CENTRE FOR SEXUAL AND REPRODUCTIVE HEALTH

ANTIRETROVIRAL THERAPY IN RESOURCE-POOR SETTINGS

TECHNICAL GUIDANCE NOTE

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by

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Contents

Acronyms and abbreviations

AIDS	**Acquired Immune Deficiency Syndrome**
ART	**Antiretroviral Therapy**
ARV	**Antiretroviral**
BMS	**Bristol-Myers Squibb**
CIPLA	**Chemical, Industrial and Pharmaceutical Laboratories**
CRN	**Clinical Research Network**
DART	**Developments of ART**
DFID	**Department for International Development**
DOT	**Directly Observed Therapy**
GSK	**GlaxoSmithKline**
HAART	**Highly Active Antiretroviral Therapy**
HIV	**Human Immune-deficiency Virus**
MRC	**Medical Research Centre**
NGOs	**Non Governmental Organisations**
NNRTI	**Non-Nucleoside Reverse Transcriptase Inhibitors**
NRTI	**Nucleoside Reverse Transcriptase Inhibitors**
PIs	**Protease Inhibitors**
PMTCT	**Prevention of Mother-to-Child Transmission**
STD	**Sexually Transmitted Disease**
TASO	**The AIDS Support Organisation**
TB	**Tuberclosis**
TRIPS	**Trade-related Aspects of Intellectual Property Rights**
UNAIDS	**Joint UN Programme on HIV/AIDS**
US	**United States**
VCT	**Voluntary Counselling and Testing**
VL	**Viral Load**
WHO	**World Health Organisation**
WTO	**World Trade Organisation**

1 Background and context

1.1: Antiretroviral (ARV) drugs can effectively be used to treat HIV infection. Single drug and dual combination antiretroviral therapy (ART) has limited potency. However triple drug therapy (HAART - highly active ART) is highly effective. It has the potential to prolong life expectancy and restore quality of life; and is the only clinical intervention which directly affects the disease process caused by HIV (disease modifying for HIV).

1.2: ARVs are costly, complex to use and potentially toxic. HIV is only held in check – it is not cured. Virus reappears when treatment stops and disease progresses. Therapy thus is for life. Resistance to drugs can rapidly develop with poor ARV use, especially with single drug therapy.

1.3: HAART is now standard of care in industrialised countries, where HIV/AIDS has become a chronic disease over which physicians and patients now have control. It is unquestionably seen and accepted as part of the comprehensive response to HIV/AIDS.

1.4: Developing countries, particularly in Africa, with the highest burden of disease, have been bypassed by these developments. The huge disparity in outcome between those who can and cannot access ARVs has been highlighted and is viewed universally as unjust and unacceptable.

1.5: Quite unprecedented changes in ARV prices have been announced. Both proprietary and generic manufacturers have been involved in this process. The price barrier still exists but it is far less of an obstacle. Some feel that the access problem has now been largely been resolved.

1.6: Financing mechanisms are now being developed for Governments, and perhaps NGOs, to take advantage of these cheaper drugs – eg the Global Health Fund. Exactly how these funds are to be dispersed is currently being worked out. Drug purchase seems the main target of the fund though there remains some uncertainty around this.

1.7: DFID needs to respond to the challenges posed by ART through engagement at country and international levels. Constructive dialogue with emphasis on the main elements that need to be in place should be developed, tempered with caution about what can be achieved rapidly. DFID can play an important role, in partnership with other agencies, in increasing the pool of expertise in the field and expanding the knowledge base around ARVs.

1.8: The field is rapidly evolving with far more problems and dilemmas than clear answers or solutions. This technical guidance note (the third in 15 months) aims to summarise some of the complex issues, give up to date information, identify best practice and the current evidence base.

2 Where we are (June 2001)

2.1: ARVs are available in most cities in the developing world. Price cuts have increased the availability considerably and the volume of drug in country will only rise as prices decrease. It appears the public is knowledgeable about ART and demand, even desperation for these drugs undoubtedly exists. The private-for-profit ARV market is thriving. Drug resistance is emerging.

2.2: There is widespread expectation that Governments and NGOs will take advantage of price shifts and Global Funds to make ART more widely accessible. Indeed some Governments have already pledged to purchase sufficient ART for thousands of patients (e.g. Nigeria).

