Response to Blower et al' s response to our correspondence "Will ART rollout in Africa drive an epidemic of drug resistant HIV?"

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We happily concur with Blower *et al* (1) that ART combination have been a huge success in developed countries, life expectancy has increased dramatically and the spread of resistance has been slowed compared to when monotherapy was used although, worrying, a large proportion of people eventually fail treatment . The success of these ARTs has been enhanced by close clinical monitoring of patients, the drug regimen(s) being changed if viral loads increase, if adverse reactions occur to the drugs, or if resistance mutations are detected. We are less happy in the extension of these observations to African settings. Most deployment in this setting will occur without close clinical monitoring and changes in treatment regimen will be based on clinical indicators of failure (such as AIDS-defining secondary infections) rather than viral load and/or detection of resistance mutations. Consequently, a large number of patients with highly viraemic resistant infections may be sexually active. Furthermore, problems with infrastructure may interrupt drug supplies and we can easily envisage a significant black market of antiretrovirals, both factors contributing to widespread non-adherence to ART regimens and use of monotherapies on a casual *ad hoc* basis. We are therefore deeply concerned about being too complacent during the roll-out phase. If this pushes resistance to even a 'low' level of 1 to 2% it may create the conditions ideal for the rapid expansion of resistance once ART scale-up occurs. Initial results suggest this will be case: a recent trial in Uganda and Zimbabwe using WHO standard therapies and no viral load or resistance-mutation monitoring found that at least 18 out of 300 recruits (i.e >6%) had " key resistance mutations in reverse transcriptase" 24 weeks after starting therapy (2). We therefore strongly recommend that stringent precautions be put in place to slow the spread of resistance and that widespread surveillance be deployed to monitor the spread of resistance. This is the current status for antimalarial drugs deployed in the same geographic areas where it is recommended that widespread surveillance be put in place to give early indications of antimalarial drug failure. The casual use of antimalarial drugs, lack of compliance, misdiagnosis of infections, and problems in supply are all widely recognised as contributing to antimalarial drug resistance in these settings. The same problems will undoubtedly occur with ARTs and researchers proposing to deploy ARTs in the same settings need to learn these lessons

The strength of mathematical modelling is that the consequences of different beliefs about clinical settings and on the underlying biology can be investigated by different calibrations of models. This is what we argued should happen, and is what we set out to achieve. We are disappointed that Blower *et al* chose not to address our chief objection, which was that the underlying assumptions of the model may not be appropriate for the African setting. Instead they chose to question the technical validity of our approach in their penultimate paragraph, and we respond as follows.

Firstly they say that our modifications to their equations are 'incorrect' and that we have 'misunderstood' their approach. We remain deeply sceptical and include a detailed explanation of our concerns below as an Appendix. Specialist will easily see

which approach is more appropriate but we have been explicit to allow non-specialists to also reach a decision.

Secondly they state that our use of difference equations would result in 'numerical errors' in our calculations. This is clearly not the case else this approach would not be so widely used. For the non-specialist the distinction is as follows: differential equations with integration occurs in infinitesimally small time periods, whereas difference equation 'updates' the number of people in each group after daily time periods. The small daily probabilities of events means that the same results will be obtained from both approaches. Blower *et al* will be relieved to learn that we did in fact also use the differential approach with integration, and that the numerical differences (or 'errors') between the two methods were imperceptible. The reason we chose difference equations is because the models can be easily distributed on an Excel spreadsheet and most people are comfortable working with this programme.

Thirdly they point out that we did not perform an uncertainty analysis. This was due to space (correspondence is limited to 750 words) but also because our main point was that changes in underlying, and we think inappropriate, assumptions lead to qualitative different predictions for the spread of ART resistance. There is little point in undertaking a sensitivity analysis until the most appropriate basic model has been identified, so are largely irrelevant in this context.

Finally, they assert that we assumed that 40% of infected individuals would receive treatment. In fact we state quite clearly in the figure caption that it is 20% per year, a figure we chose because it appeared this was used in their original calculations (3). In fact we now learn that it was 5 to 10%. One of the reasons we wrote our letter was because it was impossible to repeat their calculation, and hence gauge the validity of their argument, because they were never explicit about the underlying parameters used to calibrate their model. Their suggestion that we repeat their calculations with the same parameter values to replicate their results also seems pointless because we consider both their mathematical model and the underlying assumptions to be questionable.

Finally, our ethos of mathematical modelling appears to differ quite markedly from theirs. It is important to be clear about the limitations of modelling, to be explicit about the inherent assumptions made in the calculations, and to provide details about exactly what parameter values were selected and why. This is much more transparent than asserting a quantitative result which people cannot duplicate, the ethos 'trust me I'm a mathematician' being almost as alarming as 'trust me I'm a doctor', both being fairly robust indicators of impended doom. This is why we made our calculations freely available as an Excel spreadsheet. Researchers can then select parameter values reflecting their own beliefs about the underlying epidemiology, play around with the inputs values, and gain an understanding of how the various clinical and epidemiological factors contribute to driving ART-resistant HIV through a population. This type of engagement between theoreticians and empiricists is mutually beneficially and contributes to a better understanding of how to slow the spread of resistance.

Appendix Notes on the equations.

