ART in Myanmar

Dr. Mar Mar Aye

Consultant Physician

Mandalay General Hospital (MGH)

GreenShoots FOUNDATION

“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the

Medical Assistance & Medical Education (MAME) Programs

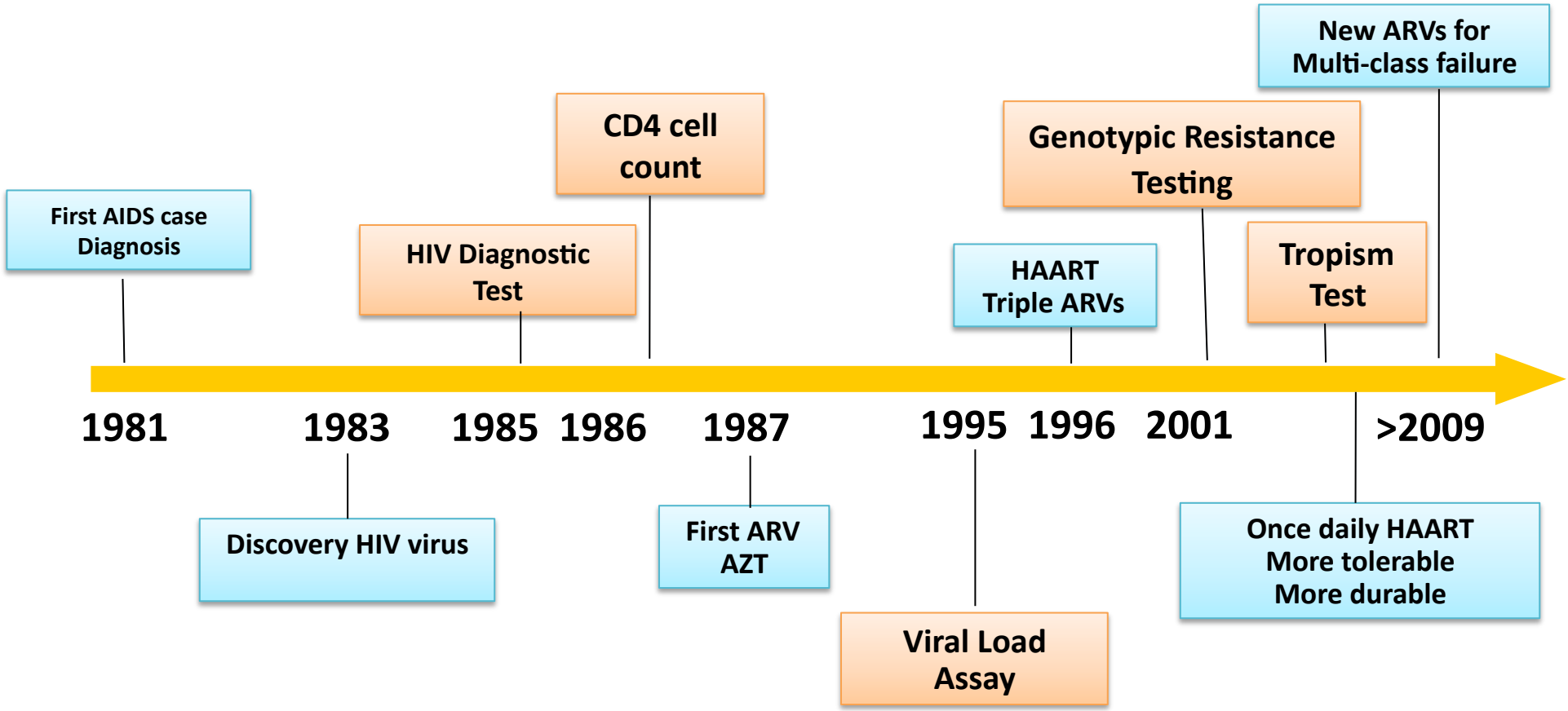
GreenShoots FOUNDATION

Antiretroviral therapy in myanmar

Dr Mar Mar Aye
Consultant Physician
Mandalay General Hospital (MGH)
9.1.2015

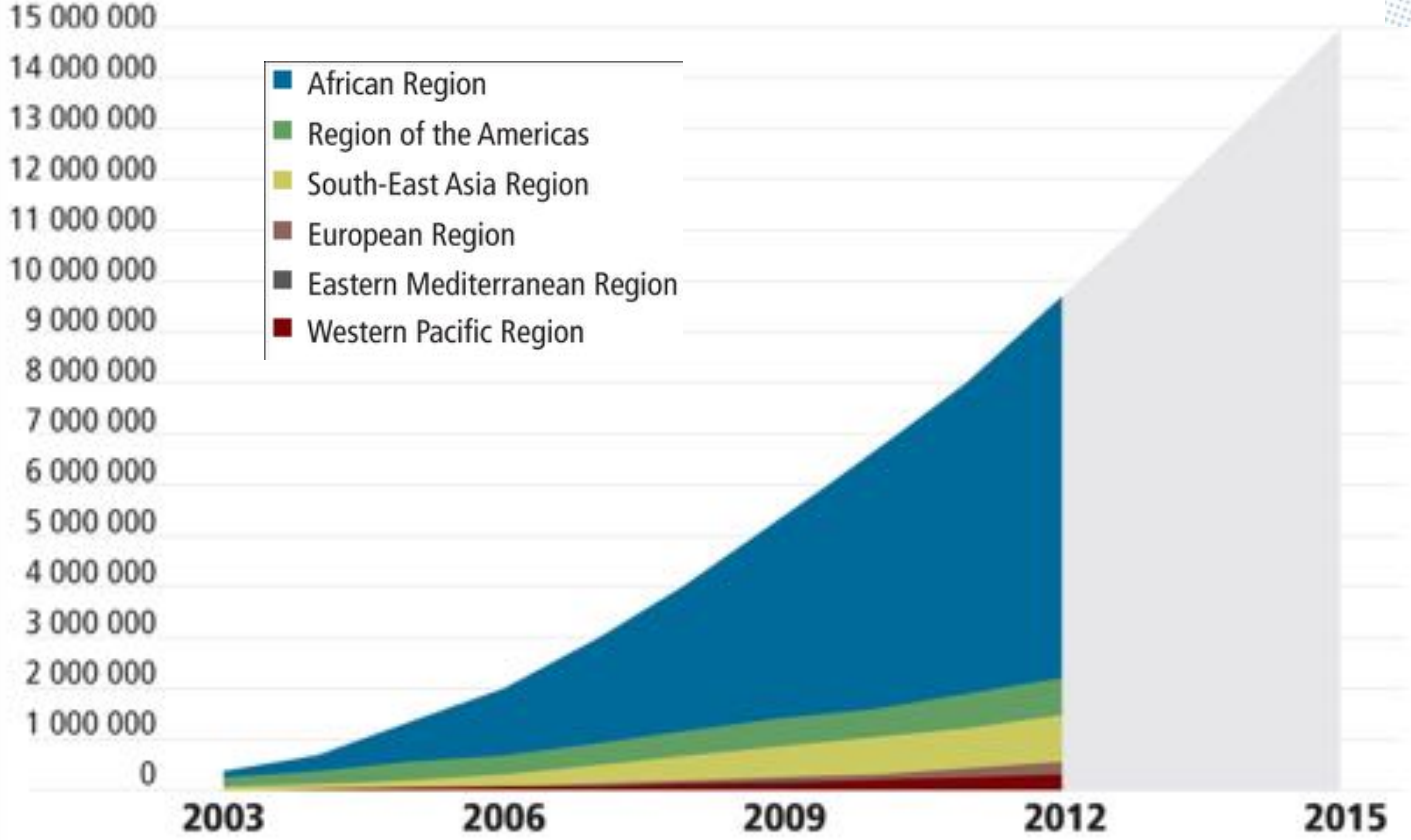
