



A randomised trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa

Development of AntiRetroviral Therapy in Africa

DART

ISRCTN 13968779



Background

- intensive laboratory monitoring of ART is standard of care in industrialised countries
 - toxicity (haematology, biochemistry)
 - efficacy (T cell subsets, viral load)
- its need has never formally been assessed
- alternative approaches are needed where this level of support is not available
- **Structured Treatment Interruptions (STI)** are a strategy for giving ART which has also not been assessed in these situations



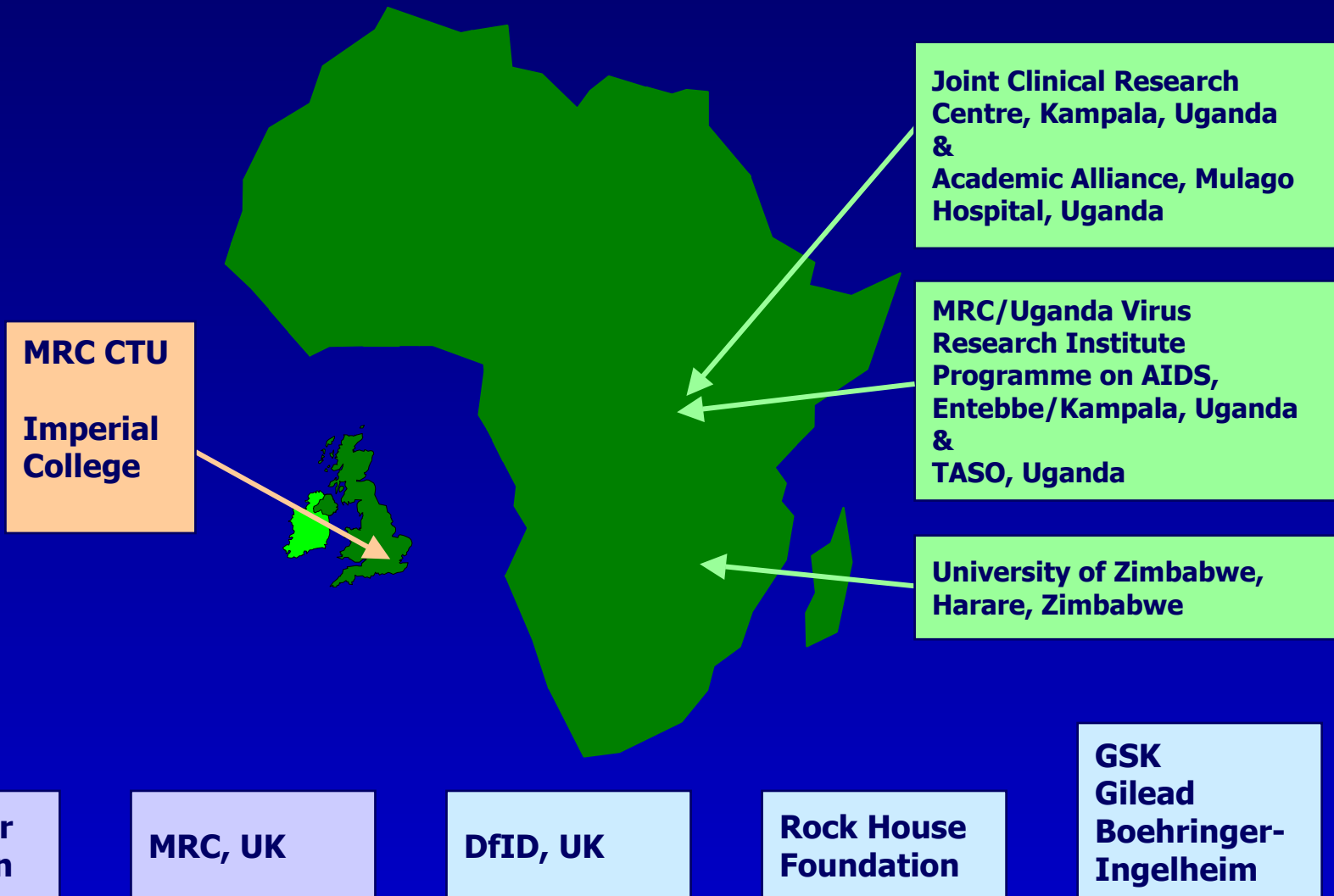
Objectives of DART



- to compare routine Laboratory and Clinical Monitoring (LCM) versus Clinical Monitoring Only (CMO)
- in those with CD4 count increases to above 200 cells/mm³ after 24 or 48 weeks on ART
 - to compare Continuous Therapy (CT) versus Structured Treatment Interruption (STI)
 - **STI**: 12 weeks on ART, 12 weeks off ART