The equations used in this spreadsheet were those of Blower *et al*, corrected as described later.

$$\frac{dX}{dt} = \pi - X[c(\lambda_S + \lambda_r) + \mu] \qquad (1)$$

$$\frac{dY_S^u}{dt} = Xc\lambda_S + Y_r^u q + Y_S^t g_S - Y_S^u(\sigma_S + \nu_S^u + \mu) \qquad (2)$$

$$\frac{dY_S^t}{dt} = Y_S^u \sigma_S - Y_S^t(g_S + r + \nu_S^t + \mu) \qquad (3)$$

$$\frac{dY_r^u}{dt} = Xc\lambda_r + Y_r^t g_r - Y_r^u(q + e\sigma_r + \nu_r^u + \mu) \qquad (4)$$

$$\frac{dY_r^t}{dt} = Y_r^u e\sigma_r + Y_S^t r - Y_r^t(g_r + \nu_r^t + \mu) \qquad (5)$$

The above equations are unchanged. The following are changed slightly:

$$\lambda_S = \frac{\beta_S^u Y_S^u + \beta_S^t Y_S^t + \rho_S^u \beta_r^u Y_r^u + \rho_S^t \beta_r^t Y_r^t}{N} \qquad (6)$$

[note that the subscripts in β in the last two terms have been changed from the form given in Blower et al which was

$$\lambda_S = \frac{\beta_S^u Y_S^u + \beta_S^t Y_S^t + \rho_S^u \beta_S^u Y_r^u + \rho_S^t \beta_S^t Y_r^t}{N}$$ (see note [1] below)]

$$\lambda_r = \frac{(1-\rho_S^u)\beta_r^u Y_r^u + (1-\rho_S^t)\beta_r^t Y_r^t}{N} \qquad (7)$$

[note that these terms now contain the factor (1-*p*). The original form of this equation in Blower *et al* was

$$\lambda_r = \frac{\beta_r^u Y_r^u + \beta_r^t Y_r^t}{N}$$ (see note[2] below)]

Blower *et al* seem unconvinced by our (gentle) pointing out of inconsistencies between their parameter definitions and equations. The following two notes should make them obvious even to non-specialists.

Note [1]. Their original equation 6 is

$$\lambda_S = \frac{\beta_S^u Y_S^u + \beta_S^t Y_S^t + \rho_S^u \beta_S^u Y_r^u + \rho_S^t \beta_S^t Y_r^t}{N}$$

There are 4 terms in the denominator (i.e. above the line). They give the number of sensitive transmissions from each of the infection type (sensitive/resistant denoted by subscripts *s* and *r*) and treatment groups (untreated/treated, denoted by superscripts *u* and *t*), giving four combinations in total. Intuitively the number of transmissions from each group equals the infectiousness of people in each group (β) multiplied by the number in each group (Y); this is how Blower *et al* described it in the last line of their figure caption in Ref(4). The first term is from sensitive infections (subscript=*s*) in untreated (superscript =*u*) people. Note that the sub- and super-scripts are identical in Y and β. The next term is from sensitive infections (subscript= *s*) in treated (superscript =*t*) people; once again the sub- and superscripts are identical in Y and β. The third term is from resistant infections (subscript=*r*) in untreated (superscript =*u*) people; note the mismatch between sub- and superscripts in Y and β, the latter being incorrect. The fourth term is from resistant infections (subscript=*r*) in treated (superscript =*t*) people; note again the mismatch between sub- and superscripts in Y and β, the latter being incorrect.

Note [2]. The original equations for forces of transmission were:

$$\lambda_s = \frac{\beta_s^u Y_s^u + \beta_s^t Y_s^t + \rho_s^u \beta_s^u Y_r^u + \rho_s^t \beta_s^t Y_r^t}{N} \qquad \text{(Eqn A)}$$

$$\lambda_r = \frac{\beta_r^u Y_r^u + \beta_r^t Y_r^t}{N} \qquad \text{(Eqn B)}$$

The symbol *p* (with appropriate sub- and super-scripts) is the probability of a person with a drug resistant infection transmitting a sensitive infection (footnote 27 in Ref(4). The probability of that person transmitting a resistant form is therefore (1-*p*) and this needs to be incorporated into the equations, hence our modified equation 7. As a concrete example suppose that infectiveness has been estimated from average viral loads so that estimated infectiveness of an sensitive untreated infection β_s^u is 0.8 (in arbitrary units) and of an resistant untreated infection β_r^u is 0.7, the lower value reflecting a putative fitness reduction associated with the resistant mutation(s). Further assume, for the sake of using an numerical value, that ρ_r^u=0.5 although its exact value does not alter the argument

The number of infections per sensitive untreated infection is calculated, as expected, as 0.8 from the first term in the denominator of Eqn A. However the number of infections per resistant untreated infection is 0.7 (first term of Eqn B) plus 0.8x0.5 (third term of Eqn A) for a total of 0.7+0.4 =1.1 which is far higher than the

infectivity of 0.7 estimated on viral load. In essence people with resistant infections have entered the calculations twice, once as a source of resistant infections and again as a source of sensitive infections. This needs to be recognised and the contribution of the two types needs to be normalised to equal the original infectiousness. Reassuringly, the contribution of untreated resistant infection under our modified equations 6 and 7 is 0.7x 0.5 (3^{rd} term of Eqn 6) plus 0.7 x (1-0.5) (1^{st} term of Eqn 7) whose sum is, as expected, 0.7.

Reference List

(1) Blower S, Bodine E, Kahn J, McFarland W. Response to correspondence from Hastings et al. title "Will ART rollout in Africa drive an epidemic of drug resistant HIV?". Aids **2006**;in press.

(2) DART Virology Group and Trial Team. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1 infected adults in Africa. Aids **2006**;in press.

(3) Blower S, Bodine E, Kahn J, McFarland W. The antiretroviral rollout and drug-resistant HIV in Africa: insights from empirical data and theoretical models. Aids **2005**;19(1):1-14.

(4) Blower SM, Gershengorn HB, Grant RM. A tale of two futures: HIV and antiretroviral therapy in San Francisco. Science **2000**;287(5453):650-4.