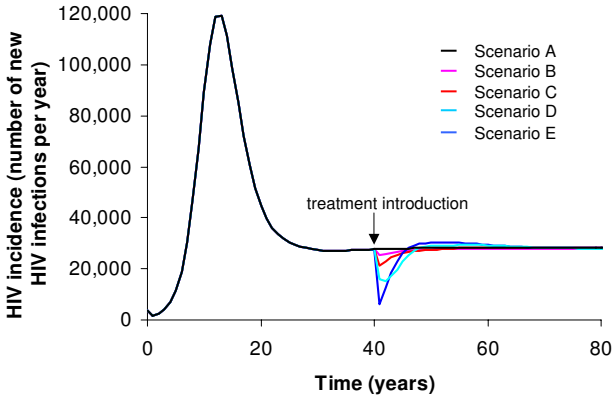

Figure 2
Predictions of the impact of ART by stage of infection at which treatment is initiated. Predictions of the impact of the introduction of ART in terms of HIV incidence, by stage of infection at which treatment is initiated (for a brief description of the four stage infection model used, see Endnote). Scenario A – No treatment. Scenario B – ART uptake: AIDS patients only (after a mean of 1 month). Scenario C – ART uptake: AIDS patients (after mean 1 month) and pre-AIDS (after mean 6 months). Scenario D – ART uptake: AIDS patients (after mean 1 month) and pre-AIDS (after mean 6 months) and incubation stage (after mean 4 years). Scenario E – ART uptake: all four stages, after mean 1 month.

illustrates the urgent need for cheap and reliable second-line treatment options to be available for ART roll-out.

Despite our view that Blower et al are over-optimistic [5], Gray et al's assumptions of the effects of ART may similarly be over-pessimistic [2]. The authors assume that ART leads to an average proportional reduction in HIV log viral load of between 26.8% and 43.6%, based on data from the Women's Interagency HIV Study (WIHS) [48] and the John Hopkins Clinic [49] respectively. However, other studies distinguish between patients who respond to a regimen (who typically experience reduction in viral load to undetectable levels (<50 copies/ml)), those who do not respond and those who subsequently experience treatment failure (viral rebound). With these distinctions, an individual responding successfully to ART will have a far greater reduction in viral load than Gray et al assume. Furthermore, the proportion reduction was the value recorded one month and three months after treatment initiation for the WIHS and John Hopkins Clinic patients, respectively. It can take much longer than this for complete reduction of viral load, often to undetectable limits [50] (models generally do not explicitly account for a delay between treatment initiation and effect, but it can be assumed that this is implicitly accounted for in the treatment uptake rate). Gray et al also included the possibility of behavioural disinhibition; the average number of partners for those on treatment was increased by 50% or 100%. Again, the values appear pessimistic and were essentially chosen arbitrarily, probably in order to complement other models [4,5].

Emergence of ART drug resistance

Many models of ART have concentrated on predicting the emergence and spread of ART drug resistance, which has been of concern [51-54]. Once again it is very difficult to make such predictions, as the spread of drug-resistant virus is highly dependent on the replicative fitness of the resistant strains that evolve and their ability to superinfect individuals infected with wild-type strains (i.e. to co-infect someone already infected with wild-type virus, and successfully replicate). Superinfection is perhaps only likely in the successfully treated individual, where suppression of viral load allows the target cell population to recover, hence increasing the chance of successful replication and establishment of a new strain. In the untreated individual, it is unlikely that low frequency resistant virus, typically less fecund than wild type in this environment, would be able to compete against the established viral population sufficiently successfully to allow long-term persistence of the invading strain.

In a context where ART use is common in core groups, the possibility of superinfection of those on ART means that the likely maximum rate of spread of resistance epidemics may be similar to the speed of the initial HIV epidemic. HIV co-infection with different wild-type viruses [55,56], and by wild-type strains re-infecting patients harbouring drug-resistant viruses after a short period of treatment interruption [57,58], have both been documented. Chakraborty et al postulate that it is possible for patients infected with wild type HIV-1 isolates and under successful ART to become exposed to drug-resistant strains that would have significant selective advantage, leading them to outcompete the original wild-type strain and instigate treatment failure [59]. They concede that the probability of an individual undergoing successful treatment of a wild-type strain being exposed to a drug-resistant strain is low, but the large-scale roll-out of ART in high prevalence, resource-poor settings may increase this probability substantially.

The rate at which drug resistance evolves within the individual is likely to become higher in resource-poor settings than industrialised countries; even though there are reports of patient adherence being no lower than in the West [60], potential interruptions in supply due to transport problems and a lack of sophisticated laboratory monitoring systems will limit the success of any ART