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DART : a fact sheet

Introduction

Since fall 2005, Ugandan activists have raised on various activist listserves some concerns about the rights of the participants of the DART trial (Development of AntiRetroviral Therapy in Africa). Act Up-Paris has taken an interest and tried to help voice their concerns during the presentation of the preliminary results of the study at the International Aids conference in Toronto in August 2006.

What is the DART trial ?

The protocol of DART is available on the Act Up-Paris website, www.actupparis.org/article2798.html. The protocol is the official document issued by the trial investigators to describe their study. It states that :
"DART is a randomized trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa. It evaluates two strategic approaches for management of antiretroviral therapy (ART) in symptomatic HIV infected adults in Africa. The first strategy compares clinical monitoring only (CMO) with laboratory plus clinical monitoring (LCM). » The trial which has enrolled 3310 patients, is also planning, for a portion of the patients enrolled, structured treatment interruptions (STI) to determine if this strategy could reduce toxicity without reducing efficacy of the treatment.
Eligible patients had symptomatic HIV disease (WHO stage 2, 3 or 4) and CD4 cell counts <200 cells/mm^3, no prior ART and no clinical or laboratory abnormalities contra-indicating start of ART."
DART is conducted in 2 referral hospitals in Uganda and 1 in Zimbabwe

Act Up-Paris' action in Toronto

During the latebreaker session at the 15th International Aids Conference in Toronto, Act Up-Paris activists deployed a large banner reading « Shame » in front of one of the DART trial investigator, who was presenting the results of the STI arm. Other activists were holding posters reading: « DART = unethical trial ». This action was silent (there were no slogans or chants) because unfortunately the Ugandan activist who had asked us to organize this protest was sick at his hotel and could not come speak. Others weren't able to come to Toronto.

What is Act Up-Paris asking for ?

Our aim is to improve safety, information and consent for DART participants (see specifics below). We are not asking for the interruption of DART.

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Problems with the DART trial

Problems associated with clinical-only monitoring

1. Some clients enrolled in DART were outpatients at the two best referral hospitals in Uganda (the Medical Research Council in Entebbe, and the Joint Clinical Research Centre in Kampala). These leading hospitals have the capacity to provide laboratory monitoring of HIV care to all their clients. The result is a situation where the clients enrolled in the Clinical Monitoring Only arm actually receive inferior quality care inside the research than outside.
   To avoid this situation, DART could have chosen instead to set up in rural clinics where laboratory monitoring is *not* available, and could have brought it there. This would have improved the quality of care in these rural clinics, and increased general access to lab monitoring in the country.

1. DART tests a hypothesis for patients on ARVs which is highly disputed by the scientific community: "*Clinical Monitoring only (CMO) will result in similar outcomes to Laboratory + Clinical Monitoring in terms of progression of clinical HIV disease or death"* (DART protocol, page 21). Ethics require scientists to be especially cautious when testing a hypothesis that pertains to death under treatment – and even more cautious when their hypothesis happens to be disputed. Caution dictated that DART test its highly disputed hypothesis on a very limited number of patients at first or, at least with very tight monitoring by the DSMB. Instead, DART went on and directly exposed 1600 patients to clinical-only monitoring (page 12 of the protocol).

2. Participants whose health is deteriorating on DART can only access their lab results if they suffer from a **grade 4 event** (see page 46 of the protocol), knowing that grade 5 is death. To ensure the safety of participants randomized into clinical-only monitoring arm, unblinding of lab results needs to be triggered much earlier, especially since the protocol schedules only two unblinding review sessions per year (as opposed to weekly review of unblinding needs).

