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Improving the validity of mathematical models for HIV elimination by incorporating empirical estimates of progression through the HIV treatment cascade

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Abstract

Background: Optimism regarding prospects for eliminating HIV by expanding antiretroviral treatment has been emboldened in part by projections from several mathematical modeling studies. Drawing from a detailed empirical assessment of rates of progression through the entire HIV care cascade, we quantify for the first time the extent to which models may overestimate health benefits from policy changes when they fail to incorporate a realistic understanding of the cascade.

Setting: Rural KwaZulu-Natal, South Africa

Methods: We estimated rates of progression through stages of the HIV treatment cascade using data from a longitudinal population-based HIV surveillance system in rural KwaZulu-Natal. Incorporating empirical estimates in a mathematical model of HIV progression, infection transmission, and care, we estimated life expectancy and secondary infections averted under a range of treatment scale-up scenarios reflecting expanding treatment eligibility thresholds. We compared the results to those implied by the conventional assumptions that have been commonly adopted by existing models.

Results: Survival gains from expanding the treatment eligibility threshold from CD4 350 to 500 cells/μL and from 500 cells/μL to treating everyone irrespective of their CD4 count may be overestimated by 3.60 and 3.79 times in models that fail to capture realities of the care cascade. HIV infections averted from raising the threshold from CD4 200 to 350, 350 to 500, and 500 cells/μL to treating everyone may be overestimated by 1.10, 2.65, and 1.18 times.

Conclusion: Models using conventional assumptions about cascade progression may substantially overestimate health benefits. As implementation of treatment scale-up proceeds, it is important to assess the effects of required scale-up efforts in a way that incorporates empirical realities of how people move through the HIV cascade.

Keywords: cascade, longitudinal, treatment as prevention, empirical

Introduction

Ambitious global targets have been established to bring an end to the HIV/AIDS epidemic. The Sustainable Development Goals and the United Nations General Assembly endorsed the goal to end the AIDS epidemic by 2030 (1,2). The Joint United Nations Programme on HIV/AIDS (UNAIDS) continues to urge countries to adopt a "Fast-Track" approach toward this goal, operationalized in terms of targets known as 90-90-90: 90 percent of people living with HIV knowing their HIV status, 90 percent of those with known status being on antiretroviral treatment (ART), and 90 percent of those on treatment with suppressed viral loads (3). While the 90-90-90 framework has been prominent in policy discussions around ending AIDS, there remain substantial gaps in the availability of evidence on attainment of the targets across countries (4).

Optimism regarding prospects for eliminating HIV stems in part from positive research findings regarding the efficacy of treatment as prevention (TasP) (5) and immediate initiation of ART upon diagnosis, known as 'test-and-treat' (6). Several mathematical models were constructed to estimate the potential health impacts of TasP. However,

models often assume treatment uptake (7–9), coverage (7,10), and adherence rates (6,7,11) that are higher than what would be expected in real life, without specifying how these high rates will be achieved nor including costs that reflect the additional activities and interventions that might be needed. In contrast to the conventional assumptions in many modeling studies, empirical studies have produced mixed results for TasP (12–15), reporting relatively poor or inconsistent results for linkage to care (12) and retention (13). Mathematical models often are instrumental in informing strategic directions towards ambitious elimination targets. As implementation of treatment scale-up continues, it is important to assess costs and effects of required scale-up efforts in a way that incorporates empirical realities of how people move through the HIV care cascade (16). This is crucial both in terms of setting realistic expectations and making feasible plans for what can be achieved at a certain cost, and for focusing on specific aspects of the cascade that require a suite of interventions that collectively comprise a scale-up strategy. While some of the existing literature have discussed the importance of reflecting the treatment cascade in HIV modeling, to date, no one has quantified the extent to which the results change when models do not incorporate a realistic understanding of the cascade. Drawing from a detailed empirical assessment of rates of progression through the HIV care cascade from an individual-level longitudinal data, this paper aims to measure the potential discrepancies between model projections and the health benefits that may be realized in real life.

Methods

This study is composed of two parts: a longitudinal data analysis from an empirical cascade of care, and the construction of two models, one that reflects the structure of the empirical cascade as well as the leakages and delays in receiving care, and another that reflects the conventional assumptions observed in published models. We compared the health benefits derived from the two models under different treatment eligibility thresholds, and estimated the incremental health benefits of increasing the threshold.