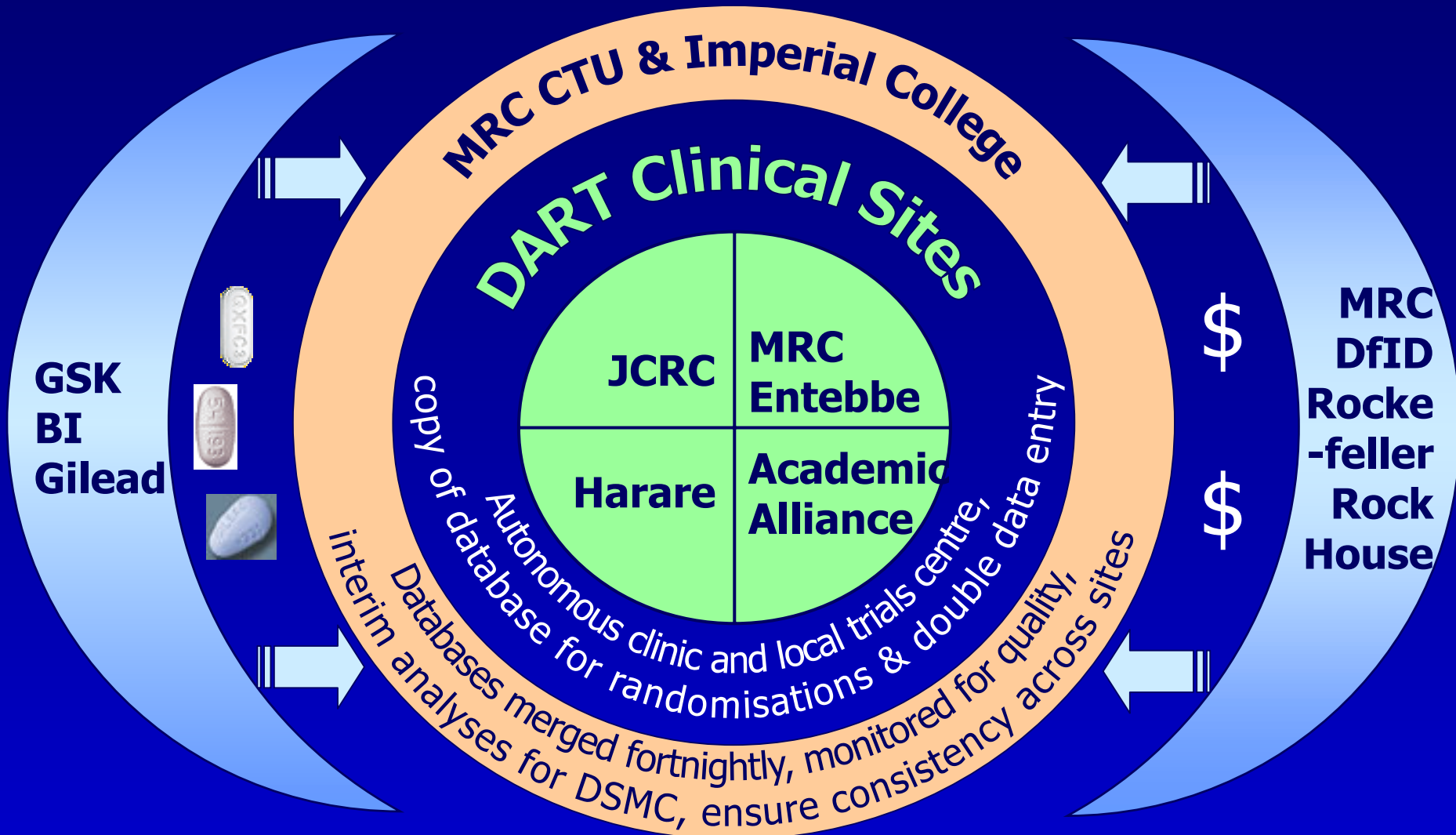


Parties involved in DART



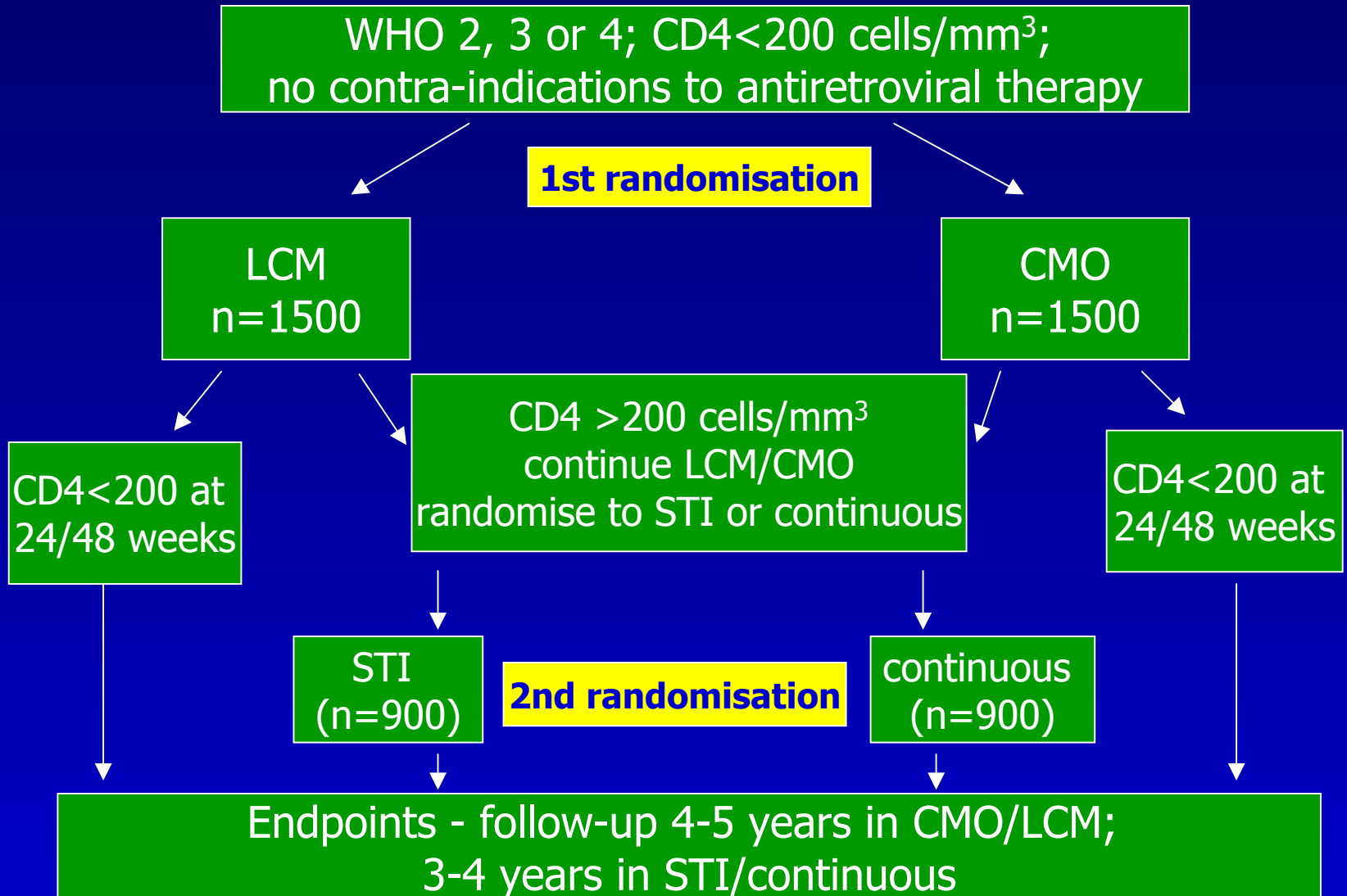


Contributions to DART





Study Design





Numbers and follow-up



DART is an international, multicentre, randomised controlled trial in **Uganda** and **Zimbabwe**

- **3000 patients** for the two monitoring strategies
- **1800 expected** to be eligible for the STI versus continuous ART
- Total duration of the trial would be 5 years
 - minimum follow-up 4 years for LCM/CMO
 - minimum follow-up 3 years for STI/CT



Antiretroviral Therapy



- ART is provided for 5 years for 3000 patients as triple therapy first-line and second-line regimens
- first-line drugs are provided by:
Boehringer-Ingelheim, Gilead, GlaxoSmithKline
 - Combivir (ZDV+3TC) plus Tenofovir (TDF) or Nevirapine (NVP) or Abacavir (ABC)
- after the trial, patients will continue to receive care through drug access programs under the respective governments of Uganda and Zimbabwe



Endpoints - Primary



- **Efficacy:**
Progression to a new WHO stage 4 event or death
- **Safety:**
Any serious adverse event which is not only HIV-related



