Will we ever know when to treat HIV infection?

Andrew N Phillips, George Davey Smith, Margaret A Johnson

No. 587

Confidence in the efficacy of using antiretroviral drugs to treat HIV infection has grown in the past year as a result of the prolonged survival of those randomly allocated to receive an additional drug in comparative controlled trials. HIV remains, however, the only serious infectious disease for which antimicrobial treatment is deliberately delayed. This is because infected subjects can often be symptomless for more than a decade in the absence of any treatment, and results from trials with the nucleoside analogue reverse transcriptase inhibitor zidovudine have failed to show any evidence for extended survival in those beginning treatment early compared with those who deferred treatment. The new confidence in currently available treatments, and in the prospects for new ones, inevitably leads to renewed questioning of the current strategy of waiting for signs of immune deficiency before electing to intervene. A new randomised controlled trial comparing strategies of early and deferred treatment is required to assess whether the time has come for intervention immediately after HIV has been diagnosed.

Recent evidence that combinations of antiretroviral drugs prolong survival compared with zidovudine alone (B Gazzard, third conference on retroviruses and opportunistic infections, Washington, DC, 1996; S Hammer, fifth European conference on clinical aspects and treatment of HIV, Copenhagen, 1995) and that the addition of the protease inhibitor ritonavir prolongs survival in late stage HIV infection (B Cameron *et al*, third conference on retroviruses and opportunistic infections, Washington, DC, 1996) has reopened the long running debate: when should antiretroviral treatment be started?

Since 1987, when zidovudine was shown to prolong survival in patients with AIDS,¹ the key question of whether patients would be better off if treatment were started before the development of severe immune deficiency, reflected by clinical symptoms or low CD4 lymphocyte counts, has divided clinical opinion.²⁻⁹ Those in favour of early treatment argue that as HIV is actively replicating throughout the clinically asymptomatic period¹⁰⁻¹² it is probably vital, as in other infections, to treat as early as possible to gain the best results from treatment. This may be true, say those in favour of late treatment, but given that only around 50% of people develop AIDS 10 years after infection,¹³⁻¹⁴ it must be proved that any benefits of early treatment outweigh the possible harm from long term treatment.¹⁵⁻¹⁶ In other words a survival benefit for early treatment compared with late treatment has to be clearly shown in a randomised controlled trial.

To date, the clinical trials that have addressed this question have not resolved this controversy.¹⁷⁻²³ The largest trial, Concorde, showed that there was no difference in survival over three years' average follow up between those in whom treatment was started early and those in whom it was delayed until a low CD4 lymphocyte count or clinical symptoms had developed.¹⁷ If zidovudine were the only drug to be used few would now argue that early treatment is appreciably better than late treatment. Herein lies the problem. By the time a trial to answer the question for one drug or a combination of drugs has been completed, new drugs have been developed and the trial findings are no longer

directly applicable. Still, Concorde was a useful trial to have performed. Had it shown a benefit from early treatment, the issue of whether early intervention could be beneficial would have been essentially resolved once and for all. With its negative result, however, Concorde has clearly indicated that early treatment may not be the best course of action, but as treatments improve and the extent and importance of viral replication during the asymptomatic phase become better understood,¹⁰⁻¹² the possibility that treatment should begin earlier inevitably comes back on to the agenda.^{9, 24}

With several promising new drugs (including both reverse transcriptase and protease inhibitors) in the process of obtaining approval from the regulatory authorities, the time for a new trial of early treatment may have arrived. Any new enthusiasm for earlier treatment may be somewhat tempered by one aspect of the preliminary results from the Delta trial (B Gazzard, third conference on retroviruses and opportunistic infections, Washington, DC, 1996), the ACTG 175 trial (S Hammer, fifth European conference on aspects and treatment of HIV, Copenhagen, 1995), and from a recently reported CPCRA 007 trial (L Saravolatz *et al*, third conference on retroviruses and opportunistic infections, 1996). Combinations of ddI or ddC with zidovudine seem to have a greater impact if used in patients who have not been treated with zidovudine before. This may lead people to want to wait before they start treatment, thinking that it is important to start with the best possible combination and that this combination is probably not yet available.

If the efficacy of antiretroviral drugs has now improved sufficiently from the zidovudine monotherapy days of Concorde, and the time is right to ask again the question of when to start treatment, how do we design the trial to provide the answer? The box outlines a possible design. What is needed is a design along the lines of Concorde that compares strategies of early versus deferred treatment over several years, but realistically, clinicians cannot expect to allocate patients to specific treatments nor to try to blind patients by using a placebo. New treatments will become available during the course of the trial and patients cannot be expected to commit themselves at the time they are allocated to a treatment arm to long term treatment with certain regimens, nor can they be excluded from participation in other clinical trials when they do start treatment. Besides, when the early versus late trial is finished it must be as widely applicable as possible, so it should contain patients taking later treatments. Indeed, some view it as a potential drawback that the results of any such trial will inevitably be out of date at the end of the trial. Those who started treatment early might well have started with drugs known by the end of the trial to be inferior to newer drugs.