Study site and population

The Africa Health Research Institute (AHRI), located in KwaZulu-Natal, South Africa, has maintained an HIV-focused health and demographic surveillance system in the region since 2003, including individual HIV testing, annual household survey data, and clinical records. This region has a very high prevalence of HIV and poor socioeconomic indicators (17). Rates of reaching subsequent stages of the cascade were obtained through individually-linked longitudinal analysis (18) within the same population, avoiding concerns of double-counting the recurring patients as a separate individual and misclassifying deaths or those that sought care at other locations as lost to follow up (LFU) (19). Detailed description of the data source is available elsewhere (17,18).

We identified 7,707 patients with records of first HIV-positive test results, which is recorded in the surveillance data and does not reflect the time of infection nor when they first learn their positive status, and followed them through their subsequent interactions with the health system. All dates in which patients accessed care, including whether they

are aware of their positive status, enrolled in pre-ART care, and initiated ART, are recorded. Individuals were considered eligible for ART if they had a CD4 count that met the eligibility criteria, which varied over time. The eligibility threshold was CD4 count ≤200 cells/μL up to July 2011, and the threshold was raised to CD4 count ≤350 cells/μL afterwards during the study period. Every six months, pre-ART patients were scheduled to return to care to determine eligibility, and patients on ART were scheduled for follow-ups. If they did not return on expected dates, their LFU dates as well as return dates (if they return) were documented. Approximately half of the sample (n=3,533) had records of their CD4 count before or at the time of being linked to pre-ART care. Everyone was censored in January 2014. Detailed definitions of each health state and its associated activities are in Appendix S1, http://links.lww.com/QAI/B221.

Statistical analysis

First, on analyzing the empirical data, we estimated time varying monthly probabilities of transition between cascade stages. Seven transitions were estimated: (1) from undiagnosed to diagnosed; (2) from diagnosed to linked to pre-ART care; (3) from retained in pre-ART care to LFU; (4) from LFU from pre-ART to returning to pre-ART care; (5) from pre-ART care to receiving ART; (6) from retained in ART to LFU; and (7) from LFU from ART to resumed ART. Viral suppression was not routinely measured during the study period, so we were not able to include this step as a model stage. For steps between being undiagnosed to diagnosed and diagnosed to linked to pre-ART care, we applied Kaplan-Meier non-parametric survival analysis on the full dataset (n=7,707), pooled across CD4 levels, to derive the monthly transition probabilities. For steps

between being linked and lost to follow from ART, given the different rates in which people with different CD4 counts initiate and adhere to ART (20), we estimated CD4-specific monthly transition probability using Kaplan-Meier non-parametric survival analysis, stratifying the dataset by CD4 cell count at time of linkage to pre-ART care. Detailed explanations of the methods applied for deriving monthly transition probabilities for each transition are in Table S1, http://links.lww.com/QAI/B221.

Model design

We developed two discrete-time Markov models, one reflecting the structure of the empirical cascade data (the "cascade" model) and another reflecting the conventional assumptions typical of existing models (the "conventional" model), to compare the differences in the estimated health benefits between the two models. The empirically-based cascade model includes 25 mutually exclusive health states, representing four CD4 count stages, four cascade stages, two lost-to-follow-up stages, and death (as an 'absorbing' state, in modeling parlance) (Figure 1a). We applied the sets of transition probabilities along the treatment cascade described above. Model parameters related to the natural progression of and recovery from the disease and mortality were derived from published literature, listed in Appendix S2, http://links.lww.com/QAI/B221.

<Insert Figure 1a here>

In comparison to the empirically-based cascade model, the conventional model reflects more optimistic assumptions that have been typical of several existing models. In this conventional model, the cohort advances through treatment stages with minimal leakages and time delays in being linked to care (7,8,10) (Figure 1b). Nine health states were constructed, representing different CD4 count stages, treatment stages, and death. The transition probabilities were derived from published literature (7,8,10). For example, once their CD4 count drops below the eligibility criteria, they are immediately initiated on treatment, and throughout their lifetime experience low rates of dropouts (only 1.5 percent drop out every year) (7). Those who drop out return to treatment at the same rate as the treatment naïve patients.

<Insert Figure 1b here>

Both models started with a hypothetical cohort of HIV patients with CD4 counts greater than 500 cells/μL, and modeled the transitions the cohort faces along the cascade. We used a transition cycle length of one month. To ensure compatibility between the models, we standardized the proportion of people being linked to care at 86% within four years after their first positive HIV test starting from the lowest CD4 level, consistent with levels in the empirical dataset (18).