Trial Status

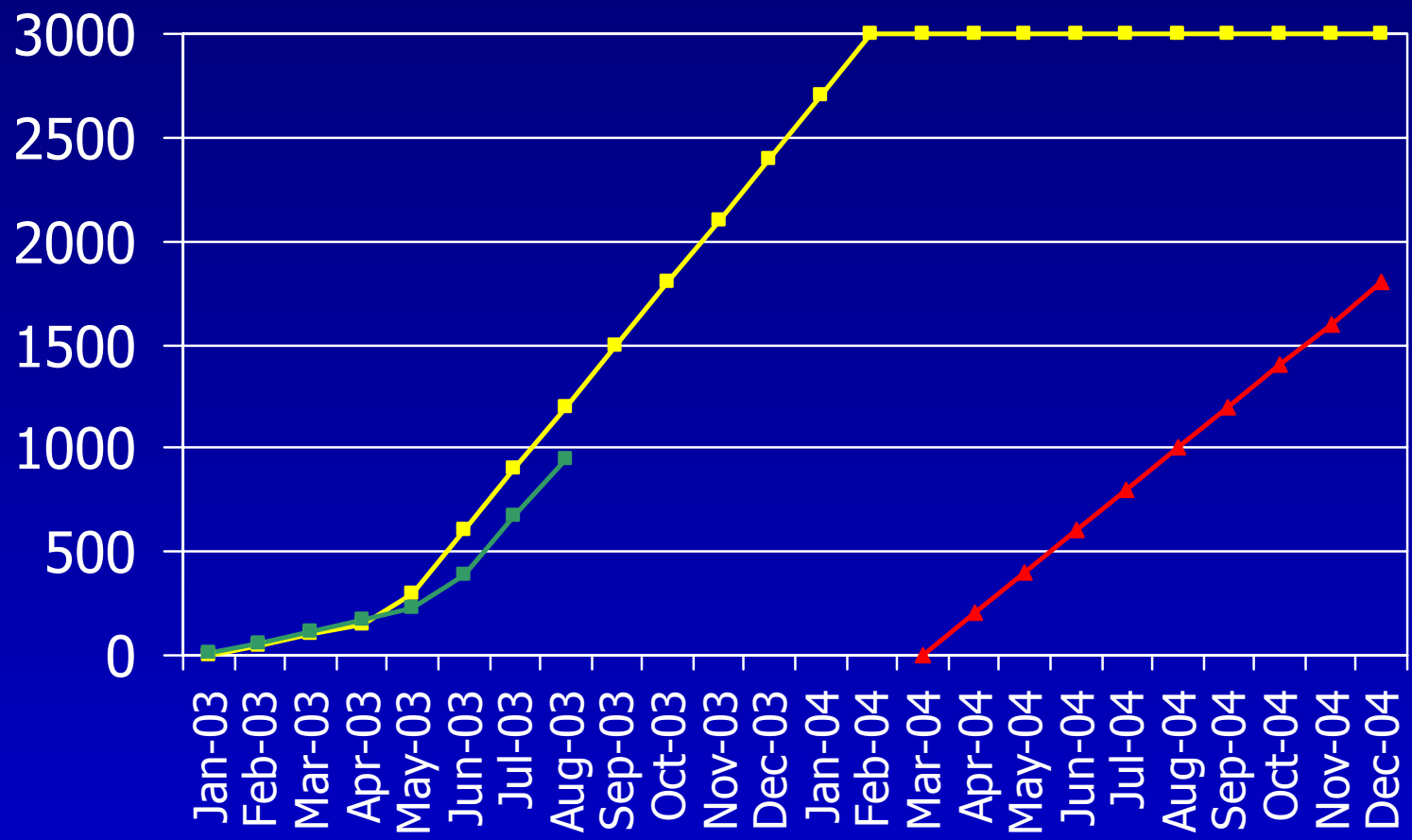


- 4 centres (Entebbe, Harare, JCRC/Academic Alliance) are currently screening and randomising patients
- first patient randomised on 15 January 2003
- currently all enrolled patients receiving ZDV+3TC+TDF as first line therapy
- 1969 patients screened to 9 September 2003
- 985 patients randomised to 9 September 2003 (50%)