2.3: It is unclear how severely constrained and under-resourced health systems will be able to deliver complex long-term therapy to large numbers of people. Health workers are falling sick with HIV/AIDS and retention of trained staff is poor. No examples of chronic care delivery exist.

2.4: There is growing realisation internationally that cost is not the only issue; and the problems only really start when the drugs arrive. The capacity to use these drugs effectively is emerging as the rate-limiting step in effectively widening access.

2.5: The debate is slowly taking a reality check; and beginning to focus on the challenge of how to implement ART lifelong - in countries where health care delivery is inadequate, where basic infrastructure and capacity is lacking, and where access is already hugely inequitable.

2.6: This shift in the debate means it is easier to discuss the very real barriers that exist to any implementation strategy without being viewed as negative or against widening access to ART. Constructive discussion with caution and realism is possible.

2.7: It is becoming obvious that there are no clear route maps to navigate through the ferociously complex issues that are emerging. These new and evolving problems are without precedent, with little prior knowledge or experience to call upon. WHO, through the Department of HIV/AIDS (co-ordinating director Dr Arata Kochi), will probably assume global leadership in this area.

3 Best practice and current evidence base in Industrialised countries

3.1: There are 3 different classes of drugs: nucleoside reverse transcriptase inhibitors (NRTIs – eg AZT, 3TC/lamivudine, d4T, ddI and abacavir); non-nucleoside RTIs (NNRTIs; two drugs - nevirapine and efavirenz); and the protease inhibitors (PI - eg saquinavir, ritonavir, indinavir). New classes of drug are being developed. Some classes are very "brittle" and drug resistance mutants cover the whole drug class (eg NNRTIs and PIs). With the NRTIs there is considerable heterogeneity in cross-resistance. There are 17 separate licensed ARV drug in use.

3.2: Best practice on ART comes almost exclusively from industrialised countries. It is derived from cumulative clinical trials and the experience of well-organised treatment centres and patient groups. The norm in resource-rich countries is a physician-led service with unlimited access to high-technology therapeutic monitoring. These practices are not easily transferable to resource-poor settings, or amenable to rapid scale-up. In addition, good quality information about the risks and benefits of HAART is more readily available in industrialised countries.

3.3: Therapeutic monitoring involves measuring markers of infection: CD4 cell count and viral load (VL). Some centres regularly use drug-resistance testing although the clinical significance of the results are not universally accepted. Monitoring is usually used in the west to assess clinical response; and especially to switch drug regimens if there is evidence of failure.

3.4: Universally applicable results are available from industrialised countries. Single drug therapy is of marginal benefit and dual therapy has limited efficacy. Only triple therapy HAART offers substantial survival benefit. Drug resistance rapidly emerges with single drug therapy and is intimately linked with adherence in combination therapy. Resistant HIV strains can readily be transmitted and are regularly isolated from recently infected patients (note parallels with TB).

3.5: Lifelong, chronic adherence to toxic therapy is problematic. Poor compliance is difficult to quantify accurately; when documented it is seen in between 15 –20% of patients. It is assumed to be critical for emergence of drug resistance, especially when some ARVs are not taken, resulting in effective monotherapy. Even with well-trained HIV physicians and fully resourced treatment programmes, adherence to therapy is sub-optimal in the west. Drug resistance is now widespread and readily identifiable in recently transmitted virus (ie resistance does not reduce infectivity).

3.6: Some regimes can be very complex with multiple doses of individual drugs taken three or four times daily under specific circumstances (eg with food). This is thought to impact greatly on adherence but this is difficult to show definitively. The tendency now is to use simple twice-daily ARV regimens to start with, usually using co-formulated drug. Currently, GSK's drug Combivir – dual AZT and 3TC – is the world's leading prescribed ARV. More complex regimens are often now reserved for second-line therapy in those with treatment failure and drug resistance.

3.7: HAART is regarded as very cost-effective in the US. This is because substantial savings have been made in health spend by markedly reducing episodes of intercurrent infections and time in hospital. These more than offset the costs of drug purchase and drug delivery.

