AIDS. Author manuscript; available in PMC 2010 September 13.

Published in final edited form as:
AIDS. 2010 March 13; 24(5): 729–735. doi:10.1097/QAD.0b013e32833433fe.

Examining the Promise of HIV Elimination by 'Test and Treat' in Hyper-Endemic Settings

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Abstract

Background—It has been suggested that a new strategy for HIV prevention, "Universal Test and Treat", whereby everyone is tested for HIV once a year and treated immediately with antiretroviral therapy (ART) if they are infected, could 'eliminate' the epidemic and reduce ART costs in the long-term.

Methods—We investigated the impact of Test and Treat interventions under a variety of assumptions about the epidemic using a deterministic mathematical model.

Results—Our model shows that such an intervention can substantially reduce HIV transmission, but that impact depends crucially on the epidemiological context – in some situations less aggressive interventions achieve the same results, whilst in others the proposed intervention reduces HIV by much less. It follows that testing every year and treating immediately is not necessarily the most cost-efficient strategy. We also show that a Test and Treat intervention that does not reach full implementation or coverage could, perversely, increase long-term ART costs.

Conclusions—Interventions that prevent new infections through ART scale-up may hold substantial promise. However, as plans move forward, careful consideration should be given to the nature of the epidemic and the potential for perverse outcomes.

Introduction

The rate of new HIV infections has stabilised in recent years (2.7 million infections in 2007 [1]) and concomitantly the global number of those infected on anti-retroviral treatment has increased dramatically [2]. Despite this, the rate of new infections in developing countries still out-paces the rate at which individuals are started on treatment [2] and there is growing concern that this situation is unsustainable [3, 4]. Incidence must be further reduced, but disappointingly few HIV interventions have been shown to be effective in randomised controlled trials in developing countries: behaviour changes following counselling and testing are likely to have a minimal effect or even increase incidence [5, 6]; two models of peer-education for promoting reductions in risk behaviour have failed [7, 8]; risk compensation and low adherence potentially contributed to no effect being found in trials to prevent HIV infection through diaphragm use [9] and herpes treatment [10]; and, in the last year another trial of herpes treatment showed no effect on the rate of HIV transmission from co-infected individuals [11]. These results bring the tally of trials showing no efficacy in

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Contributions The paper was jointly conceived and written by the authors.

Conflicts We declare no conflicts of interest exists.

reducing HIV incidence to more than 30 [12]. Male circumcision has been shown to reduce the risk of men acquiring infection [13-15], although it is understood that this will not be enough to eliminate HIV, even under the most optimistic conditions [16, 17].

In contrast, scale-up of ART has substantially reduced mortality [2, 17-19]. As the availability of treatment expanded, Montaner *et al.* proposed using treatment as an intervention to prevent infection [20], and Grannich *et al.* recently used a mathematical model to evaluate that argument [21]. The model suggested that in a high prevalence setting, with incidence of 2/100 person-years at risk (pyar), an intervention that tested everyone annually and initiated treatment immediately if they were infected ("Universal Test and Treat" intervention), could reduce incidence to below 1/1000 pyar – more than a 95% reduction (described by the authors as elimination). The model predicted that despite high costs during the roll-out phase, long-term ART costs would be much lower than the current strategy of treating on the basis of clinical need.

This result has stimulated extensive comment and sparked interest in rolling-out "Test and Treat" type interventions [22-28]. However, it is worth further exploring the findings since the model provided a limited representation of some aspects of HIV epidemiology and investigated only one type of intervention in one type of epidemiological context. In this article we investigate the potential of alternate test and treat interventions under a range of contexts, and using a different mathematical model that incorporates updated information on the course of HIV infection and transmission rates on treatment along with a more explicit exploration of the potential role of heterogeneity in sexual risk behaviour [29, 30].

Methods

An HIV transmission model was developed that was defined by a set of partial differential equations incorporating variation in sexual risk behaviour [31], changes in HIV transmissibility over the course of infection [29] and observed HIV survival rates from an African setting [32] (full technical details in online appendix). In the model there are two sub-populations, with key parameters being the relative degree of risk-behaviour for acquiring/transmitting infection between the two (π), the relative size of the lower risk sub-population (θ), the value of basic reproductive number in that sub-population (R_0^L), and the degree of sexual contact between individuals in the two sub-populations (ε). It was assumed that the relative size of the two risk-groups remained constant over time [33].