The main health outcomes of interest were HIV survival, measured as life expectancy, and HIV transmission, summarized in terms of the cumulative number of secondary infections transmitted per infected person. In order to reflect variation in transmission

risks that depend on different types of sexual risk behavior, we derived two different measures of secondary transmission, corresponding to serial monogamy and random mixing among sero-discordant partnerships. In both cases, the measures represent the number of secondary infections that would occur for each infected case in a fully susceptible population caused by this cohort (which is known as the basic reproduction number R_0). To compute secondary infections for the serial monogamy model, we used the approximation developed by Hollingsworth and colleagues. (21), which accounts for transmission hazards at successive stages of infection, rates of partner change, and the duration of each health stage. To compute secondary infections for the random mixing model we multiplied the stage-specific transmission rates by the duration of each health stage. Details on the transmission calculations are provided in Appendix S3, http://links.lww.com/QAI/B221. For both mortality and secondary transmission under the two scenarios, we estimated the distribution of these outcomes across different stages of the cascade.

Finally, we compared the incremental benefits of expanding treatment eligibility from CD4 count 200 to 350, 350 to 500, and 500 cells/μL to treating everyone. The comparisons reflect both the retrospective experience of broadening eligibility and the prospective expectation of broadening the eligibility further in the movement toward a universal test and treat approach.

We conducted one-way sensitivity analyses on all constant transition probabilities to examine the robustness of our results. In addition, we applied cascade transition probabilities from a published paper that were derived from a real-life study and compared our results to this new model.(22) All results are presented in Appendix S4, http://links.lww.com/QAI/B221.

Role of the funding source

The funders had no role in the design of the analysis, interpretation of the results, or the decision to submit for publication. The corresponding author had final responsibility for the decision to submit for publication.

Results

Empirical measures of transitions in the care cascade

Among the overall sample, 55% of those being diagnosed transitioned to pre-ART care within four years of their first positive HIV test. Before July 2011 when treatment eligibility threshold in South Africa was CD4 200 cells/μL, among those with a CD4 record (n=1,947), 53, 73, 70, and 81% of people with CD4 of less than 200, 200-350, 350-500, and above 500 were LFU from pre-ART care. Among those with CD4 less than 200 cells/μL and were linked to pre-ART (n=1,248), 82% initiated ART, and no one with a higher CD4 count initiated ART. Among those who initiated ART (n=1,024), 28% were LFU during the study period. Between July 2011 and January 2014 when treatment

eligibility threshold was CD4 350 cells/μL, among those with a CD4 record (n=379), 31, 44, 35, and 37% of people with CD4 of less than 200, 200-350, 350-500, and above 500 were LFU from pre-ART care. Among those with CD4 less than 200 and 200-350 cells/μL, 73% (n=119) and 71% (n=77) of initiated ART, and among them, 8 and 17% were LFU from ART, respectively (Table 1).

<Insert Table 1 here>

Estimated life expectancy in empirical cascade model and conventional model

Under the empirical cascade model, life expectancy for a cohort of HIV patients with CD4 greater than 500 cells/μL was estimated to be 16.9, 20.7, 23.9, and 24.6 years under the treatment eligibility criteria of CD4 count 200, 350, 500 cells/μL and treating all individuals with HIV, respectively. In comparison, life expectancy estimates under the conventional model given the four eligibility thresholds were 17.9, 22.0, 33.6, and 36.3 years (Figure 2a). In looking at the distribution of mortality by cascade stages, in the empirical model, the majority of deaths occur before pre-ART care, since more than half of the population stay in this stage without ever being linked to pre-ART care or initiating ART (Figure 3a). Expansions of treatment eligibility lead to increases in the proportion of deaths occurring during treatment, reflecting risks of death from causes other than AIDS. Changes in the eligibility threshold have a more pronounced effect on the distribution of mortality in the conventional model, from 10% of deaths occurring in treated patients with eligibility at CD4 200 cells/μL to 82% when everyone is treated irrespective of CD4.

<Insert Figure 2a-c here>

<Insert Figure 3a-b here>

Estimated infections averted by treatment in empirical cascade model and conventional model

The numbers of estimated secondary infections transmitted by each source infection were higher in the empirical cascade model than in the conventional model for both behavioral scenarios. Under the random mixing scenario, there would be an estimated 2.14, 2.09, 1.84, and 1.29 secondary infections per case under the four treatment eligibility criteria, respectively (Figure 2b). The majority of transmissions would occur before the person is linked to pre-ART, and the proportion would decrease with higher treatment thresholds (Figure 3b). In comparison, the number of secondary infections per case would be 1.74, 1.68, 1.14, and 0.46 in the four different eligibility criteria, respectively, in the conventional model. Nearly all transmissions occur when patients are undiagnosed under most treatment thresholds. When treatment is available to everyone irrespective of CD4 count, 31% of transmissions occur among people on ART because the time spent being on treatment is much longer than not being on treatment, compared to less inclusive treatment threshold scenarios. Under the serial monogamy scenario, the numbers of secondary infections per case were estimated at 1.54, 1.53, 1.40, and 0.92 in the empirical cascade model, and 1.27, 1.26, 0.92, and 0.35 in the conventional model, respectively (Figure 2c).

