simulation (Scenario 1).

Because each male can have more than one sexual partner, the model calculated a number of coital acts per partnership per month, which was assumed to be a function of the number of partnerships for each individual. This function was defined as $c_{\text{p}} = c \cdot N^{-0.75}$ [27], where $c$ is the number of coital acts per month estimated in the previous step, and $N$ is the number of partnerships for an individual in a specific month. This function represents individuals with multiple partnerships and more coital acts but maintains a realistic assessment of the number of coital acts each month.

The number of unprotected coital acts was estimated from a binomial distribution, assuming a 50% condom use frequency, which was also assumed in the Partners in Prevention trial simulation (Scenario 1). If a female partner of an individual in the control group is HIV infected, the HIV transmission process was then simulated as described for the Partners in Prevention trial simulation with the same probability of HIV transmission, $p_{\text{treat\-treat}}$ (Scenario 1). For individuals in the intervention group, we assumed that male circumcision decreases the risk of HIV acquisition by 60% [21,23,30,31]. Therefore, the probability of HIV transmission per unprotected coital act for individuals in the intervention group was $p_{\text{treat\-treat}} = 0.0006$.

The same procedure described in the Partners in Prevention trial simulation for HIV transmission per unprotected coital act was implemented to determine whether the HIV sero-negative male remains uninfected or becomes HIV-positive. If a transmission occurs, the time is recorded to perform a log-rank survival analysis.

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Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time</td>
<td>24 months</td>
<td>[19,21]</td>
</tr>
<tr>
<td>Average number of coital acts per month</td>
<td>9 (95% CI 7.8–10.2)</td>
<td>[22]</td>
</tr>
<tr>
<td>Percentage of unprotected sexual contacts per month</td>
<td>50%</td>
<td>[21,23]</td>
</tr>
<tr>
<td>Number of individuals in Scenarios 1 and 2</td>
<td>1700</td>
<td>[19]</td>
</tr>
<tr>
<td>Control group</td>
<td>1700</td>
<td>[19]</td>
</tr>
<tr>
<td>Intervention group</td>
<td>1700</td>
<td>[19]</td>
</tr>
<tr>
<td>Number of individuals Scenario 3</td>
<td>2500</td>
<td>[21]</td>
</tr>
<tr>
<td>Control group</td>
<td>2500</td>
<td>[21]</td>
</tr>
<tr>
<td>Intervention group</td>
<td>2500</td>
<td>[21]</td>
</tr>
<tr>
<td>Probability of HIV transmission per unprotected coital act in the control group</td>
<td>0.0015 (95% CI 0.0003–0.0017)</td>
<td>[24,25]</td>
</tr>
<tr>
<td>Probability of HIV transmission per unprotected coital act in the intervention group</td>
<td>0.0012 (95% CI 0.0009–0.0014)</td>
<td>Estimated</td>
</tr>
<tr>
<td>Scenario 1</td>
<td>0.00061 (95% CI 0.0004–0.0008)</td>
<td>Estimated</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>0.00017 (95% CI 0.0001–0.0008)</td>
<td>Estimated</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>0.00014 (95% CI 0.00005–0.0007)</td>
<td>Estimated</td>
</tr>
</tbody>
</table>
analysis. Table 1 summarizes the values of the key parameters used in this simulation. A flow diagram and the MATLAB code for this simulation are included in the Supplementary material.

2.4. Standard power calculations

Using simple power calculations with the software OpenEpi [32], we estimated the power of the trials (the Partners in Prevention study and Rakai male circumcision trial) to detect the statistically significant effectiveness of the intervention. These calculations required the input of the sample size in the control and intervention group as well as the percentage of individuals with outcome (HIV infection) in each group. The parameter assumptions for these calculations were derived from the actual trials; therefore, the Partners in Prevention study sample size was 1700 individuals in each group. Likewise, the assumed percentages of individuals infected with HIV during the trial were 4% and 2% in the control and intervention groups, respectively. For the Rakai male circumcision trial, the assumed sample size was 2500 in each group, and the percentages of individuals infected with HIV during the trial were 2.4% and 12% in the control and intervention groups, respectively. We used \( \alpha < 0.05 \) to estimate the power of both trials.