We modelled different "Test and Treat" interventions by altering the time since infection that treatment is started, and assuming that individuals on treatment are, on average, 13-fold less infectious than untreated individuals [30, 34]. Since patients tend to live longer on ART if they start treatment earlier [18, 35], survival on treatment was related to the timing of initiation, with a maximum of 28 years overall survival if treatment is started within one year of infection (sensitivity analyses showed that the results could be reproduced assuming no relationship between survival and timing of ART initiation). The timing of treatment initiation was related to the interval between HIV tests, and the expected average CD4 cell count at initiation. The trend in CD4 cell count over time since infection was calculated using information from a recent a meta-analysis [36] showing mean time from infection to a level of 200 cells/microlitre of 7.6y, and other observational data of the rate of CD4 cell decline during earlier HIV infection among African populations [37].

The impact of the intervention was evaluated in different types of populations where the epidemic was sustained in the both groups or only the higher risk group (R_0^L=1.1 or R_0^L=0.7), and where mixing between the two groups was extensive or limited (ε = 0.1 or ε =

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0.9). In each case, we assumed that most of the population was at lower risk and a small minority was at higher risk, in accord with observational studies [31]. The π parameter was then adjusted so that the HIV incidence rate was exactly the same in each scenario: 1.5/100 pyar before the intervention, which is typical of many countries in Eastern and Southern Africa currently [1]. Thus, the three scenarios were: (*A*) more homogenous distribution of risk ($\pi = 1.6, \theta = 0.9, R_0^L = 1.1, \varepsilon = 0.5$); (*B*) heterogeneous risk distribution with random mixing ($\pi = 4.3, \theta = 0.9, R_0^L = 0.7, \varepsilon = 0.1$); (*C*) heterogeneous risk distribution with assortative mixing (i.e. most sex contacts are between individuals in the same sub-population) ($\pi = 13.1, \theta = 0.9, R_0^L = 0.7, \varepsilon = 0.9$).

It was assumed that the sensitivity and specificity of the HIV test was 100%.

We quantify the impact of the intervention as the reduction in incidence at equilibrium following its introduction, compared to the pre-intervention incidence rate. Treatment load was calculated as the fraction of individuals in the population that are on treatment at equilibrium. Annual costs per capita of the intervention are approximated by summing the product of the number on treatment and $800, and the product of the annual number of HIV tests and $10 (JG Kahn, *personal communication*), assuming a fixed population size. A cost-efficiency measure was calculated as the reduction in equilibrium incidence divided by annual costs per capita.

Results

Our results broadly confirm the main findings of Montaner *et al.* [20] and Grannich *et al.* [21]: treatment has the potential to substantially reduce HIV transmission. Figure 1 shows the eventual predicted impact of Test and Treat interventions under three different epidemiological contexts. The contour lines indicate the reduction in incidence for an assumed level of coverage (vertical axis) and treatment start time (horizontal axis). Two other horizontal axis show how this treatment start time corresponds to the average interval between tests required to initiate treatment at that time, and the average CD4 cell count (per microlitre) among patients starting treatment. As expected, the impact is greater with higher coverage levels and earlier initiation of treatment (top-left corner of each panel). However, we also find that the expected impact varies depending on the epidemiological context assumed. In a population with a more even risk distribution (‘Scenario A’), testing 80% of the population every two years and treating immediately, is expected to reduce incidence by more than 95% (Figure 1(a)). The same intervention in a population with greater variation in risk (‘Scenario B’), generates a smaller impact, reducing incidence by ~85% and fails to reduce the epidemic to the level termed ‘elimination’ [21] (Figure 1(b)). In this scenario, all individuals would need to be treated within 1 month of infection for incidence to be reduced by 95%. If more partnerships are formed between individuals in the same sub-population (‘Scenario C’), incidence is reduced by ~60% if individuals start treatment 1 year after infection (Figure 1(c)). The reason is that in scenarios B and C, transmission is more dependent on a few individuals who spread infection rapidly once infected.