<Insert Figure 3a-b here>

Incremental benefits from expanding treatment eligibility

Considering the benefits in moving from one eligibility criterion to the next, we estimated smaller health benefits with each expansion of treatment eligibility in the empirical cascade model compared to the conventional model, reflecting the impact of the cascade (Table 2), and the differences were especially pronounced as more inclusive eligibility criteria were adopted. In the empirical cascade model, raising the eligibility criteria from CD4 count 200 to 350 cells/μL increased population life expectancy by 45.9 months (3.8 years) and reduced the average number of new infections caused by an individual by 0.04 (2.0%) and 0.01 (0.7%) for the two behavioral scenarios, respectively. The conventional model suggests slightly greater health benefits with this expansion of eligibility, producing an increase in life expectancy by 49.5 months (4.1 years) and a reduction in secondary infections by 0.06 (3.5%) and 0.01 (0.8%) for the two behavioral scenarios, respectively. In comparison, increasing the treatment threshold from CD4 500 cells/μL to treating everyone would add only 8.7 months (0.7 years) of life expectancy in the empirical cascade model, compared to 32.9 months (2.7 years) in the conventional model, and to reduce secondary infections by 0.54 (29.3%) and 0.48 (34.3%) under both behavioral scenarios, compared to 0.68 (59.6%) and 0.57 (62.0%) in the conventional model.

Comparing the two models in relative terms, the conventional model produces estimated increases in health outcomes (both life years gained and transmissions averted) that are slightly greater, at 1.08 to 1.38 times, than those in the empirical cascade model under an eligibility expansion from CD4 count 200 to 350 cells/μL, 2.09 to 3.60 times higher with a change from 350 to 500 cells/μL, and 1.18 to 3.79 times higher with the expansion from 500 cells/μL to treating everyone.

<Insert Table 2 here>

Discussion

In this study, we compared the expected health benefits from expansion of ART treatment eligibility under two different models, one that reflects conventional assumptions found in a number of prior models and another that reflects the structure and empirical observations of a cascade of care. The main finding of this study was that conventional models that do not account for the delays and leakages in the continuum of HIV care may be substantially overestimating the health benefits gained from these policy changes, by up to nearly four-fold.

The current World Health Organization guideline recommends ART to be initiated in everyone living with HIV at any CD4 count (23), and evidence on the incremental health benefits or cost-effectiveness of expanding from one treatment eligibility criterion to another are needed to make decisions. Overestimation of health benefits associated with expansion of eligibility may lead to unrealistic expectations that can be counterproductive:

on a more general level, if overly optimistic predictions guide resource allocation and program planning, some programs may seem cost-effective due to higher predicted benefits or lower predicted program costs, even though in reality they may not be, and may contribute to adoption of sub-optimal decisions and policies. Finally, our findings also emphasize the need for effective interventions to increase HIV testing and ART linkage, retention and adherence to realize the promise of HIV treatment-as-prevention.

Many conventional models implicitly assume that the targets of achieving high linkage, high retention, and minimal delays can be achieved without additional resources (6–10). For example, by applying a HIV testing rate of 90 percent (7), the models assume that no additional investments for outreach programs are needed to increase testing rates from baseline, which is often much lower than 90 percent. In light of the specific findings in our study, of potential for substantial bias, we suggest that models should either reflect the leakages and delays in the treatment cascade, which will reduce the estimated incremental health benefits, or assign costs that are associated with programs that have demonstrated effectiveness in increasing of testing (24), linkage (25), and adherence rates (26,27), which will increase costs.

Our study has several limitations. First, there are limits to the generalizability of the specific numerical findings from the AHRI to other settings, including its high HIV prevalence observed in a rural sub-Saharan African population. Others have estimated the potential impact of TasP and/or raising treatment thresholds in other context (10,28). For example, the SEARCH trial in rural Kenya and Uganda achieved a significant