4 Broadening the evidence base to the developing world

4.1: Relevant experience exists with widespread delivery of ART in Brazil, where it is provided free of cost to anyone who is sick. High quality ART has been delivered and, as in the US, it is seen both as cost saving and cost-effective; although hospital costs are far lower cheap generic drugs have been used. Because the main burden of HIV/AIDS disease is in the south, most care is delivered there, in regions where there is a good health infrastructure. The next challenge is to widen coverage and replicate this service in the rural interior and poorer North-east, which does not have such a good infrastructure. This will have more resonance with low-income countries

4.2: Thailand committed in 1992 to supply ARVs free of charge to low-income patients. Interim review (1995) concluded it was not affordable to pursue this policy. Following this the Clinical Research Network was formed and an increased budget commitment was made to research ARV use including PMTCT. Despite a national network of hospitals and research institutions, and drug prices falling significantly coverage has remained limited. Reorganisation of the CRN is underway and it is expected that Thailand will rapidly scale up ART delivery and reaffirm free access. There are valuable lessons to learn from the problems this programme has experienced.

4.3: Uganda and Ivory Coast, in the UNAIDS pilot programme, and Senegal have demonstrated that ART can be successfully implemented in resource poor settings either with subsidy or with patients paying full costs. On close audit however, even with significant inputs to training, sub-optimal regimens are being used; few are enrolled; and drug resistance is now being identified.

4.4: There are now attempts to set up clinical trials centres in Africa that have the resources to conduct large-scale trials of ART relevant to resource-poor countries. The UK effort centres on the DART study (Liverpool School and MRC Clinical Trials Unit) in Uganda at the MRC/DFID AIDS Programme and TASO. DART is funded by MRC. Structured treatment interruptions or controlled drug holidays will be investigated, one way to spare an individual from taking lifelong uninterrupted therapy and reduce costs. Other studies are planned but are some time off starting.

4.5: Generic ethical problems exist in trying to evaluate ARVs in resource-poor settings. These have bedevilled several countries efforts to date. If regimens are evaluated that are not standard of care (in the USA) then this may be seen as evaluating sub-standard or less effective therapy. At the end of the trial what happens to the patient? It is widely deemed to be unethical then to stop therapy. In the West, State programmes would assume clinical responsibility. In the absence of any guarantee of long-term access to ARVs in poor countries, some say the trials are unethical and cannot start. No donors or drug companies can or will provide open-ended access to ART.

5 Strengths in promoting wider access to ART

5.1: If properly used, triple-drug ART will prolong life and improve the quality of life. No other intervention is disease modifying to this extent; or can offer such potential benefit to so many who are sick. The lives of millions of people living with HIV/AIDS could be transformed and huge amounts of human suffering will be averted.

5.2: A comprehensive approach to HIV/AIDS in which real (ie ART) care and prevention are linked is now deliverable. This can only improve the limited success of HIV control activities. Seeing HIV just as a disease to avoid with little to offer those unable to stay free from infection has undoubtedly compromised the efficacy of prevention campaigns. Uptake of voluntary counselling and testing (VCT) will increase with effective care on offer. Any reluctance to identify HIV infection will be reduced with for example wider use of ART to reduce mother to child transmission or the health of the mother. HIV control activities will be strengthened.

5.3: Being able to treat and take control over HIV/AIDS disease may change public perception of the epidemic. Fatalism about inevitable death should be replaced by more optimism and hope that something can be done for the sick. This is widely predicted to reduce stigma and normalise societal attitudes to the epidemic. It is difficult to see other ways this could quickly happen.

5.4: HAART (and less effective dual nucleoside therapy) reduces viral load in bodily fluids. Although it has not been definitely proven, it seems intuitively obvious that such an effect will (all other things being equal – see 7.5) reduce onward transmission of HIV. Such an impact on transmission dynamics has not been modelled properly but may under some circumstances have substantial impact on HIV incidence. One such scenario is to treat HIV-positive sex workers.

5.5: The HIV/AIDS epidemic has shattered the comfortable dichotomy between tropical and temperate medicine. For the first time in generations the same major public health problem is a top priority in both resource rich and resource poor countries. The huge difference in responses generated, dictated by resource rather than need, is highlighted by differential access to ART. This has major benefits and spin-offs beyond HIV/AIDS (eg malaria, trypanosomiasis and TB).

5.6: The inescapable need for the west to start to bridge the huge equity gap between rich and poor nations is addressed by responding to the price issue and financing ARV purchase. The major commitment that is being made was not forthcoming for STI control and condoms.