Problems associated with treatment interruptions

3. **DART tested treatment interruptions on a population of patients for whom this was well known at that time to be dangerous.**
   In 2000, H. Hatano and S. Bonhoeffer published two separate studies in the medical journal *AIDS*, respectively titled "Pre-HAART HIV burden approximates post-HAART viral levels following interruption of therapy" and "Risks and benefits of structured antiretroviral therapy interruptions".
   In 2002, medical recommendations in France[1] and other countries interpreted these studies as meaning that "treatment interruptions may only be contemplated for patients with undetectable viral load, CD4 count superior to 400, and CD4 nadir superior to 350".
   Yet in 2003 DART started testing treatment interruptions on patients with 200 CD4, and an average CD4 nadir of 84 instead of above 350 : treatment interruption was known to be dangerous to these patients. Since 2002, several studies have confirmed that low nadir is

[1] Rapport 2002 du groupe d'experts sur la prise en charge des personnes infectées par le VIH, sous la direction du Professeur Jean-François Delfraissy. See section on treatment interruptions, page 57.

associated with worse outcomes in patients on treatment interruption.
It can be necessary to assess the consequences of STI given that the patients in Africa are sometimes forced to interrupt their treatments (lack of money to pay for the medicine, shortages, interregional migration). This assessment should nonetheless be strictly monitored and enforced so as to be as little risky as possible for the patients involved in the treatment.

The double jeopardy of treatment interruptions + no lab monitoring

4. **DART exposed some participants to *a combination of two* non-validated care standards: treatment interruptions + clinical-only monitoring. Yet the 2002 recommendations warned specifically against such a combination**: "upon initiation of treatment interruption, it is indispensable to monitor CD4 count and percentage on a monthly or bimonthly basis" state the French recommendations of 2002, written by Jean-François Delfraissy, the current head of the French National AIDS Research Agency (page 57 of the recommendations).
This combination thus puts participants in a double jeopardy. Instead, both approaches should have been evaluated separately, well before they were studied in combination.
The calls for help which Act Up-Paris got from Ugandan activists before Toronto had precisely to do with the fate of low-nadir participants exposed to treatment interruptions without laboratory monitoring. DART has still not provided data as to how these participants have fared on the trial.

Substandard information of participants

5. The consent form gives the potential participants no information whatsoever on the increased risks associated with clinical only monitoring (see the consent form on pages 68-71 of the protocol). Yet these are serious risks: clinical only monitoring can lead to suboptimal treatment and avoidable drug resistance, as well as avoidable toxicity which biological markers can help be detected early .

6. The consent form paragraph on the effects of treatment interruption fails to mention the main risk associated with treatment interruption: a highly increased risk of resistance (see page 70 of the protocol).

7. The consent form (page 68-70) makes no mention of the fact that patients who voluntarily withdraw from DART can expect nothing more in terms of care than what the national health system offers. While this information is not mentioned in the consent form given to potential participants, it is explicitly mentioned in the protocol given to clinicians (page 31 of the protocol).
The Ugandan activists who criticize DART have raised that this is a real-life issue. They gave the example of participants who developed drug resistance on the treatment interruption + clinical-only monitoring arm, until they had to go on a lopinavir-containing regimen. They pointed out that these participants are no longer free to leave DART, because if they did the Ugandan health system would expect them to pay for their Kaletra – which they cannot afford.

Misleading presentation of preliminary results

8. In Toronto, DART presented results only in the « on treatment » format, and not also in the « intent to treat » format (which would have been the standard thing to do), and without mentioning in the presentation the very high number of participants who had been lost to follow-up. DART investigators asserted that there was "no statistical difference in the number of deaths on treatment interruption (5 deaths) compared to continuous treatment (4 deaths)". Because there was no mention of the fact that 102 participants had been lost to follow-up, their assertion about mortality was disingenuous. It was elsewhere (www.ctu.mrc.ac.uk/dart/CurrentStatus.asp) that DART has revealed that, among these 102, only 3 were actually known to still be alive. How many of the 99 remaining have in fact died? How many of those dead had been on STI?
9. DART investigators failed to present data on the subgroup of participants who had been exposed to the most risky treatment: those who had both interrupted treatment and no lab monitoring. DART should not be silent on the crux of the matter.