Our analysis shows that, depending on the epidemiological context, similar reductions in HIV incidence could be generated by less ambitious interventions. For instance, in a population with little variation in risk behaviour and random mixing (‘Scenario A’), incidence is still reduced by 95% if 80% of the population is tested only every 3-4 years, corresponding to a mean CD4 cell count at initiation of 400 cells per microlitre.

In each case, it would take ~30 years for these reductions in incidence to be fully realised, and there is the potential for incidence rates to rebound as the first cohorts starting treatment progress to AIDS (see Figure 2 in the Technical Appendix).

We investigated the impact and approximate costs of implementing the test and treat intervention where the intervals between HIV tests ranged between 1 and 20 years (Figure 2). Although shorter intervals between tests lead to greater reductions in incidence, the convex shape of the curves indicates a ‘diminishing returns’ relationship (Figure 2(a)). The sharp up-turn in the impact if individuals are tested more frequently than every 6 months reflects treatment interrupting the period of primary infection when individuals are highly infectious.

The numbers on treatment at equilibrium and the numbers of tests each year for alternative test and treat strategies are shown in Figure 2(b and c). For 80% coverage, the treatment load increases as the interval between testing is reduced from 15 to 10 years, since more treatment is provided to those in late-stage disease, without an associated large effect on HIV transmission. Further decreases in the interval between testing from every 10 to 1 years leads to lower treatment loads, since, in this phase, ART is directly reducing the endemic level of HIV and treatment needs. In contrast, if the test and treat intervention is scaled-up to only 30% or 50% of the population, more testing give greater years on treatment per person without attracting large reductions in incidence, so the ART load only increases.

An approximate indication of cost-efficiency is presented in Figure 3. The highest parts of the curves correspond to the test and treat strategy that generates the greatest reduction in incidence per unit cost. The optimal position varies according to the epidemiological context, the level of coverage achieved and the relative costs of treatment and testing. For more fragile epidemics (‘scenario A’ (Figure 3(a)), the optimal strategy is testing every 4-5 years or initiating treatment at a CD4 count 350-400 cells per microlitre. Here, the position of the optimum at 80% coverage is determined largely by the frequency of testing that is necessary for HIV elimination.

For the most robust epidemic (‘scenario C’ (Figure 3(b)), the optimal strategy (at 80% coverage) is testing every 2-3 years, corresponding to treatment at CD4 count above 450 cells per microlitre. In this scenario, the optimum is determined by a balance between providing ART for longer and the greater reductions in incidence, as the testing interval decreases.

For scenario B, the optimum is 1-2 years; the suggested strategy of Granich et al. [21]. Here, equilibrium treatment loads do not change substantially with testing frequency since the increased duration of treatment is almost exactly offset by concomitant reductions in incidence; so, the position of the optimum is mainly determined by the relative costs of treatment and testing.

Discussion

It is important that our modelling approach (incorporating recent estimates of transmission in acute infection, transmission rates on treatment and heterogeneity in sexual risk behaviour) has partially confirmed the finding that earlier initiation of ART can lead to substantial reductions in HIV transmission [20, 21]. However, our analysis has highlighted three important aspects of ‘Test and Treat’ interventions that should be carefully considered as plans for implementing such an intervention move forward. First, the impact of the intervention depends crucially on the epidemiological context: under some circumstances, we find the effect to be as large as estimated by Grannich *et al.* [21] but in others, the effect is much less. The context is proximally determined by many properties of the sex partner network (such as heterogeneity, concurrency and mixing [38, 39]), and it is not easy to determine which of the modelled contexts (A, B or C) is most like a particular population. Thus, earlier model assumptions [21], accurately represent a particular population even if the prevalence/incidence level appear similar (i.e. the fit of a model to data does not imply the model is validated). The uncertainty in the specification of the epidemiological context can be reduced by incorporating local behavioural data into more detailed models of HIV transmission [40], but the remaining variance in projections should be fully reflected in cost-effectiveness calculations. It is likely that the 'Test and Treat' approach is much better suited to some populations and poorly suited to others.