improvement in linking individuals with HIV to care and high levels of retention in care through a resource-intensive HIV test-and-treat strategy (14,29,30). As data accumulate on the HIV treatment cascade in a range of settings, we expect that the general finding in this paper, on overestimation of health benefits (or underestimation of resources required) attributed to changes in treatment eligibility, may be broadly applicable. Second, we created a model using empirical data for both simplicity and to avoid modelling assumptions. Estimates of the effects of the treatment cascade on HIV incidence and mortality are approximations based on a cohort analysis, which confines our results to two summary outcomes of benefit, whereas more sophisticated models allow for more detailed characterizations of the dynamics of evolving epidemics and estimation of a broader range of outcomes. However, we have designed the analysis such that the conventional model reflects commonly applied assumptions used in published literature. For example, the estimated percentage reductions in secondary transmission from increasing eligibility from CD4 350 to 500 cells/μL, and to treating everyone irrespective of their CD4 count are comparable to those in prior published models (6–8). We intentionally created a simplistic model with straightforward computations to devise heuristics regarding the potential magnitude of cascade effects on HIV transmission and mortality. We did not account for the heterogeneity of sexual behaviors in the population, including possibly different sexual mixing behaviors by CD4 counts, as well as background scale ups of programs such as PrEP and voluntary medical male circumcision, all of which may impact our estimates. Third, the use of a Markov model assumes that the probability of moving between states in the model does not depend on the states a patient may have experienced before entering that state, which is a limitation here, as it is

in many other models. Those who were linked to pre-ART care longer may be more likely to be adherent when they receive ART, or those that were LFU at some point may have a higher probability of becoming lost again. Fourth, to ensure comparability between the models, we applied a constant transition rate from being undiagnosed to diagnosed, based on empirical estimates. This is likely not reflective of reality, however we cannot determine whether this assumption over- or under-estimates the results. Fifth, empirical estimates on the transition rates for higher threshold scenarios are not available because they were not implemented during the study period. Our assumptions of how the transition rates would change were based on empirical estimates of hazard ratios between two lower threshold scenarios. However, it is unclear which direction we are biased towards: we may be underestimating the transition rates since people may be getting linked to care much faster with more inclusive thresholds, or overestimating since people are in general healthier and may be lost to follow up more frequently. Finally, we acknowledge that accurate estimation of both costs and health effects are critical in generating a cost-effectiveness study to answer a specific policy question. Due to lack of data we do not explore how the cost of implementing HIV care programs is impacted by the treatment cascade.

The need for modeling studies to inform decisions regarding alternative policy scenarios will persist as the global public health community continues to advance towards goals for HIV elimination. This paper aims to facilitate better decision making by highlighting the importance of capturing the empirical realities of the care cascade in HIV models and

quantifying the magnitude of overestimation of health benefits from policy changes when analyses do not include an accurate accounting for these factors.

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Figure 1a-b. Schematic view of the mathematical models

Arrows indicate transitions between states. Arrows that exit a state but do not point to another state represent mortality.

Figure 1a. Empirical cascade model

Figure 1b. Conventional model

Figure 2a-c. Comparison of health benefits under the conventional and empirical cascade models, by treatment eligibility

2a. Life expectancy

2b. Secondary transmission under random mixing scenario

2c. Secondary transmission under serial monogamy scenario

Figure 3a-b. Distribution of mortality and secondary HIV transmission (random mixing) by cascade stages

Figure 3a. Mortality

Undx: undiagnosed, Dx: diagnosed, ART: antiretroviral therapy, LE: life expectancy, LFU: lost to follow up.

conventional all/500/350/200: the conventional model with treatment threshold of treating everyone, CD4 count 500, 350, 200 cells/μL.

cascade all/500/350/200: the empirical cascade model with treatment threshold of treating everyone, CD4 count 500, 350, 200 cells/μL.

Figure 3b. Secondary HIV transmission (random mixing)

Undx: undiagnosed, Dx: diagnosed, ART: antiretroviral therapy, LE: life expectancy, LFU: lost to follow up.

conventional all/500/350/200: the conventional model with treatment threshold of treating everyone, CD4 count 500, 350, 200 cells/μL.

cascade all/500/350/200: the empirical cascade model with treatment threshold of treating everyone, CD4 count 500, 350, 200 cells/μL.

Table 1. Descriptive statistics of the HIV care cascade

		Proportion of people who transitioned to the next stage among those who reached the previous stage			
	Observed time period	CD4 >500 cells/μL	CD4 350-500 cells/μL	CD4 200-350 cells/μL	CD4 <200 cells/μL
Diagnosed → pre-ART	Jan 2004 - Jan 2014	55 %			
Pre-ART → loss to follow up under treatment threshold CD4 <200 cells/μL	Jan 2004 - Jul 2011	81 %	70 %	73 %	53 %
Pre-ART → loss to follow up under treatment threshold CD4 <350 cells/μL*	Aug 2011- Jan 2014	37 %	35 %	44 %	31 %
Pre-ART → ART initiation, under treatment threshold CD4 <200 cells/μL	Jan 2004 - Jul 2011	0 %	0 %	0 %	82 %
Pre-ART → ART initiation, under treatment threshold CD4 <350 cells/μL	Aug 2011- Jan 2014	0 %	0 %	71 %	73 %
ART care → loss to follow up under treatment threshold CD4 <200 cells/μL	Jan 2004 - Jul 2011	0 %	0 %	0 %	28 %
ART care → loss to follow up under treatment threshold CD4 <350 cells/μL	Aug 2011- Jan 2014	0 %	0 %	17 %	8 %