This should not impede interpretation of the final trial result, however. If patients in the early treatment arm fare better than those in the deferred treatment arm then the balance of evidence would shift towards early treatment being the better strategy. If early treatment does not look as if it confers significant advantage then we would be in a similar position to that which we were in after Concorde. Again, however, it will have taught us something—even given the drug combinations available at the start of the trial, it would still not clearly be better to treat early. Yet another trial of similar design would then be needed with the new—hopefully improved—drugs if it is to be proved that early treatment is better. In either case secondary analyses investigating

HIV Research Unit,
Department of Primary
Care and Population
Sciences, Royal Free
Hospital School of
Medicine, London
NW3 2PF
Andrew N Phillips, reader in
epidemiology and biostatistics

Department of Social
Medicine, University of
Bristol, Bristol BS8 2PR
George Davey Smith,
professor of clinical
epidemiology

Department of Thoracic
Medicine, Royal Free
Hospital, London
NW3 2QG
Margaret A Johnson,
consultant in HIV/AIDS

Correspondence to:
Dr Phillips.

BMJ 1996;313:608-10

Outline design of a proposed trial

Patients	Those with CD4 count $>300 \times 10^6/l$
Equipoise	Not sure whether best to (a) start now or (b) aim to wait for low CD4 count or symptoms (say "aim to wait" in recognition that opinion of patient or clinician may change)
Randomisation	To (a) or (b) above
Outcome measure	Survival
Dealing with "dropouts"	No such thing: comparison is of treatment policies
Analysis	Comparison of survival between those randomised to (a) versus (b)
Participation in other trials	Yes. This is a "background" trial, unlike most trials, in that therapies are not specified. When a patient starts treatment this can be in the context of another clinical trial
Duration	At least five years

which drugs patients actually took would provide useful additional information.

The primary outcome measure would have to be survival as results from some trials have suggested that use of zidovudine alone delays the development of AIDS but not death.²⁰⁻²⁵ Use of national death registers also means that this may be the most reliably obtainable endpoint, a crucial consideration in a long term trial. Development of AIDS would be a secondary endpoint, but these data are less likely to be complete.

Given the long time scale over which HIV infection develops into AIDS and death, a trial of at least five years' duration is probably necessary. It is important to reiterate, however, that this does not mean that a patient is committed to one combination of drugs for the trial period, only that a patient and his or her clinician have agreed to try to be guided by the treatment strategy (early versus late treatment) to which they were allocated, on the understanding that they may change their minds. Given that the trial will have to allow such a large degree of freedom to the clinician and patient to make decisions about treatment, some patients allocated to "aim to wait" (box) will, in fact, probably start treatment quite soon after randomisation, and some allocated to start treatment immediately may stop after only a few days or weeks. This kind of blurring of the distinction between the two groups, and the fact that it is important to detect even small differences in efficacy between the two strategies, means that a large sample size running into several thousands would be required. For example, over 16 000 patients would be needed to give 95% power to detect a mortality difference of 11% compared with 9%, with a two sided 1% significance level.

Will patients agree to be randomly allocated to such a protocol? Clinicians are used to asking patients to be randomly assigned to take one drug or another. Often the strong incentive for the patient who has already decided he or she wishes to start treatment is the potential access to the latest drugs. Attempting to randomise patients to a long term strategy for their care—using only drugs which would be available even if they did not enter the trial—might be more problematic. It can, of course, be argued that many patients in the trial may themselves benefit from the trial results, and other future patients almost certainly would benefit, but it is not clear how patients would respond.

A small preliminary survey was carried out last year at the Royal Free Hospital, before the release of preliminary data from the ACTG 175, Delta, and CPCRA 007 trials. Clinicians asked consecutive patients whether

they felt they would be prepared to be randomly assigned to a protocol such as that described above. Of 38 patients asked, 17 (45%) said they would "definitely" or "probably" agree, seven (18%) were undecided, and 14 (37%) said they "definitely" or "probably" would not agree. Clearly, a more widespread inquiry would be required before beginning a trial, but these results provide some encouragement.