Unsound scientific justifications for exposing participants to inferior care

10. In an effort to justify its treatment interruption arm, **DART falsely represents why such trials were conducted in developed countries**.
    The protocol states that "*STI trials are being undertaken in chronic HIV infection in developed countries with the aims of reducing toxicity, costs, and possibly improving adherence, without compromising efficacy. In Africa reduction of costs, in particular, would have major advantages.*"
    It is untrue that researchers in developed countries tested treatment interruptions in hopes of reducing costs. When these trials took place in developed countries, it was already acknowledged that treatment interruptions could be dangerous to the health of participants. AIDS activist would not have stood for research that endangers participants just to find out whether it was possible to *save money on drugs*. The intention there was rather to increase tolerance and quality of life for participants, by allowing "treatment holidays", where one can take a holiday from the pill regimen.

11. In its efforts to justify its treatment interruption arm, **DART asserts the assumption that reducing the quantity of medicines used by patients is the proper response to their inability to continuously cover the financial costs associated with accessing HIV care**.
    This assumption is highly disputed, and was disputed even at the time when DART started exposing participants to treatment interruptions.
    As early as 2004, renowned health economists led by South African expert Alan Whiteside were calling for 100% free care for HIV care clients. Their core rationale is that the financial contribution fees exacted from clients can only represent an insignificant share of the cost of a genuinely large HIV care program, whereas such fees force the poorer clients to intermittently discontinue care, which in turn increases costs through increased resistance, morbidity and mortality. Some health economists are even pushing for HIV care programs to take charge of all care-related costs incurred by clients, including transport and food.
    The objective pursued by DART of reducing drug intake is thus far from being the consensual response to patients' inability to continuously cover the financial costs associated with accessing HIV care.

12. There is a contradiction in the scientific questions that DART is meant to investigate. The contradiction is about whether it is the *medical* or the *economic* superiority of laboratory monitoring and continuous therapy that DART aims to evaluate.
    If DART proposes to compare the *medical value* of CMO-vs-CLM, or CTs-vs-STI, then DART should have been a very cautious trial (either in size or in DSMB unblinding review frequency), because the scientific consensus at the time was that indeed laboratory monitoring and continuous are medically superior to no-laboratory or to treatment interruptions (except for very specific categories of patients that are doing exceedingly well on treatment).
    And if DART proposes to compare the *cost-effectiveness* of laboratory+clinical versus clinical-only monitoring, or continuous versus interrupted treatment, then DART should have had cost-effectiveness indicators among its study endpoints. As it happens, all of DART's endpoints are medical: there is not a single economic indicator among them (see endpoints on pages 21-22 of the protocol).
    This contradiction in the scientific question which DART is asking has the consequence that DART can presumably not produce an answer to its own question. Which means that participants are randomized into suboptimal clinical-only and treatment interruption arms *in vain*.

Potential ways to improve safety and information for DART participants

- Every participant whose health or sensitivity to ARVs has suffered while on the treatment interruption arm (which has since been discontinued) needs to have access, if she so wishes, to laboratory monitoring HIV care. They should be switched to a follow up study open as well to the people who voluntarily withdrew from DART.

- As for participants in the clinical-only monitoring arm, clear criteria must be established for lifting the blind on lab results *before* the patient encounters a grade 4 event. The DSMB must be able to monitor *in real time* (not twice a year) the individual lab results of participants in the lab-blinded arm, so as to be able to react swiftly when someone meets the alert criteria for lifting the blind on lab results.

- Ideally, participants who feel the need to withdraw from the trial should be able to continue receiving at least the lifesaving drugs that they have commenced inside the trial, in order to avoid a situation where their need to remain on the drugs bars them from leaving.

- Investigators must publish intermediate results on the whole study with intent-to-treat data and the share of patients lost to follow-up in each arm, including for patients exposed to both treatment interruption and clinical-only monitoring. Seats should be reserved on the trial board for representatives of trial participants. *Regular* meetings must be scheduled between investigators, participants and local activists.

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