ART: antiretroviral treatment

Table 2. Incremental benefits of changing treatment eligibility

		Incremental benefit of eligibility change from CD4 200 to 350	Ratio of incremental benefits, conventional to cascade	Incremental benefit of eligibility change from CD4 350 to 500	Ratio of incremental benefits, conventional to cascade	Incremental benefit of eligibility change from CD4 500 to treat all	Ratio of incremental benefits, conventional to cascade
Gain in life expectancy (months)	Conventional	49.5	1.08	138.8	3.60	32.9	3.79
	Cascade	45.9		38.6		8.7	
HIV infections averted (random mixing)	Conventional	0.06	1.38	0.53	2.09	0.68	1.26
	Cascade	0.04		0.26		0.54	
HIV infections averted (serial monogamy)	Conventional	0.01	1.10	0.34	2.65	0.57	1.18
	Cascade	0.01		0.13		0.48	

Figure 1a

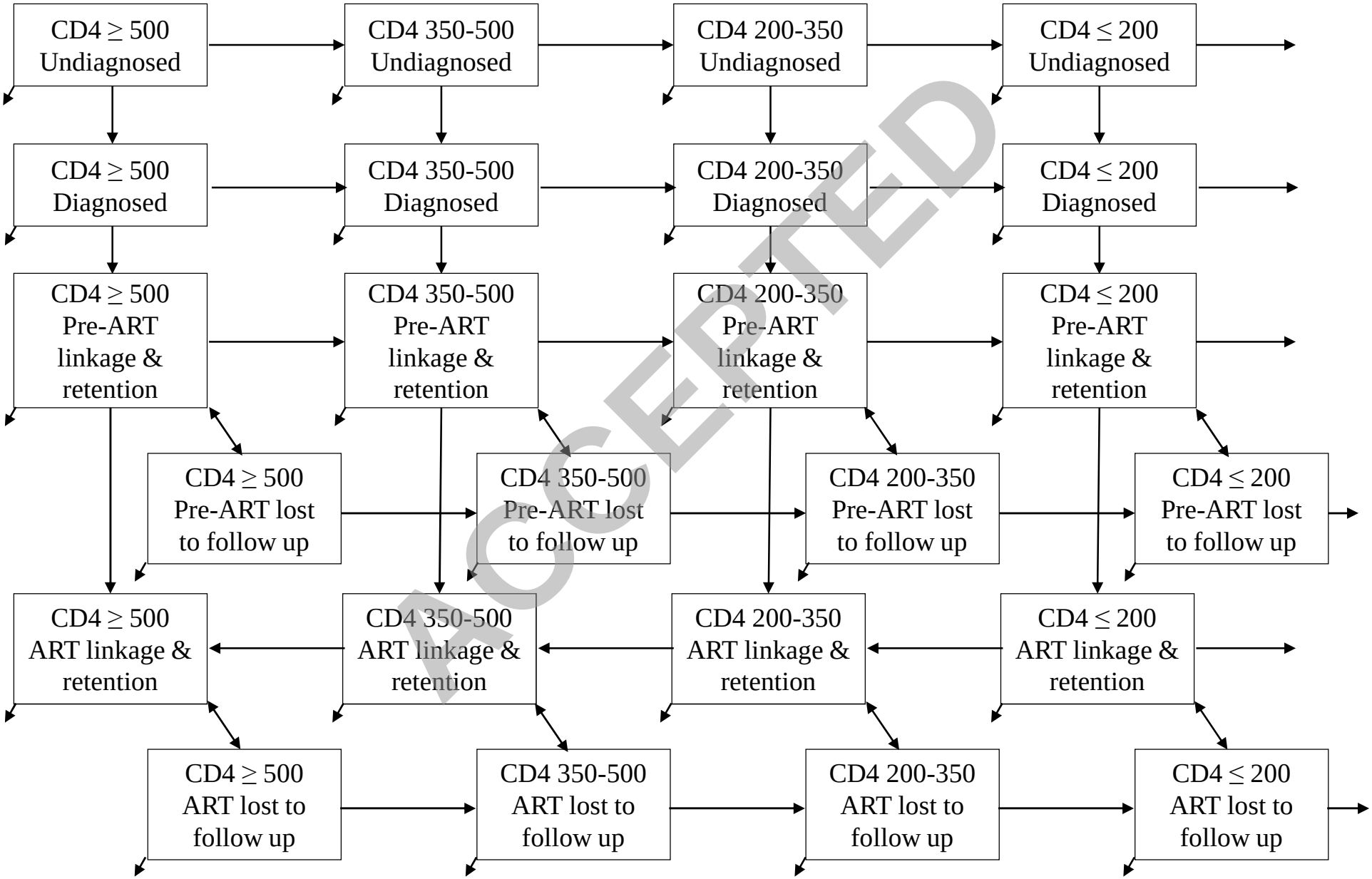


Figure 1b

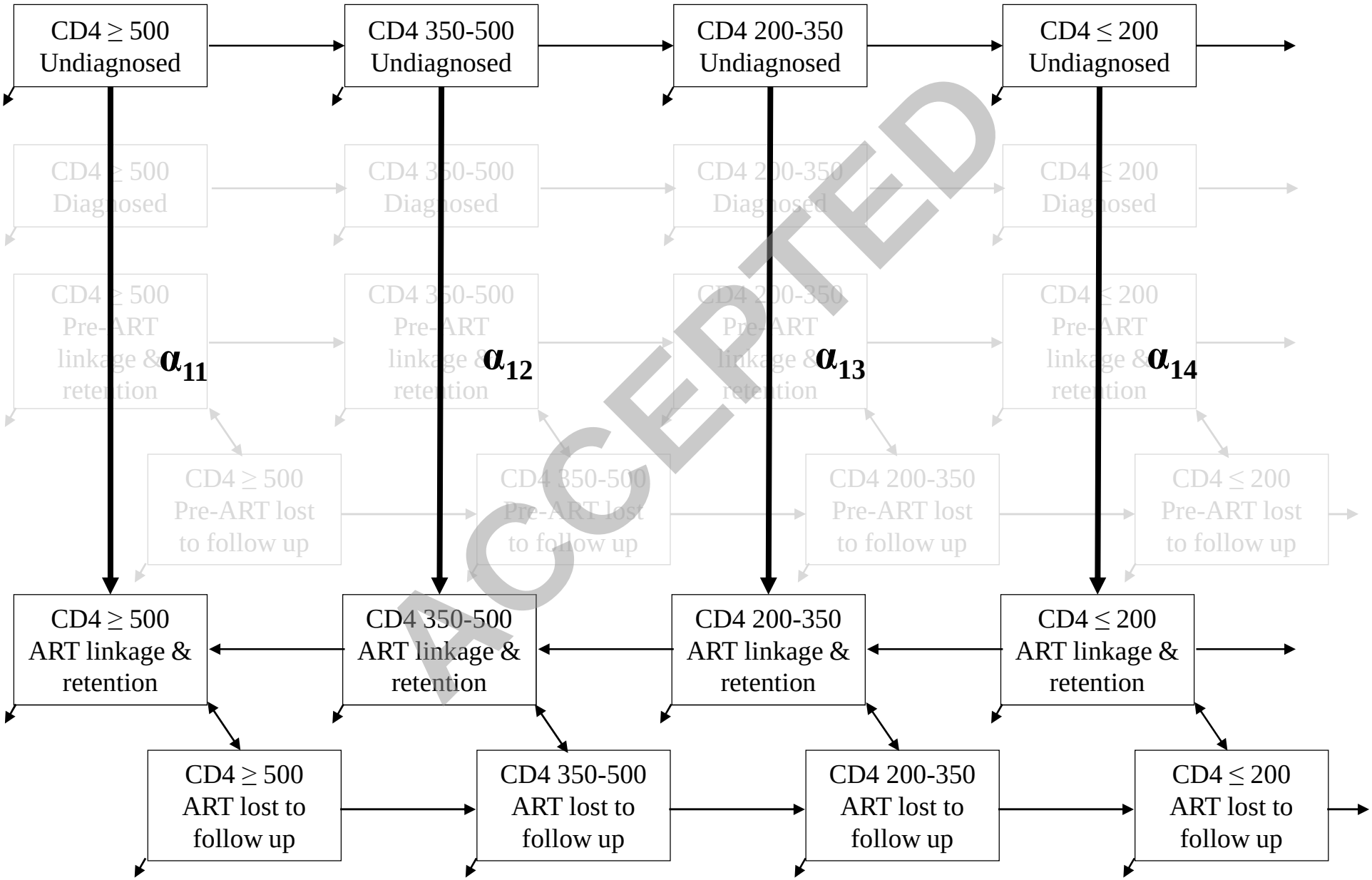
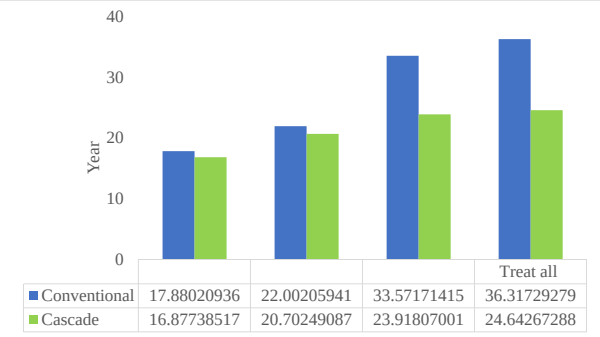
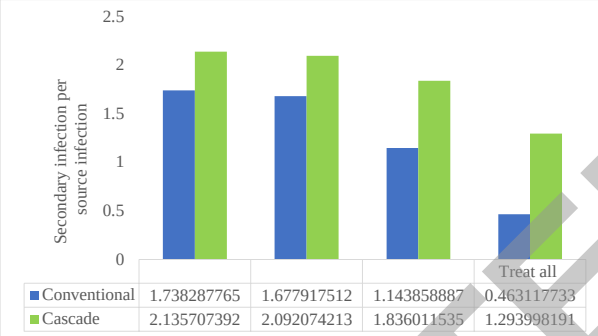