A trial with a similar design—CompACT1—was attempted in the United States (D Abrams *et al.*, second national conference on human retroviruses and related infections, Washington, DC, 1995). The low recruitment could have reflected the timing—before the recent renewed optimism over treatment—and could also differ from the response that such a trial might receive in Europe. If HIV specialists are convinced that a trial such as that outlined here is important to perform, on an international level at least, sufficient numbers of patients would probably be recruited. It should be noted that as this would be a "background" strategy trial, with many of the patients, when they did start treatment, participating in other trials of specific treatments, it would not be competing for patients from these trials.

In discussing the implications of the Delta trial results, Pinching has recently highlighted the issue of drug costs in HIV infection.²⁴ It is worth noting that the 50-75% increase in costs which may follow Delta and ACTG 175 would pale into insignificance beside the hugely increased costs were it to become standard to instigate antiretroviral treatment immediately on diagnosis of HIV infection—especially if this involved use of one or more protease inhibitors.

If a randomised trial that attempts to find out whether early treatment is beneficial to patients is not started soon then clinicians will have to accept that they still will not know in five years' time when is the best time to start patients' treatment. The trial that we suggest may seem too liberal and therefore difficult to interpret, but in making the compromises necessary to ensure that it is feasible the vital ingredient of a randomised comparison is maintained. We have the choice between an imperfect answer to the question or no answer at all.

We acknowledge extremely useful discussions on this issue with Professor Jim Neaton, Dr Janet Darbyshire, Dr Abdel Babiker, Professor Ian Weller, Mr Andrew Hill, Dr Brian Gazzard, Dr Anton Pozniak, Dr Mike Youle, Dr Tim Peto, Mr Ed King, Professor Joep Lange, Dr Stefano Vella, Dr Jens Lundgren, Dr Caroline Sabin, and Ms Amanda Mocroft. We thank the clinicians and patients at the Royal Free Hospital involved in the survey of patients' attitudes.

- 1 Fischl MA, Richman DD, Grieco MH, *et al.* The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. *N Engl J Med* 1987;317:185-91.
- 2 Bartlett JG. Zidovudine now or later? *N Engl J Med* 1993;329:351-2.
- 3 James JS. AZT, early intervention, and the Concorde controversy. *AIDS Treatment News* 1993;No 173.
- 4 Gazzard BG. After Concorde. *BMJ* 1993;306:1016-7.
- 5 Anonymous. Zidovudine for symptomless HIV infection. *Lancet* 1990;335:821-2.
- 6 Swart AM, Weller I, Darbyshire JH. Early HIV infection: to treat or not to treat. *BMJ* 1990;301:825-6.
- 7 Pinching AJ. Zidovudine in asymptomatic HIV infection: knowledge and uncertainty. *Int J STD AIDS* 1991;2:157-61.
- 8 Corey L, Fleming TR. Treatment of HIV Infection - progress in perspective. *N Engl J Med* 1992;326:484-5.
- 9 Ho DD. Time to hit HIV, early and hard. *N Engl J Med* 1995;333:450-1.
- 10 Wei X, Ghosh SK, Taylor ME, Johnson VA, Emami EA, Deutsch, *et al.* Viral dynamics in HIV-1 infection. *Nature* 1995;373:117-22.
- 11 Ho DD, Neumann AU, Perelson AS, Chen W, Leonard J, Markowitz M. Rapid turnover of plasma virens and CD4 lymphocytes in HIV-1 infection. *Nature* 1995;373:123-6.
- 12 Pantaleo G, Graziosi C, Demarest JF, Butini L, Montrani M, Fox CH, *et al.* HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. *Nature* 1993;362:355-8.
- 13 Pezzotti P, Phillips AN, Dorrucci M, Cozzi Lepri A, Galai N, Vlahov D, *et al.* and the Italian Seroconversion Study. HIV exposure category and age in the progression to AIDS in a longitudinal study of 1199 individuals with known seroconversion dates. *BMJ* 1996;312:000-0 (press).