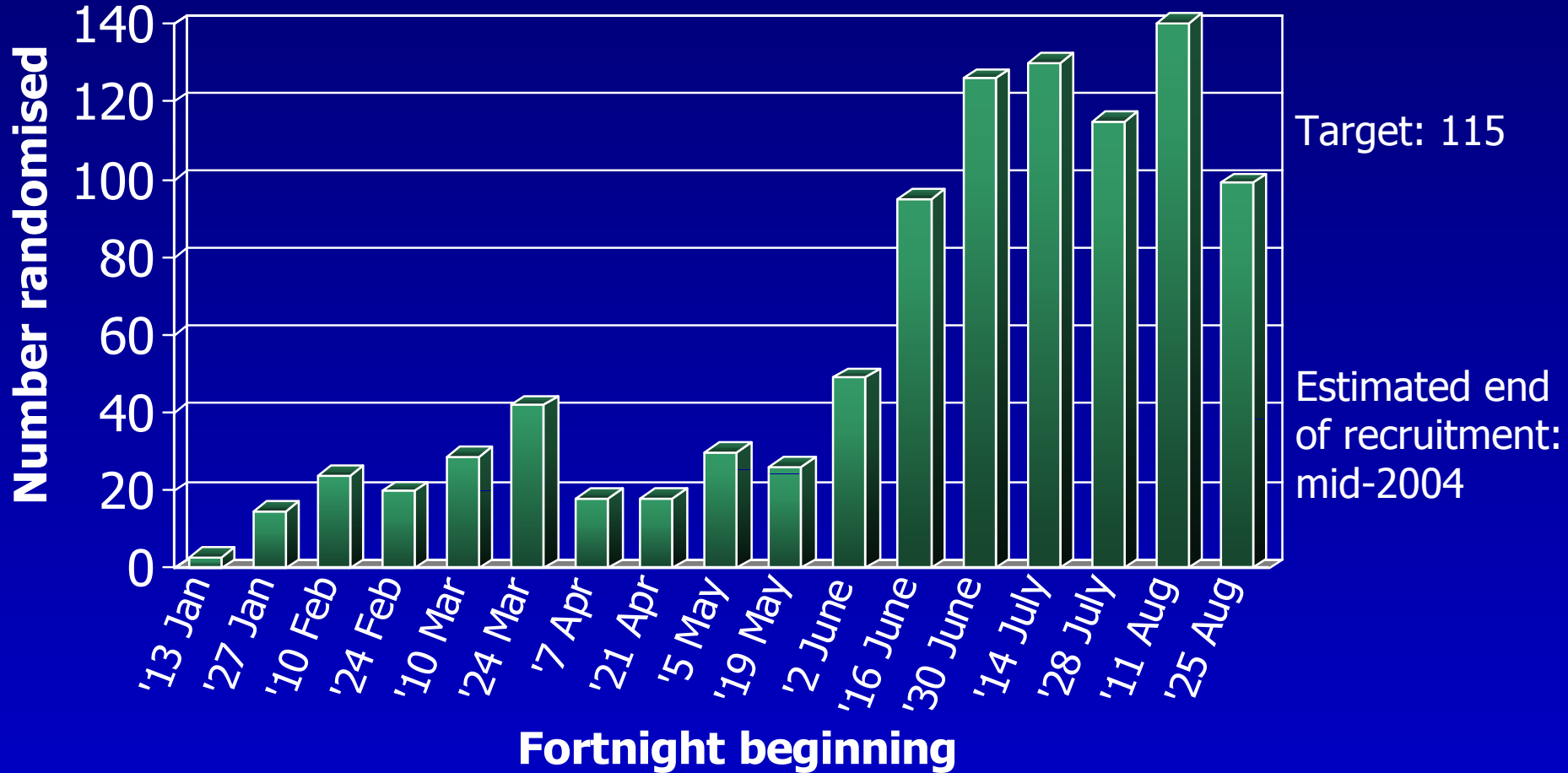
Accrual

—■ CMO vs LCM Target —■ CMO vs LCM Actual —▲ STI vs CT Target





Enrolment by fortnight





Follow-up



- detailed data on all adults randomised to 18 August 2003 (N=813)
- 7 patients have substituted d4T for ZDV for toxicity (1.0% of those seen after randomisation)
- no other ART switches