2.5. Measure of effectiveness

To measure the intervention’s effectiveness for each scenario, we performed a log-rank survival analysis for each trial realization and its corresponding relative risk (RR) estimation. The power of the RCT to yield a statistically significant result was then determined as the fraction of realizations that reject the null hypothesis (\( \alpha < 0.05 \)) [33]. The results reported in this study are based on 1000 realizations from the models for each trial.

We also assessed the effect of the number of unprotected coital exposures (which is affected by the number of coital acts during the trial and condom use frequency) on the RR estimate for an RCT by varying the number of unprotected coital exposures from five to 200 for both the acyclovir (Scenario 1) and male circumcision (Scenario 3) interventions as described above.

3. Results

Table 2 summarizes the main results from all simulations.

### 3.1. Scenario 1: partners in prevention study with a 0.27 \( \log_{10} \) HIV plasma viral load reduction

In this scenario, the mean number of HIV sero-conversions was 47 in the intervention group and 60 in the control group (Fig. 2A), which yielded the mean \( RR = 0.80 \) (95% CI: 0.55 – 1.17), where the CI represents the upper and lower bound means estimated from 1000 realizations. The log-rank test indicates that 79% of the RCT realizations reject the null hypothesis, which has no effect from the intervention. \( RR \) distribution (Fig. 2B) showed a wide variation in \( RR \) outcomes across the 1000 realizations with the \( RR \) point estimates ranging from 0.44 to 1.52.

### 3.2. Scenario 2: valacyclovir therapy with a 1 \( \log_{10} \) HIV plasma viral load reduction

In this scenario, the mean number of HIV sero-conversions was 24 in the intervention group and 60 in the control group (Fig. 2C), which yielded the mean \( RR = 0.40 \) (95% CI: 0.26 – 0.65). The log-rank test indicates that 96% of the RCT realizations reject the null hypothesis, which was no effect from the intervention. Fig. 2D illustrates the \( RR \) distribution across the 1000 realizations with the \( RR \) point estimates ranging from 0.18 to 0.88.

### 3.3. Scenario 3: male circumcision

In this scenario, the mean number of HIV sero-conversions was 15 in the male circumcision group and 35 in the control group (Fig. 2E), which yielded the mean \( RR = 0.44 \) (95% CI: 0.24 – 0.80). The log-rank test indicates that 81% of the RCT realizations reject the null hypothesis, which has no effect from the intervention. Fig. 2F illustrates the \( RR \) distribution across the 1000 realizations with \( RR \) point estimates ranging from 0.02 to 1.11.

### 3.4. Standard power calculations

The simple power calculation results indicate that the Partners in Prevention study had 93% power to detect the statistically significant effectiveness of the intervention compared with 20% from our simulations. Likewise, the Rakai male circumcision trial had 89% power to detect the statistically significant effectiveness of the intervention compared with 81% from our simulations.

### 3.5. The effect of the number of unprotected coital exposures on the relative risk estimates

We explored the effect of the number of unprotected coital exposures on the \( RR \) by varying the number of unprotected exposures from five to 200 for the total duration of the follow-up. As expected, the results indicate that few unprotected coital acts per partnership during the trial yields a broad CI. It also indicates that, as the number of unprotected coital acts increases, the CI decreases (Fig. 3). Thus, the CI of the effectiveness measure strongly depends on the number of unprotected coital acts in the trial.

### Summary of the results from the randomized controlled trial simulations of the different scenarios.

<table>
<thead>
<tr>
<th>Result</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HIV incidence rate per 100 person-year</td>
<td>1.76</td>
<td>1.76</td>
<td>0.70</td>
</tr>
<tr>
<td>Control group</td>
<td>1.38</td>
<td>0.71</td>
<td>0.30</td>
</tr>
<tr>
<td>Intervention group</td>
<td>0.80</td>
<td>0.40</td>
<td>0.44</td>
</tr>
<tr>
<td>Percentage of simulations with statistically significant results</td>
<td>20%</td>
<td>96%</td>
<td>81%</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>95% CI*</td>
<td>0.55–1.17</td>
<td>0.26–0.65</td>
</tr>
</tbody>
</table>

* The CI represents the means of the upper and lower bounds estimated from each of the 1000 realizations.

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4. Discussion

This study illustrates the value of agent-based HIV clinical trial simulations to inform trial design. Using prior knowledge of the clinical trial’s epidemiological context, the agent-based RCT simulation can provide informed input for RCT statistical designs. Furthermore, agent-based RCT simulation can play an integral role in interpreting the trial outcome (Fig. 1), as discussed below.