The second main finding is that although increasing the frequency of testing does lead to a larger reduction in HIV transmission, there are diminishing returns for increasing testing frequency to the once-per-year levels proposed in Granich *et al.* [21]. Under some situations, much later initiation can still stall the epidemic. Grannich *et al.* [21] suggest that testing every year and treating immediately was an effective and cost-saving strategy compared to later initiation, but, in our model, the most cost-efficient strategy could be testing everyone 3-5 years, depending on the epidemiological context and the coverage achieved (Figure 3). However, the position of the optimum is highly sensitive to aspects of the epidemic context, life expectancy on treatment and relative costs of treatment and testing, especially when interventions do not reach universal coverage, making it difficult to formulate firm recommendations without further information and specification.

Our third main finding was that whilst a high coverage implementation of test and treat could lead to reductions in incidence and ART use, failing to achieve sufficiently high coverage levels or failing to test frequently enough, could just lead to a dramatic spiralling of treatment costs. In this scenario, the intervention does not interrupt transmission, so the pool of those developing treatment needs continues to grow. It is essential that this eventuality is avoided, especially in the many countries where health-care systems already struggle to provide care for HIV-infected patients in clinical need. Losses to follow-up, imperfect adherence or the evolution of resistance [41, 42] could all contribute to reducing the effective coverage of the programme.

Our analysis was intended to provide qualitative insights rather than precise quantitative predictions about the effect of test and treat interventions, and we have not considered the logistical challenges presented by implementing such an intervention. Thus, our estimates of cost and cost-efficiency analysis are simplified, and our consideration of the epidemic is most focussed on the equilibrium incidence level. The impact and costs of the roll-out phase of interventions is therefore not fully captured in all our analyses. Also, our modelled costs are not sensitive to scale, as they can be in practice [43] (e.g. through clinicians' time being occupied with testing rather than other activities), and we have not explicitly considered the increased chance of adverse events, toxicities and viral evolution and need for second-line therapies associated with long-term use of ART [42, 44]. To reinforce our main findings, in this analysis we have we not included how the chance the complying with repeat testing and treatment can vary according to how frequently tests and offered, nor how sexual behaviour can change as a result of learning one's sero-status where HIV negative or positive [45, 46]. This could mean that our estimates of costs for testing very frequently are under-estimated, and if this were reflected in our analysis, the optimum test and treat strategy would be longer intervals between tests. However, we have also not quantified the extra life-years saved associated with earlier treatment initiation, nor how the chance of stopping treatment or developing resistance and moving to second-line therapies could depend on the timing of initiation [18, 35], which may favour more frequent testing. All these factors interact with the generalisable issues we have highlighted in this paper, and will demand attention in further modelling work tailored to specific settings. The model does not explicitly capture

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the real variation in the risk of transmission between different sexual partnerships due to the frequency of sex, presence sexually transmitted infections and condom use, and although this detail is not expected to affect the findings presented here, incorporating these factors in further models will improve the specification of the epidemiological context and precision of the projections.

The impact of many interventions, including test and treat, can be amplified by targeting to those that are most at risk of acquiring and transmitting infections [47]. Therefore, in the generalised epidemics in southern Africa, testing women in beer halls [48] and truck drivers [49] most often might improve impact and cost-efficiency. The extent of that amplification also depends on the epidemiological context (especially extent of contact between higher and lower risk individuals [50]), so that the advantage of targeting would be modest in some situations (eg. Scenario A) but great in others (e.g. Scenario C). Combining interventions can also lead to synergies, so that applying two interventions together leads to increases in effectiveness [47]. Therefore, the opportunity to counsel those testing HIV-negative, promoting behaviour change to reduce the risk of infection [5, 46], should not be missed.

We conclude that leveraging the infrastructure and capacity that have so rapidly grown-up to support the expansion of ART programmes in Africa to also reduce HIV transmission is a promising strategy. However, by failing to capture some important features of HIV epidemiology, over-optimistic projections can be generated. It is also essential to recognise testing every year is not necessarily the most cost-efficient strategy, and that failing to fully implement the test and treat strategy could perversely lead to overall increased long-term ART costs.

Acknowledgments

For funding support, TBH thanks The Wellcome Trust and GPG thanks MRC and UNAIDS.

