START Study

Strategic Timing of AntiRetroviral Treatment (START) Study

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For the INSIGHT START Australian Study team

IAS 2015

When to Start

DHHS recommendations for initiating ART (April 2015)

- "ART is recommended for all individuals with HIV infection."
  - The strength of this recommendation varies on the basis of pretreatment CD4 count (stronger at lower CD4 levels)
  - CD4 count >500 cells/μl – Grade of evidence **BIII**

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Reason START needed to be done

- Evidence for initiating antiretroviral therapy (ART) at CD4+ counts >350 cells/mm^3 primarily comes from large cohort studies from which there are inconsistent findings.
- There is uncertainty about the effects of early ART on serious non-AIDS conditions.
- Most of the morbidity at high CD4+ counts is due to non-AIDS conditions.
- The absolute risk of AIDS is low at higher CD4+ counts, therefore the adverse effects of early ART could easily outweigh the benefits of reducing the risk of AIDS.

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START Study Design

HIV-positive ART-naïve individuals with CD4 count >500 cells/μl

Randomised

Immediate ART Group	Deferred ART Group
Initiate ART immediately following randomization	Defer ART until CD4+ count declines to <350 cells/mm^3 or AIDS
N=2,326	N=2,359

Primary composite endpoint (Anticipated target = 213 endpoints)
- Serious AIDS or death from AIDS
- Serious Non-AIDS Events and death not attributable to AIDS Cardiovascular Disease, End-Stage Renal Disease, decompensated liver disease, & non-AIDS defining cancers

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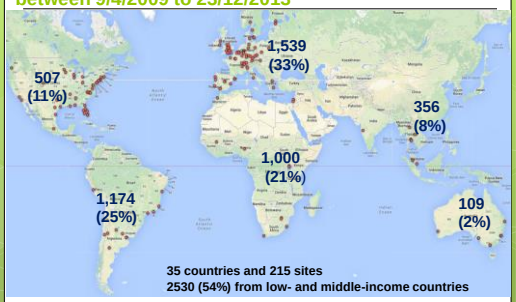
START recruited individuals from around the world between 9/4/2009 to 23/12/2013



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Baseline Characteristics - 1

Characteristic	N = 4685
Age (years)*	36 (29, 44)
Female sex [N, (%)]	1257 (26.8)
Race [N, (%)]	
Asian	388 (8.3)
Black	1410 (30.1)
Latino/Hispanic	638 (13.6)
White	2086 (44.5)
Other	163 (3.5)

* Median (IQR)

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Baseline Characteristics - 2

Characteristic	N = 4685
Mode of infection with HIV [N, (%)]	
Sexual contact	
Men having sex with men	2586 (55.2)
With person of opposite sex	1790 (38.2)
Other	309 (6.6)
Time since HIV diagnosis (yr)*	1.0 (0.4, 3.1)
Current smoker [N, (%)]	1496 (31.9)
Framingham 10-year CHD risk (%)*	1.9 (0.5, 5.1)

* Median (IQR)

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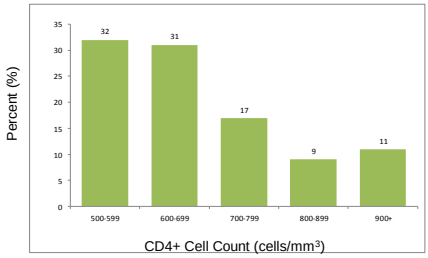
Baseline CD4+ Count Distribution

Median (IQR): 651 (584 - 765)



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Data Safety Monitoring Board Guidelines

START protocol recommended early termination only when there was clear and substantial evidence of a treatment difference

- Both major components of primary endpoint had to be consistent (favoring same treatment arm)

START DSMB recommended early termination on 15 May 2015

At that time - 59% of the expected 213 primary events had been reported

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Completeness of Follow-up

Total follow-up	14,060 PY
Mean follow-up	3.0 years
Followed for 4+ years	24%
Not seen in the last 10 months	4.5%

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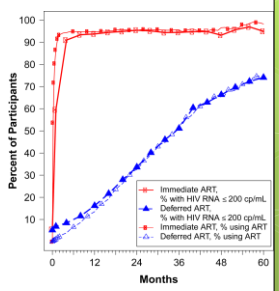
Percent on ART and with HIV-RNA ≤ 200 copies/mL

	% of follow-up on ART
Immediate	94
Deferred	28

Deferred Arm:
Median time to ART
3 years (IQR 1.6-4.8)
(projected 4 years)