6 Weaknesses of promoting wider access to ART

6.1: Health systems are inadequate in most resource-poor countries. Coverage is often patchy with many communities under-served, or with no operational facilities. The poor have the most limited access to services. Very large investments will be needed in basic health systems before wider access to ARV's can be contemplated. If initial programmes do not include major system development they will not, in the short or even medium term, be viable or equitable.

6.2: Pressing capacity issues include the integrity of the drug supply – pilfering, counterfeiting, uninterrupted supply; the ability scale up VCT services to identify HIV-infected individuals; and laboratory capacity. Paradoxically the need for therapeutic monitoring may be less of a constraint than imagined, if simple regimens are used (eg standard first-line ART and one failure regime). Monitoring is used to trigger changes in therapy; if there is limited choice it has little use.

6.3: There is a limited and finite supply of trained health staff in most resource-poor countries. Staff are increasingly demoralised and de-motivated by the hopelessness of AIDS care. HIV is itself taking its toll, and retention of trained staff may be poor. There is a limit to the extra tasks (eg ART delivery) that can be loaded on to fragile systems. There is a long lead-in time to recruit and train new health personnel; anecdotally HIV/AIDS disease is putting off many young people applying for training (across all cadres of health workers) or re-entering the profession.

6.4: Who will deliver ART and clinical care? In the US, HIV medicine is promoted as a highly complex sub-speciality and ART is a physician-led service. If services are to be scaled up, it is inevitable other cadres (clinical officers and nurse practitioners) will have to deliver simplified therapy, as with TB DOTs. ART is based on western experience (see 3.2) and it is unclear how easy it will be to design simple and robust therapeutic regimens that retain core effectiveness.

6.5: There are very few, perhaps no examples of effective chronic care delivery in resource-poor countries on which to develop ART services. Long-term management of hypertension, diabetes or epilepsy is usually haphazard. TB control aims for six months of therapy and it is difficult to get patients to adhere to and complete even this time-limited treatment. ARVs are not robust. To be effective most doses have to be taken; it is not clear how many doses can be missed.

6.6: Making wider access to ARVs one of the main and most visible components implemented as part of a comprehensive national response to HIV/AIDS is unlikely to foster a multisectoral approach. Indeed it risks "over-medicalising" the issue by

confirming that the main response – that of managing ART – comes from, and is the responsibility just of, the health sector.

6.7: If wider delivery of ART is successful, then by definition people will survive – and need continuous access to care and ARVs. There is no stopping treatment once it has started. Thus year by year the drug supply will have to increase just to keep pace with success. Eventually a steady state will be reached, but this may involve far more people on treatment (with all that that entails in service commitment). How sustainable is this likely to be?

6.8: There will always be a shortfall in what can be supplied – either through lack of resources, money or failing systems. Therefore the equity issue cannot in the near future be addressed properly especially in sub-Saharan Africa.

7 Opportunities in promoting wider access to ART

7.1: Promoting broader access to ARVs cannot go ahead without recognition of the difficulties existing health systems have in delivering chronic, long term care; and the inequity of health service coverage. There is a real opportunity to promote a health systems agenda in a new way, one for which substantial funding may be available.

7.2: Any programme will need to start somewhere as coverage is built up. No resource-poor country has the capacity to implement universal access immediately even if drugs were free, or fully financed externally. There is an opportunity to strengthen sectors like health and education by targeting health professionals and teachers in the initial wider access programme. In health, this may help increase retention, encourage recruitment and stimulate former staff to re-enter.

7.3: Having a viable care strategy that incorporates ARVs, that is comparable to what is on offer in the west, will strengthen the development and implementation of a comprehensive national response. In the absence of any significant care component (which now must include ARVs) , a national response cannot be considered comprehensive. As noted in 4.2, the uptake and impact of control measures is undermined if they are promoted on their own, without any care strategy.

7.4: Having a global fund and national programmes for widening access to ARVs increases the opportunities for rich donor countries to increase their aid spend generally and the earmarked spend targeted for HIV/AIDS activities. This assumes that new money comes into these funds rather than being diverted from other development and aid budgets; and that there is a positive impact on reducing HIV transmission with these additional resources.