Figure 2a



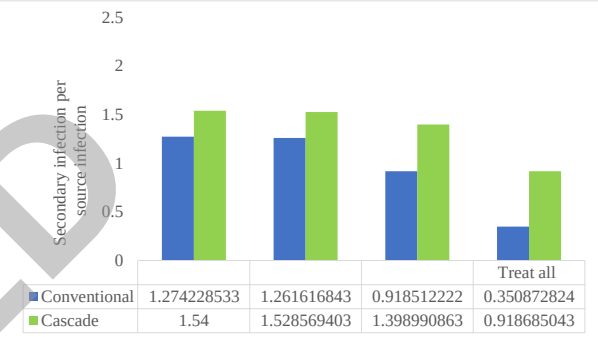
				Treat all
Conventional	17.88020936	22.00205941	33.57171415	36.31729279
Cascade	16.87738517	20.70249087	23.91807001	24.64267288

Figure 2b



				Treat all
Conventional	1.738287765	1.677917512	1.143858887	0.463117733
Cascade	2.135707392	2.092074213	1.836011535	1.293998191

Figure 2c



				Treat all
Conventional	1.274228533	1.261616843	0.918512222	0.350872824
Cascade	1.54	1.528569403	1.398990863	0.918685043

Figure 3a

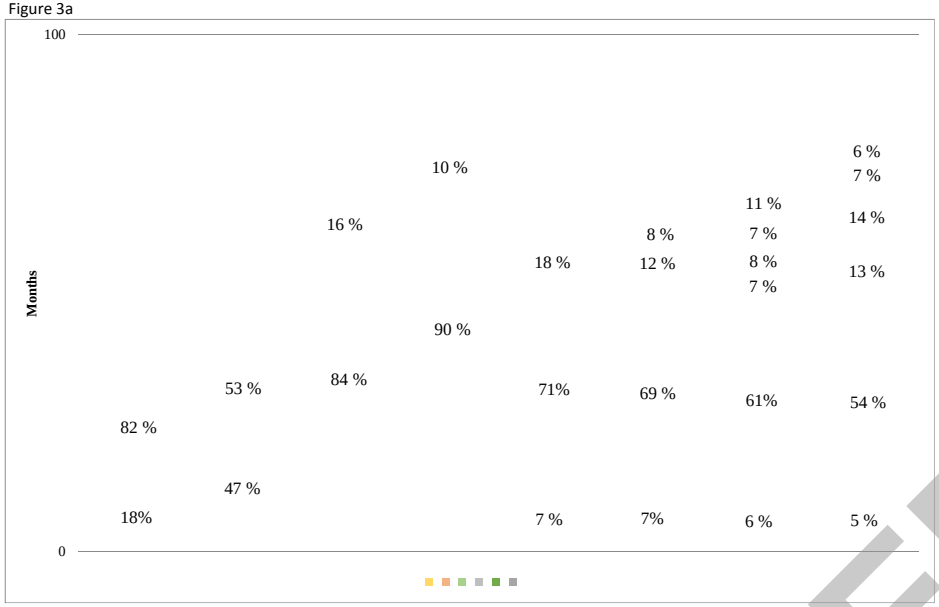


Figure 3b