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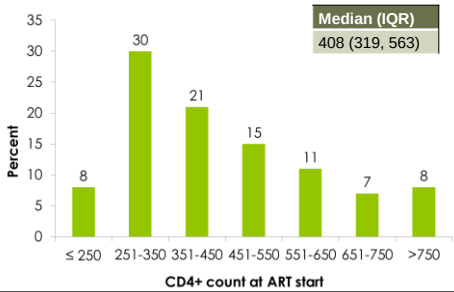
CD4+ count at ART start in Deferred Group

Median (IQR)
408 (319, 563)



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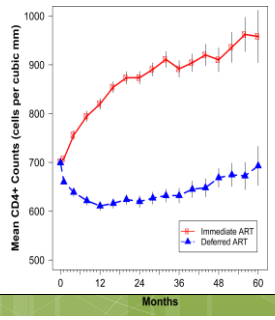
Mean CD4+ count during follow-up



Estimated difference:

194 cells/mm^3

(95% CI: 185-203)

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Primary Endpoint

	Immediate ART	Deferred ART
No. with Event (%)	42 (1.8%)	96 (4.1%)

This means a 57% reduced risk of developing an AIDS illness, a serious non-AIDS illness or dying from any cause for those that started ART immediately

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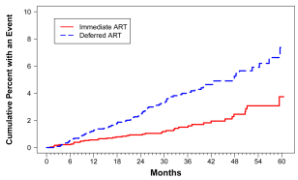
Primary Endpoint

Type of event	Immed	Defer
Serious AIDS	14	50
Serious non-AIDS	29	47
Total*	42	96



* One participant in each group had both a Serious AIDS and a Serious Non-AIDS Event

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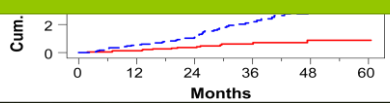
Serious AIDS Events

	Immediate	Deferred
No. with event	14	50

A 78% reduction in serious AIDS events for those who started ART immediately



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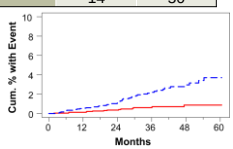
Serious AIDS Events

AIDS events	Immed	Defer
TB (pulmonary or extrapulmonary)*	6	20
Lymphoma, Hodgkin's or Non-Hodgkin's	3	10
Kaposi's sarcoma	1	11
Pneumocystis pneumonia	1	5
Herpes zoster, disseminated	0	3
Other**	3	1
Any Serious AIDS event	14	50

*Participants from Africa: 16/26 (62%) of TB cases

** Cervical carcinoma, extra-pulmonary cryptococcosis, CMV, recurrent bacterial pneumonia



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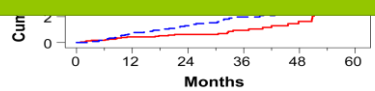
Serious Non-AIDS Events

	Immediate	Deferred
No. with event	29	47

A 39% reduction in serious non-AIDS events for those who started ART immediately



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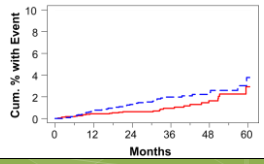
Serious Non-AIDS Events

Non-AIDS event	Immed	Defer
Cancer, non-AIDS*	9	18
Cardiovascular disease*	12	14
Liver or renal disease	1	2
Death, other	7	13
Any Serious Non-AIDS	29	47

Participants from Australia, Europe, Israel and USA:

22/27 (81%) of cancer cases
19/26 (73%) of CVD cases



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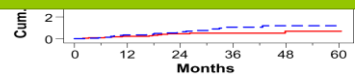
Deaths

	Immediate	Deferred
No. with event	12	21

No significant reduction in deaths for those who started ART immediately



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Cancer

	Immediate	Deferred
No. with event	14	39

A 64% reduction in all forms of cancer (both AIDS and non-AIDS) for those who started ART immediately

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Components of Primary endpoint