Characteristics at baseline



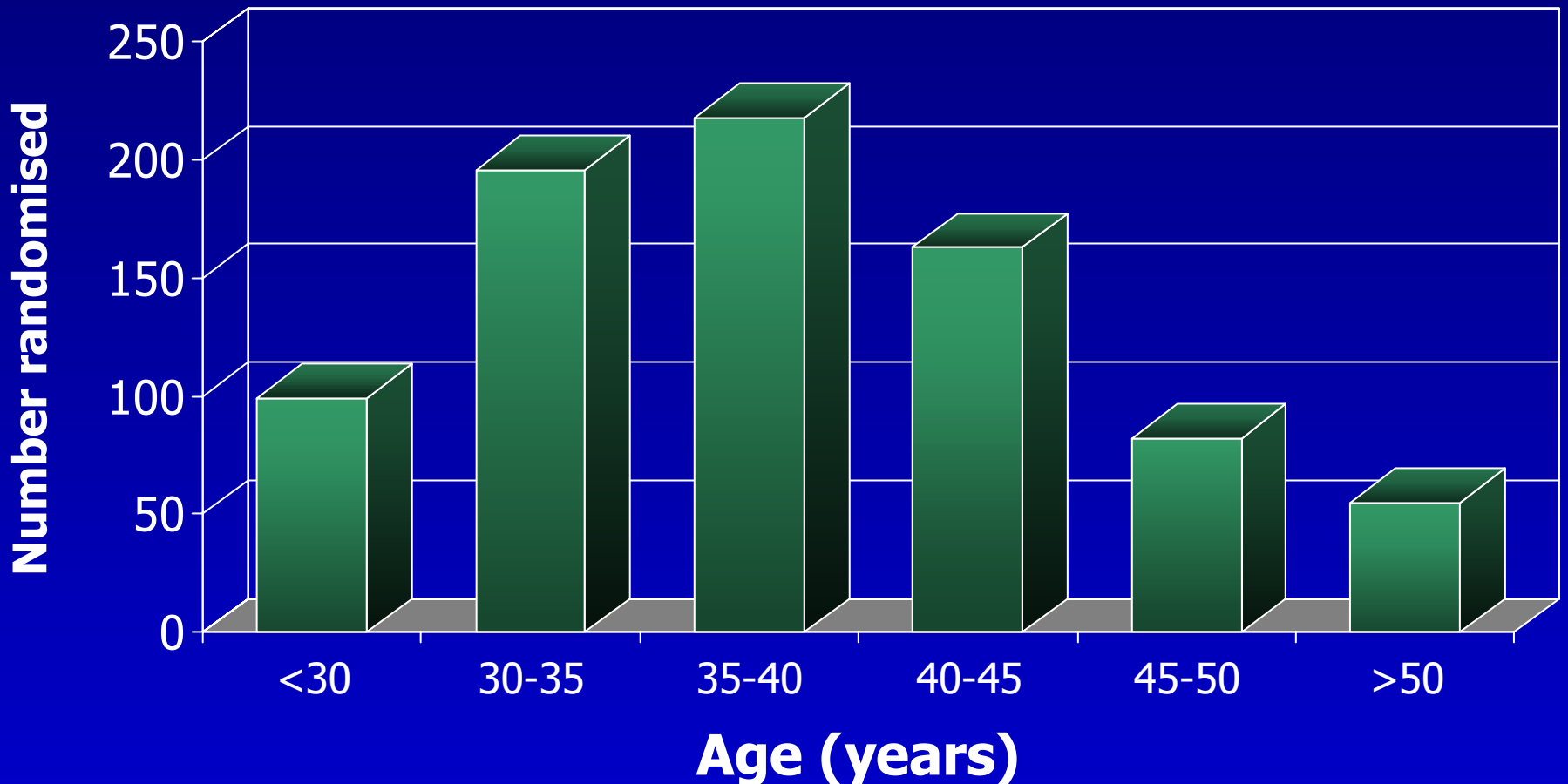
- Sex 33% male
 - 14 women have received ART to prevent MTCT
- Age (median, IQR) 37 (33-43) years
- CD4 (median, IQR) 85 (34-137)
- Randomised strategy 403 CMO: 410 LCM