- 14 Phillips AN, Sabin CA, Elford J, Bofill M, Janossy G, Lee CA. Use of CD4 lymphocyte count to predict long term survival free of AIDS after HIV infection. *BMJ* 1994;309:309-14.
- 15 Lenderking WR, Gelber RD, Cotton DJ, Cole BF, Goldhirsch A, Volberding PA, et al. Evaluation of the quality of life associated with zidovudine treatment in asymptomatic HIV infection. *N Engl J Med* 1994;330:738-43.
- 16 Egger M, Neaton JD, Phillips AN, Davey Smith G. Concorde trial of immediate versus deferred zidovudine. *Lancet* 1994;343:1355.
- 17 Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 1994;343:871-81.
- 18 Volberding PA, Lagakos SW, Koch MA, Pettinelli C, Myers MW, Booth DK, et al. Zidovudine in asymptomatic HIV-1 infection. *N Engl J Med* 1990;322:941-9.
- 19 Volberding PA, Lagakos SW, Grimes JM, Stein DS, Rooney J, Meng TC, et al. A comparison of immediate with deferred zidovudine therapy for asymptomatic HIV-infected adults with CD4 cell counts of 500 or more per cubic millimeter. *N Engl J Med* 1995;333:401-7.
- 20 Hamilton JD, Hartigan PM, Simberkoff MS, Day PL, Diamond GR, Dickinson GM, et al. A controlled trial of early versus late treatment with zidovudine in symptomatic HIV infection. Results of the Veterans Affairs Cooperative Study. *N Engl J Med* 1993;326:437-43.
- 21 Cooper DA, Gatell JM, Kroon S, Clumeck N, Millard J, Goebel FD, et al. Zidovudine in persons with asymptomatic HIV infection and CD4+ cell counts greater than 400 per cubic millimeter. *N Engl J Med* 1993;329:297-303.
- 22 Mulder JW, Cooper DA, Mathiesen L, Sandstrom E, Clumeck N, Gatell JM, et al. Zidovudine twice daily in asymptomatic subjects with HIV infection and a high risk of progression to AIDS: a randomised, double-blind placebo-controlled study. *AIDS* 1994;8:313-21.
- 23 Fischl MA, Richman DD, Hansen N, Collier AC, Carey JT, Para MF, et al. The safety and efficacy of zidovudine (AZT) in the treatment of subjects with mildly symptomatic HIV-1 infection. *Ann Intern Med* 1990;112:727-37.
- 24 Pinching AJ. Managing HIV disease after Delta. *BMJ* 1996;312:521-2.
- 25 Volberding PA, Lagakos SW, Grimes JM, Stein DS, Balfour HH, Reichman RC, et al. The duration of zidovudine benefit in persons with asymptomatic HIV infection. Prolonged evaluation of protocol 019 of the AIDS Clinical Trials Group. *JAMA* 1994;272:437-42.

(Accepted 26 June 1996)

Caring for Older People

Ethnic elders

Shah Ebrahim

The numbers of elderly people from ethnic groups within Britain is rising rapidly as postwar immigrants age. Ethnic elders face problems owing to age-associated increased risks of common chronic diseases, racial discrimination, and poor access to many health services and social services. This disadvantage will be alleviated through increased understanding of health beliefs held by ethnic elders and ensuring better access to services through mechanisms such as employment of more staff from ethnic minority groups in senior positions, better training of staff, and more appropriate and sensitive environments. The myths that family care is sufficient, that no use of services implies no need, and that assimilation into the majority population will occur must be discounted.

Since the 1870s Britain has received large numbers of immigrants from different countries and cultures (fig 1). Migration is due to "push" and "pull" factors. After the second world war, Britain actively recruited labour from Commonwealth countries to aid the reconstruction effort—a major "pull"; many came thinking they would earn enough money to return home and retire in comfort. "Push" factors are poverty, political instability, and oppression.

Immigration policy became much less flexible during the 1980s and led to reductions in the numbers of new arrivals. New migrants arrive daily from some countries (such as Somalia) where political oppression endangers life but not from others (former Yugoslavia). British immigration policies are not consistent.

It is still possible for older people from some countries to resettle in Britain by joining their children. The distribution of ethnic minorities in Britain is strongly biased towards inner city areas of major industrial towns. Bradford, Leeds, Manchester, Nottingham, Wolverhampton, Leicester, Birmingham, Coventry, and London have high numbers of elderly people of different ethnic origins.

OPCS classification of ethnicity for 1991 census

White	Pakistani
Black—Caribbean	Bangladeshi
Black—African	Chinese
Black—other	Asian—other
Indian	Other

Ethnicity

Ethnicity is a complex idea. It includes skin colour, culture, language, religion, birth place, food, beliefs, and behaviour. Ethnicity is impossible to define clearly and in most contexts refers to the "otherness" of people who do not belong to the predominant population. The classification used by the Office of Population Censuses and Surveys¹ emphasises the "visible" criterion of skin colour, reflecting British views of ethnicity. Not surprisingly, people who share a skin colour do not necessarily have much else in common. It is wrong to assume that

This is the ninth in a series of 14 articles edited by Eileen Burns, Neil Penn, and Graham Mulley

Department of Primary Care and Population Sciences, Royal Free Hospital School of Medicine, London NW3 2PF

Shah Ebrahim, professor of clinical epidemiology

BMJ 1996;313:610-3

"Woman threading a needle" by Chinnen (19th century)

BRIDGEMAN ART LIBRARY