End Point	Immediate-Initiation Group (N=2326) no.	Immediate-Initiation Group (N=2326) no./100 person-yr	Deferred-Initiation Group (N=2359) no.	Deferred-Initiation Group (N=2359) no./100 person-yr	Hazard Ratio (95% CI)†	P Value
Composite primary end point	42	0.60	96	1.38	0.43 (0.30–0.62)	<0.001
Components of the primary end point						
Serious AIDS-related event	14	0.20	50	0.72	0.28 (0.15–0.50)	<0.001
Serious non-AIDS-related event	29	0.42	47	0.67	0.61 (0.38–0.97)	0.04
Death from any cause	12	0.17	21	0.30	0.58 (0.28–1.17)	0.13
Tuberculosis	6	0.09	20	0.28	0.29 (0.12–0.73)	0.008
Kaposi's sarcoma	1	0.01	11	0.16	0.09 (0.01–0.71)	0.02
Malignant lymphoma	3	0.04	10	0.14	0.30 (0.08–1.10)	0.07
Cancer not related to AIDS	9	0.13	18	0.26	0.50 (0.22–1.11)	0.09
Cardiovascular disease	12	0.17	14	0.20	0.84 (0.39–1.81)	0.65

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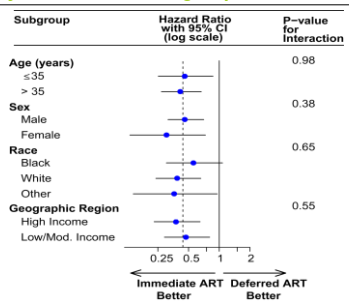
Primary End Point for Subgroups



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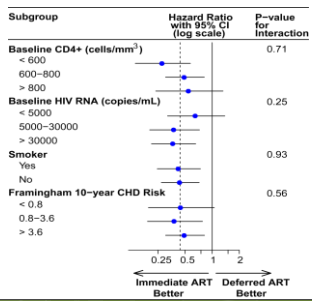
Primary End Point for Subgroups



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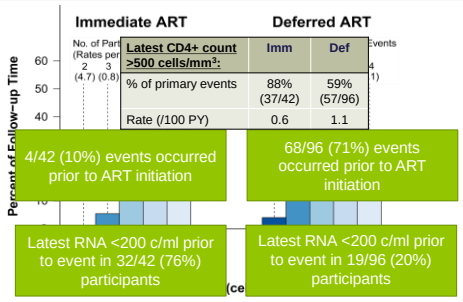
Follow-up time and primary endpoints by latest CD4+ count



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Other Serious Clinical Events*

Endpoint*	Immediate		Deferred		Hazard Ratio	p
	No	Rate/100PY	No	Rate/100PY		
Grade 4 event**	73	1.06	73	1.05	1.01 (0.73-1.39)	0.97
Unscheduled hospitalization	262	4.02	287	4.40	0.91 (0.77-1.08)	0.28
Grade 4 event, unscheduled hospitalization, or death from any cause	283	4.36	311	4.78	0.91 (0.77-1.07)	0.25

* all participants irrespective of use of ART
** DAIDS grading system – only symptomatic events

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Summary – START study

1.8% of START study participants in the immediate and 4.1% in the deferred group experienced the primary outcome (Serious AIDS Events, Serious Non-AIDS Events, or Death)

- 57% reduction in risk
- Evident for both AIDS and Serious Non-AIDS
  - Greater for Serious AIDS Events
  - For TB and cancer
- Consistent regardless of
  - Age, gender, race, region of the world
  - CD4+ count, HIV viral load at entry

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Summary - continued

- Most events occurred at high CD4+ counts (also in the Immediate Arm despite ART), including AIDS Events
- HIV-induced immunodeficiency
  - Occurs early in HIV-infection
  - CD4+ counts do not fully capture this
- Safety outcomes were similar in the two groups

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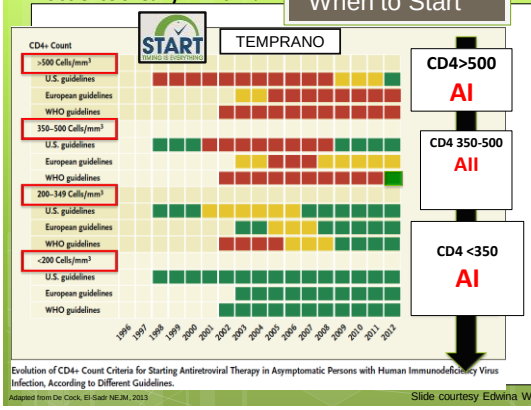
Conclusions

- Combination antiretroviral therapy (ART) should be recommended for all HIV-positive persons regardless of CD4+ count.
- The START Study results align the benefits of ART to the HIV-positive individual

to the benefits of ART in reducing the risk of viral transmission from HIV-positive persons to non-HIV-infected individuals.