7.5: The pernicious impact of HIV on development may be mitigated if sufficient people in core positions are on ART, and can continue to function economically and maintain their households. Targeted programmes from Government to key workers in all sectors will have to be matched with a similar response from the private sector. There are no other ways in the next decade of coping with the huge burden of disease, and the economic and social fall-out that will inevitably come from the ill health and premature death of those who are already infected.

8 Threats inherent in promoting wider access to ART

8.1: Everything is changing rapidly. The financing mechanisms and conditions attached to the Global Fund, and constraints that may accompany some of the drug donation schemes are not yet apparent. There may be hidden threats in these schemes that limit their uptake and attractiveness; or increase long-term debt. How available will funds really be and will they flow freely? How sustainable will funding from these initiatives really be?

8.2: ART clearly has the potential to hijack the agenda from other equally important activities. Resources may be diverted from existing HIV/AIDS control programmes or other essential health interventions (eg TB, if TB services are used to deliver ARVs). This may be financial, if global funds and donations fail to keep up with rising demand; in health system capacity which is finite; or by competition for scarce trained health professionals to implement any programme.

8.3: In most high prevalence countries, attempts to widen access are likely for cost and capacity reasons to be unable to cover more than a small percentage of potential patients (at least initially as programmes start up and try to scale up). The risk is that specific elites or favoured groups will get preferential access and thus inequity is widened; and hidden subsidies are given.

8.4: If information and education about ART is poorly designed and/or delivered or perhaps if it is seen to be a major breakthrough that most can access, the whole programme could rebound. Safer sex messages may get ignored if the risks and particularly the consequences of infection get downplayed. The number of new infections could increase rather than fall with better control.

8.5: There is a very real threat of widespread drug resistance if patients are poorly compliant or if therapy is inadequately supervised. This risk can be minimised by only providing co-formulated drug, as resistance is highly unlikely to develop to all drugs together. However the private sector somehow has to be involved in any such policy. Once widespread, treatment will be impossibly complex and costly (cf: multi-drug resistant TB).

8.6: If generic ARVs dominate the African market the future of programmes such as BMS's "Secure the Future" and GSKs "accelerated access initiative" long-term is in doubt. Incentives must exist for multinational pharmaceutical companies to engage with the epidemic in resource-poor countries; and to foster research partnerships - as has been the norm in the West. Incentives are also necessary if high cost, high-risk research and development for new classes of drugs is to continue. If the lucrative US/Europe markets

are threatened by generics (following changes in WTO and TRIPS) then industry may withdraw from the HIV field. Abbot has already pulled out.

9 Costing and Financing issues

9.1: Commodity supplies, financing opportunities, donation programmes, new training schemes – all are changing rapidly or evolving week by week (see 8.1). This needs to be taken into consideration when reading this paper, as the information may already be out of date or invalid.

9.2: The moral imperative for the West to respond, and the finances likely to be available soon are driving the agenda. International and national policy is being formed in the absence of a clear evidence base or adequate knowledge and practical experience; with a need to produce activity and generate results quickly in response to the emergency and huge daily death toll form AIDS. This is a fairly unique situation that is fraught with problems and pitfalls.

9.3: The funds for ARV procurement will need to be relatively large. Clear accounting processes will need to be in place with regular audit and monitoring. Who will disperse them?

9.4: Drug costs are probably about as low as they will go. The generic companies like CIPLA really have opened up a true marketplace in ARVs. Triple therapy (d4T, 3TC, NVP) is available at an annual price of $350. PI-containing regimens are more costly.

9.5: The cost of providing drug (strengthening systems; lab tests and patient monitoring; safe storage; staff time) may be close to the cost of the drug itself. However, some of this depends on the exact role and need for therapeutic monitoring (see 3.3 and 6.2).

9.6: As noted in 6.7, therapy is not time-limited but should be given for life. Thus once started it needs to continue. If successfully delivered then people will survive, and year by year more and more people will need ARVs. Quite when a steady state occurs is not known and will probably be quite heterogeneous. It makes medium term budgeting difficult if it is done on a needs basis.

9.7: The private sector is considering large scale provision of ART (e.g. the mining industry in S. Africa). One insurance company (in S. Africa) sector is offering a policy which includes time-limited ART care; premiums are reasonable. Private-for-profit health providers are prescribing ARVs widely (and in some regions very badly). Demand here is very price-sensitive.