Age at enrolment



Age: median 37.2 years, range 19-62 years, 17% >45 years

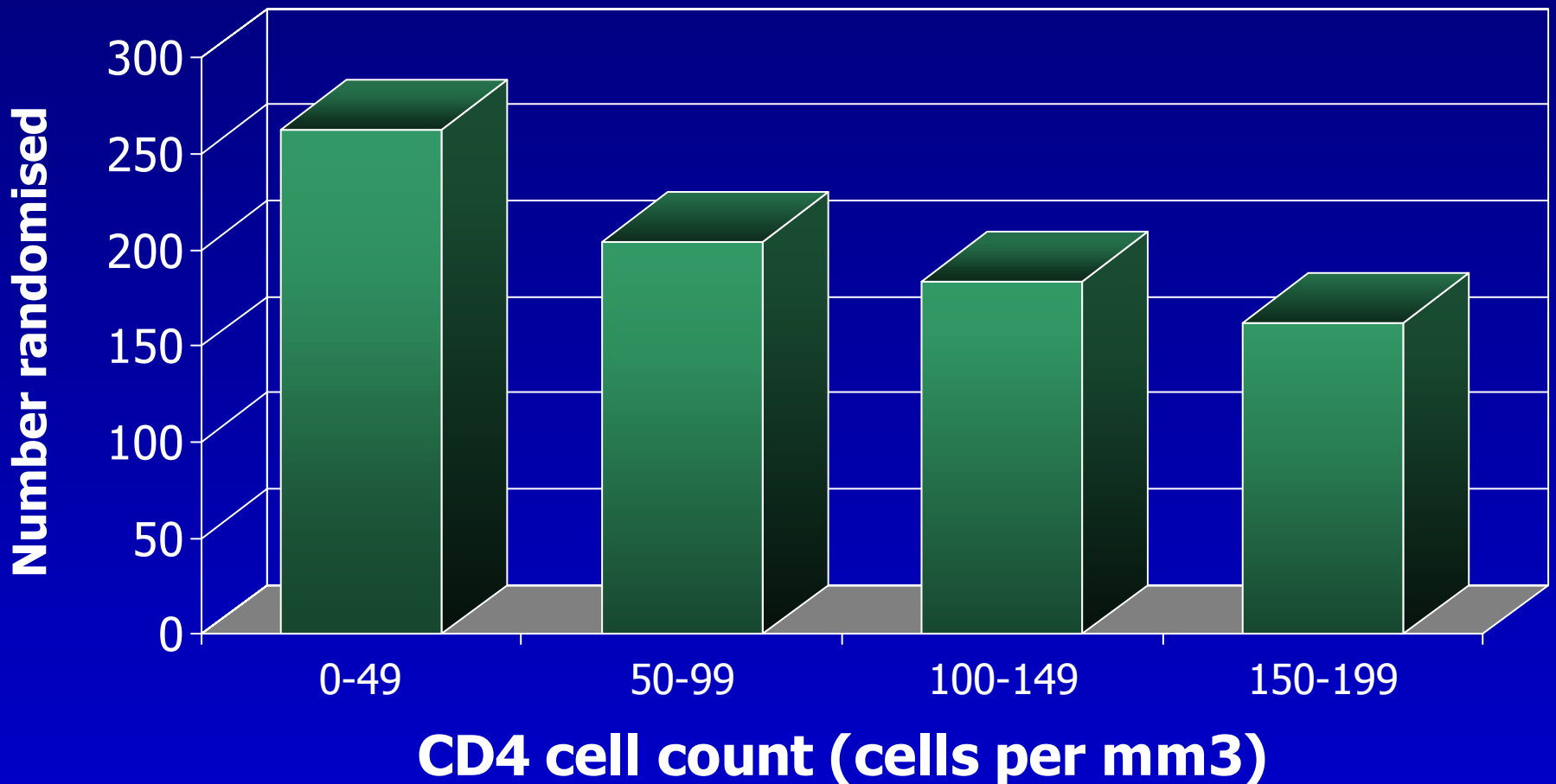




CD4 at enrolment



CD4: median 85, range 0-199; 18% <25 and 32% <50 cells/mm³

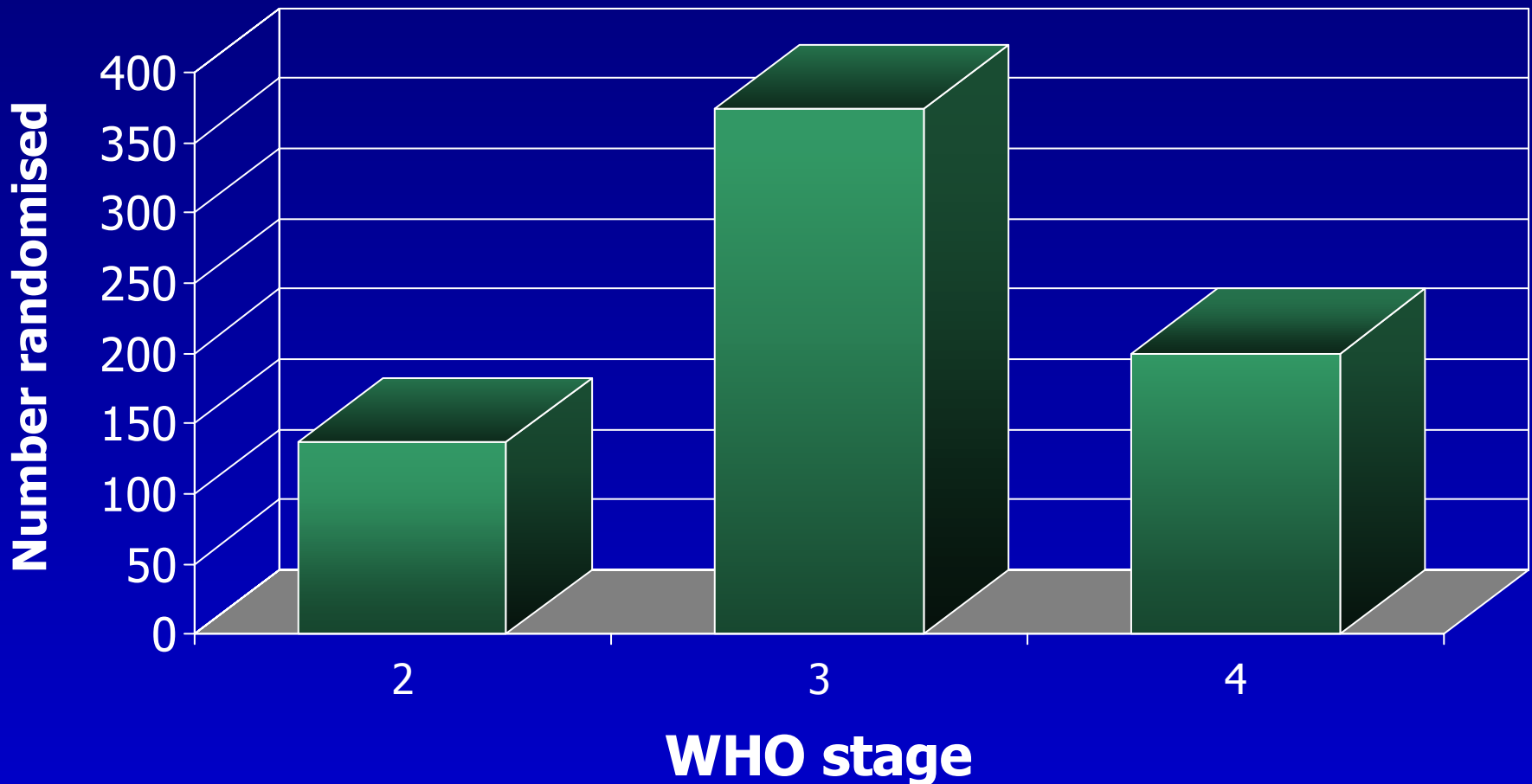




WHO stage at enrolment



19% WHO stage 2, 53% WHO stage 3, 28% WHO stage 4





STI pilot



- first patient reached 24 weeks on 2 July 2003
- first 100 patients with CD4 ≥ 200 at 24 weeks will stop ART at 28 weeks
 - stop for 12 weeks then restart same ART regimen
 - CD4 counts measured every 4 weeks
 - final analysis once 100th patient reaches 40 weeks
 - possible recommendations
 - proceed with STI randomisation as planned
 - proceed with STI randomisation with different criteria
 - 2nd final analysis after 52 weeks (12 weeks back on ART)



Summary



- obstacles to widespread ART introduction
 - drug costs
 - need for infrastructure to administer and monitor ART
 - long-term adherence
- **DART** will assess
 - whether laboratory monitoring is necessary for effective ART use