The science of early ART is IN! — When to Start



Slide courtesy Edwina Wright

START Study

Acknowledgments

- START study participants
- INSIGHT International Coordinating Center staff, INSIGHT Coordinating Center staff in copenhagen, London, Sydey and Washington, University of Minnesota (Study Sponsor), START study site research staff worldwide.
- Particular thanks to Sydney ICC, (Sean Emery, Cate Carey, Simone Jacoby, and the ICC team), the Australian investigators and especially the Australian study co-ordinators.

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START collaboration with pharmaceutical industry

Abbott: Ritonavir, lopinavir/ritonavir

Bristol-Myers Squibb: Efavirenz (EFV), atazanavir, EFV/emtricitabine (FTC)/tenofovir (TDF)

Gilead: FTC/TDF, EFV/FTC/TDF, rilpivirine/FTC/TDF, cobicistat/elvitegravir/FTC/TDF

GlaxoSmithKline/ViiV: Fosamprenavir, dolutegravir, zidovudine/lamivudine (3TC), abacavir/3TC

Merck: EFV, raltegravir, EFV/FTC/TDF

Janssen/Tibotec: Darunavir

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START Study Funding

PRIMARY FUNDER

- **Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)**

OTHER SUPPORT

- Department of Bioethics, NIH Clinical Center
- Division of Clinical Research (NIAID)
- National Cancer Institute (NCI)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute of Child Health and Human Development (NICHD)
- National Institute of Mental Health (NIMH)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute of Arthritis & Musculoskeletal & Skin Diseases (NIAMS)
- Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS, France)
- Bundesministerium für Bildung und Forschung (BMBF, Germany)
- NEAT - European AIDS Treatment Network
- **Australian National Health and Medical Research Council (NHMRC)**
- UK National Institute for Health Research & Medical Research Council
- Danish National Research Foundation

When to Start

Does early ART cause net harm ?

- Low risk of morbidity and mortality in early HIV without ART; especially in young people
  - *If* ART beneficial: many treated for one to benefit
- ART can adversely affect many organs - including kidney, bone, liver, CVD, depression, and cancer
  - Risk is low – many treated for one to be harmed
- **If the number needed for 1 to be harmed is higher than the number needed for 1 to benefit = ART is of net harm**

When to Start

Number needed to treat for one person to benefit

Immediate treatment event rate (ITER) – 1.8%

Deferred treatment event rate (DTER) – 4.1%

Absolute risk reduction = DTER-ITER = 4.1% - 1.8% = 2.3%

Relative risk reduction = (DTER-ITER)/DTER = 56.1%

Number needed to treat = 1/(DTER-ITER) = 43.5

START Study

Primary Endpoint

Clinical Endpoint Review Committee adjudication

- **Serious AIDS:**
  - AIDS (excluding esophageal candidiasis and chronic herpes simplex infection), death from AIDS and Hodgkin's lymphoma
- **Serious Non-AIDS Events:**
  - CVD: myocardial infarction, stroke, coronary revascularization
  - Chronic ESRD: initiation of dialysis, renal transplantation
  - Decompensated liver disease
  - Non-AIDS-defining cancers, excluding basal and squamous cell skin cancers.
  - Death not attributable to AIDS, including death of unknown cause

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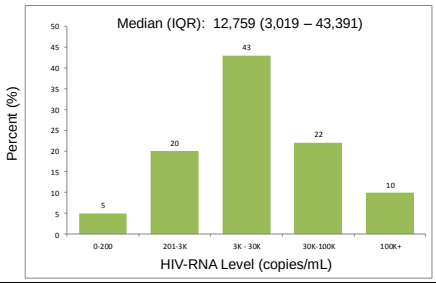
Baseline HIV-RNA Distribution



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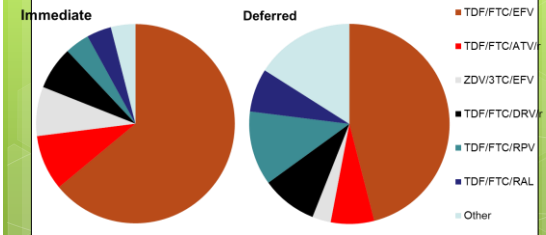
Frequently used initial ART combinations



N=2287 (98%)

N=1134 (48%)

Efavirenz: 73% vs 51%

Tenofovir: 89% in both groups

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Causes of Death

Cause	Immed	Defer
Accident/violence/suicide	4	6
AIDS, active disease	1	4
Cardiovascular disease	3	1
Non-AIDS cancer - HBV/HCV	1	1
Substance abuse	0	2
Other*	0	4
Unknown	3	3
Total	12	21

*Chronic viral hepatitis, renal failure, infection, diabetes mellitus