We assessed the utility of agent-based RCT simulation by examining the difficulty in measuring effectiveness even in the fairly simple epidemiologic system with HIV sero-discordant couples, wherein the acyclovir therapy intervention was evaluated. Our results show that only 20% of the realizations for this trial reject the null hypothesis, which was no effect from the intervention. Furthermore, assuming that parameter assumptions are met (such as the effectiveness of the intervention, the number of sexual contacts, and the probability of HIV transmission per sexual contact, and condom use, among others), the actual Partners in Prevention Study results with the RR 0.92 (95% CI: 0.60–1.41) [19] was highly probable based on the RR distribution derived from this trial simulation (0.44–1.52) (Fig. 2B). This result substantially differs from the 93% power estimated from simple power calculations using parameter assumptions derived from the actual trial. On the other hand, when the estimates for the effectiveness of the intervention and HIV incidence projections derived from our agent-based simulations were used with a standard sample size and power calculations, the results were consonant with the estimated power from our agent-based simulations.

We show that the trial should have included a minimum number of unprotected coital acts to observe a statistically significant effect from the intervention. As mentioned previously, the number of unprotected coital acts could be affected by either the total number of coital acts during the trial or condom use frequency. With the parameter values assumed in this study, it was impossible to detect a significant effect on HIV transmission with fewer than 100 unprotected coital acts (Fig. 3A). We assumed a high rate of condom use (50%) [21,23], which also contributed to the low incidence in the control group in this simulation (1.76 per 100 person-year). However, the actual Partners in Prevention trial reported a higher condom use rate, exceeding 90% [34]. Using this number, we estimated less than 20 unprotected coital acts per couple for the entire study duration. Our analysis indicates that this number of infection exposures is too low to detect a significant effect from the treatment. As such, it could be a major reason for the substantial discrepancy between the power calculated from the simple power calculations and the power estimated from our simulations.

However, this observation should be understood neither as a shortcoming in the design of this landmark study nor as a post-hoc power analysis with the hindsight of the trial results. Several unexpected factors conspired to undermine the ability of the trial to measure the intervention’s effectiveness. The high rate of
condom use reduced the expected event rates and, thus, prevented sufficient infection exposure. The lack of a significant effect from the trial was due to its success in HIV testing, sero-disclosure, and counseling. This result highlights how standard care and ethical issues are inescapable challenges that can impact clinical trial results. It can potentially reduce the expected HIV incidence in the control group, thereby compromising the study’s ability to detect a significant effectiveness from the intervention.

If the acyclovir 400 mg twice daily regimen evaluated in the Partners in Prevention Study is replaced by an acyclovir 1.5 g twice daily regimen [20], the trial would likely measure a significant effect from the intervention. Ninety-six percent of the realizations reject the null hypothesis, which has no effect from the intervention, and indicate an approximately 60% effectiveness (Scenario 3; Fig. 2E). This result is comparable to the biological effectiveness of male circumcision [21,23,30,31].

Due to the magnitude of the effect from male circumcision and the intermediate percentage of condom use (49%) in the Rakai Male Circumcision trial [21], a significant effect was observed for the intervention in the male circumcision trial even with a small number of unprotected coital acts (Fig. 3B). Our simulation-based 0.44 RR mean (95% CI: 0.24–0.80) corresponds with the Rakai study estimates (Kaplan–Meier risk ratio 0.40; 95% CI 0.23–0.70) [21]. Likewise, the power estimated from simple power calculations is consistent with the power estimated from our simulations. These results suggest that it would be highly unlikely for the male circumcision trials to fail in measuring a significant effect from the intervention.

Our simulations highlight how even in a relatively simple epidemiological context (such as observed in the HIV serodiscordant couples), predicting the outcome of an intervention RCT is not straightforward. Therefore, agent-based RCT simulation would become an important step in designing RCTs aimed at evaluating prevention interventions, such as vaginal and rectal microbicides, in which a complex array of factors and nonlinear interactions may impact the trial outcome [35]. For instance, the observed effectiveness of microbicides at reducing HIV infection results from a complex interplay of several components, such as sexual behavior, adherence, and the microbicide’s effectiveness [36]. Consequently, the potential effectiveness of a microbicide in reducing HIV transmission could differ among populations with different risk behavioral patterns. Therefore, the agent-based RCT simulation might aid in sample size and power calculations by integrating these behavioral characteristics for the target population.