 - whether toxicity can be reduced by STI without compromising efficacy



DART Teams



- **JCRC:** P Mugenyi, C Kityo, F Ahimbisibwe, D Atwine, S Atwiine, T Bakeimyaga-Grace, G Barungi, R Byaruhanga, G Kabuye, H Katabira, S Kibende, D Muebesa, G Mulindwa, M Mulindwa, S Murungi, E Nimwesiga, T Otim, E Sennungi, F Ssali, J Takubwa, S Tugume, J Tukamushaba, D Tumukunde
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- **Entebbe:** H Grosskurth, P Munderi, B Amuron, A Dralu, P Hughes, D Kajungu, A Kamali, S Kiwuwa, E Michael, G Miiro, J Mpendo, L Muhangi, P Mukiibi, G Mutonyi, J Nakiyingi, M Namyalo, S Owilla, L Shafer, E Ssenyonjo, F Wamono, K Wangati, C Watera, B Wolff
- **Academic Alliance:** E Katabira, A Ronald, E Bulume, A Kambungu, J Martin, R Nairubi, R Nalumenya, J Oyugi, F Sematala, M Teopista, C Twijukye
- **Imperial College:** C Gilks, K Boocock, L Colquhoun, C Puddephatt
- **CTU:** J Darbyshire, DM Gibb, A Babiker, D Bray, A Burke, T Heer, P Kelleher, Y Moraes, AS Walker, H Wilkes