9.8: The NGO sector may in some regions become a major supplier of ARVs but this will probably have to involve some form of cost recovery, perhaps with subsidy for special groups.

9.9: In the government/state sector several financing mechanisms are possible. Currently in the Ivory Coast some patients get fully subsidised care. Senegal operates a tiered

subsidy system but all have to contribute towards drug costs. In Uganda full costs are charged. It is likely that cost recovery will be widely used. Elite groups may receive hidden subsidies (see 8.3).

9.10: In low-income countries, ART is unlikely to be cost saving or cost-effective because of low wage costs, a limited range of interventions actually provided, and the low-cost of hospital care. It may be beneficial if a wider societal picture is taken and productivity gains are included, particularly if ART is targeted to high salaried or core professional staff.

10 Issues for DFID

10.1: DFID's response to ART needs to be considered within the framework of its own broad institutional response to the HIV epidemic and upon identification of its own comparative advantages. Short and longer-term issues need to be considered and the speed at which the situation is unfolding requires a policy response that is kept "live" rather than static.

10.2: A wide spectrum of opinion exists internationally and within DFID on the provision of ART. As an issue it cannot be ignored, nevertheless achievement of the "gold standard" of ART as provided in resource rich environments is not a practicable or achievable result in resource poor settings with high HIV/AIDS burdens.

10.3: Whilst it is not pro-poor, there are positive aspects to help development of comprehensive HIV/AIDS policies, which overall may be able to mitigate the impact of HIV on development.

10.4: It may not be viewed as a sign of weakness to be uncertain on this complex issue. Who can be clear what to do? Polarised views (wholeheartedly positive or entirely negative) are untenable and give little room for constructive dialogue. Uncertainty allows discussion and the opportunity to note clearly the strengths and weaknesses of any ART programme.

10.5: DFID can start by focussing on core messages that all agree on – and which are consensus views in house. This will include reaffirmation of the commitment to strengthen health systems and capacity (generally as well as for ARVs); the imperative to maintain or increase prevention and control activities; and the need to set up adequate monitoring and evaluation from the start of any ARV programme. Sensible advice about what can and cannot be achieved by ART can be emphasised. Pointing out that ARVs are difficult to implement properly and if poorly supervised will rapidly generate drug resistance is not controversial.

10.6: Whilst much information is out in the public domain little is of use for planning and policy making. Indeed there are few recommendations to make about how to widen access to ARVs or what to use; rather there are multiple issues to be cautious over. DFID can help support National Governments greatly here by being a conduit for information and advice and counsel. This may need to be a reality check when enthusiasm runs away from the practical; but may equally well be to input relevant knowledge in an accessible format or through appropriate "on message" experts brought in on short consultancies.

10.7: It would seem sensible now for country desks to start collecting information about who is planning to do what where. This needs to cover ART trials as well as implementation activities. There may be important lessons to share – problems not solved

as well as solutions. Often it is important to put into context what one country is attempting to implement with policy, activity achievement and experience from other countries that have faced similar issues.

10.8: DFID can support the development of appropriate knowledge through research activities. This could range from clinical trials to identify best ways to use powerful ARVs in resource-constrained settings, to a focus on health systems and capacity to implement, to monitoring the impact of ARV promotion on risky sexual behaviour and HIV incidence. It will be important to develop the local capacity to do such research (in priority setting and in carrying out the work). It may also help develop partnerships with other donors, using its good offices with these groups.

11 Summary points and conclusion

11.1: There are undoubted benefits in investing in ART as part of a comprehensive response to HIV/AIDS, which links care with prevention. Millions will benefit. There is an irresistible momentum to address global inequity in health outcome, which is epitomised by HIV.

11.2: There is growing realisation that money is not the only issue and that the problems will only really start when drugs arrive in volume. It is premature to think that because costs have dramatically fallen global inequity has been properly addressed. Building capacity to use ARVs effectively in dysfunctional health systems is the critical long-term process.

11.3: In a relative policy vacuum, in a complex and emotive area, clear voices are needed which articulate sense, reason and reality. DFID advisers are well placed to help provide that advice which should be based on clear understanding of the issues. Constructive engagement will enable such messages to get across.

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