Additionally, epidemiological evidence and outcomes from previous HIV intervention RCTs demonstrate the absence of a single “magic bullet” to control infection spreading. As a result, the HIV prevention community is currently moving towards testing multi-component HIV prevention interventions in community-based RCTs, which include evaluating universal home-based testing, antiretroviral therapy, and male circumcision [9,37]. Because each intervention component might require a different time scale for the full effect, it would be necessary to explore the development of an intervention package’s impact over time using an agent-based RCT simulation. Thus, agent-based HIV clinical trial RCT simulation could become an important tool to account for nonlinear interactions between the combination package intervention components as well as between the intervention and epidemiological context.

Thus, agent-based RCT simulations would be particularly useful for designing community-based RCTs. Far from being a direct consequence of the intervention at the individual level, the effect measured for community-based RCTs results from an interplay of the intervention and infection characteristics at the population level. In community-based trials, the level of indirect impact (herd effect) caused by decreasing HIV prevalence in the community is difficult to characterize. Moreover, agent-based simulations could account for other indirect effects that affect HIV incidence over time, thus compromising the power of the study; examples include the standard clinical care offered to the control group and the intervention scale-up in the intervention group [14,37].

Agent-based RCT simulations could also be implemented to inform trial development, monitor trial progress, and guide decision-making at latter stages of the trial. For instance, if the trial fails to measure the intervention’s efficacy after the trial has been conducted for a certain period of time, agent-based simulations using data derived from the actual trial could better inform certain decisions (such as halting the trial). This method could guide potential improvements to performing the intervention. Subsequently, the likelihood of reaching the desired intervention effectiveness during the remainder of the trial will have increased. However, the value of agent-based simulations during these trial stages depends on accessibility of data from the actual trial. As is often the case with these types of studies, the data are not easily available due to safety and data confidentiality.

In this modeling exercise, we constructed simple models to illustrate the practicality of agent-based computer simulations in designing and implementing of HIV prevention RCTs. Several study limitations and modeling assumptions may have affected our results. First, we did not include important factors that could affect the outcome for a RCT, such as treatment adherence and retention. Furthermore, other sources of individual and epidemiological heterogeneity were not included, such as age-related characteristics (e.g., number of sexual partners, number of coital acts per partnership, and condom use), different probabilities of HIV transmission according to the infection stage, variability in screening frequency, and co-infections. More realistic and complex agent-based network simulations including these factors would be more appropriate for designing new HIV prevention RCTs,
6.1. Background

The majority of HIV prevention RCTs fail to measure statistically significant efficacy for the tested interventions despite a solid epidemiological foundation for the intervention concept. In this study, we discuss implementing agent-based HIV RCT simulations as an integral step in planning, designing, and interpreting RCTs for HIV interventions. This tool would complement conventional statistical methods in designing trials by estimating the likelihood of a trial’s success and would also aid in avoiding uncertainties such as the trial subjects’ sexual behavior. In a climate of financial challenges, this approach could enhance the likelihood of a trial’s success and would also aid in avoiding evidence that obscures the effectiveness of potential interventions.

6.2. Methods

We developed agent-based Monte-Carlo models to simulate the Partners in Prevention HSV/HSV Transmission Study, variations of this study, and the Rakai Male Circumcision Trial. The models were parameterized using data from these RCTs. Each trial was simulated 1000 times, and statistical methods were implemented to assess the outcome of each trial simulation.

6.3. Results

Our analyses indicate that the Partners in Prevention Study had a low (20%) likelihood of rejecting the null hypothesis, which was no effect from the intervention. In contrast, most (96%) of the RCT realizations from a simulation with a different and more potent drug regimen for HSV-2 suppression (valacyclovir therapy) rejected the null hypothesis. For the male circumcision RCT simulation, the greater magnitude of the biological effect from male circumcision resulted in a substantial number (81%) of RCT realizations that rejected the null hypothesis.

6.4. Conclusion

Our study demonstrates the explanatory power of agent-based simulations of RCTs. It also shows how such simulations can influence HIV prevention research. A simulation approach would enhance the likelihood of a trial’s success and aid in avoiding evidence that obscures the effectiveness of potential interventions.

Conflict of interest statement

None declared.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.compbiomed.2014.03.008.

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