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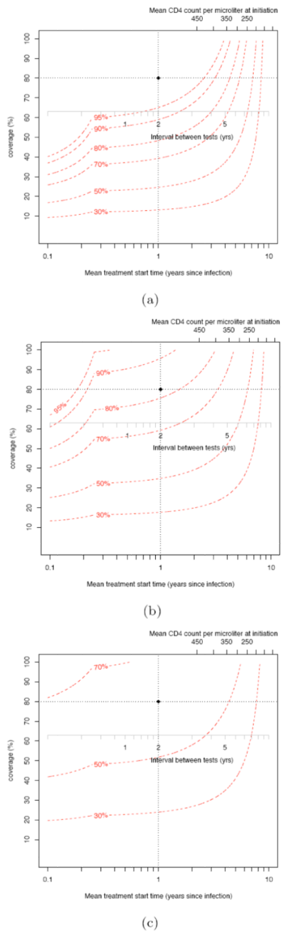

Figure 1. The impact of Test and Treat interventions depends on epidemiological context
Panels show impact of ART on incidence (percentage reduction) as contour-lines, with respect to coverage of the intervention (vertical axis), the mean years after infection that treatment is begun (horizontal axis), and the corresponding mean CD4 count at initiation (horizontal axis) and required interval between tests (horizontal axis). Panels show three types of epidemiological context: (**a**) Scenario A - Even risk distribution; (**b**) Scenario B - Heterogeneous risk distribution with random mixing; (**c**) Scenario C - Heterogeneous risk distribution with assortative mixing.

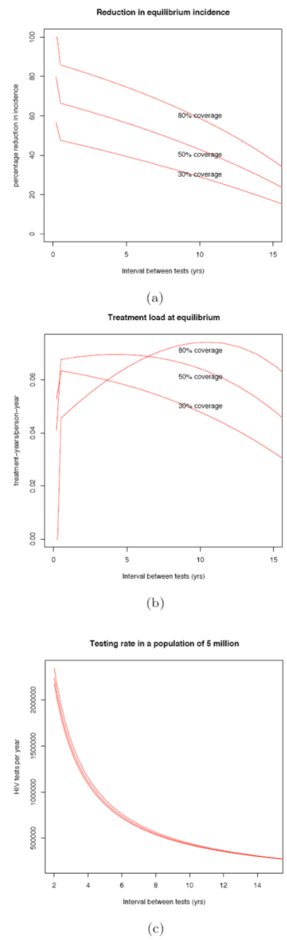

Figure 2. Test and Treat impact and costs

(**a**) Reduction in incidence (%) versus mean interval between HIV tests (years). (**b**) Person-years on ART required at equilibrium (as fraction of population) versus mean interval between HIV tests (years). (**c**) Number of tests per year at equilibrium (assuming population of 5 million adults) versus mean interval between HIV tests (years). Parameters values are for ‘Scenario B’ (described in the text). Note that treatment-years person-years is approximately equal to T/N, T is the number people on treatment that year, in a population of size N.

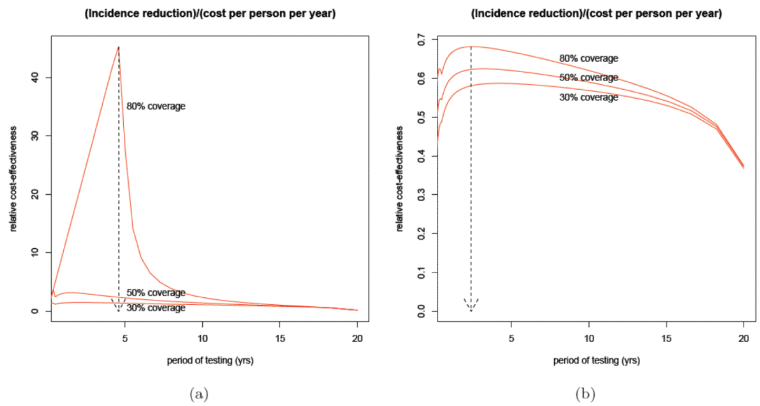

Figure 3. Test and Treat cost-efficiency

Cost-efficiency of the intervention (reduction in incidence divided by ART and HIV testing costs) of test and treat interventions reaching 30, 50 or 80% of the population, in epidemiological context Scenario A (panel **a**) and Scenario C (panel **b**). Dashed vertical lines indicate optimal strategy for each level of coverage.

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