Back ground

Milestones in HIV Medicine



9.7 million people on ART by end of 2012 - 1.6 million more than at the end of 2011

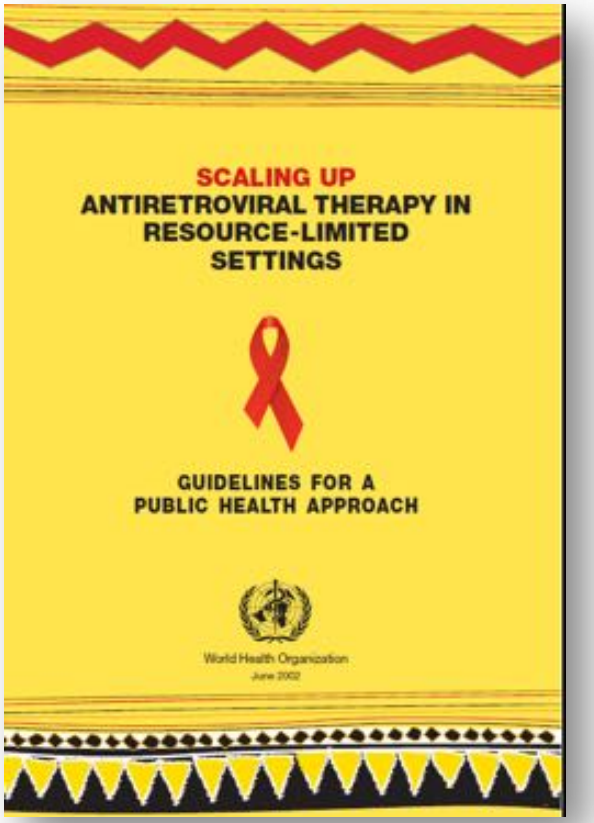
Actual and projected numbers of people receiving antiretroviral therapy in low-and middle-income countries, and by WHO Region, 2003–2015



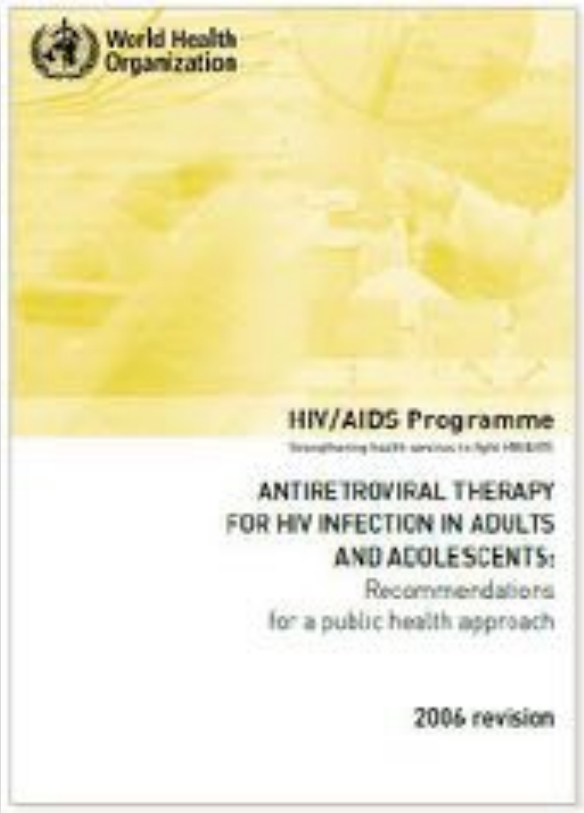
Source: 2013 Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS).

World Health Organization

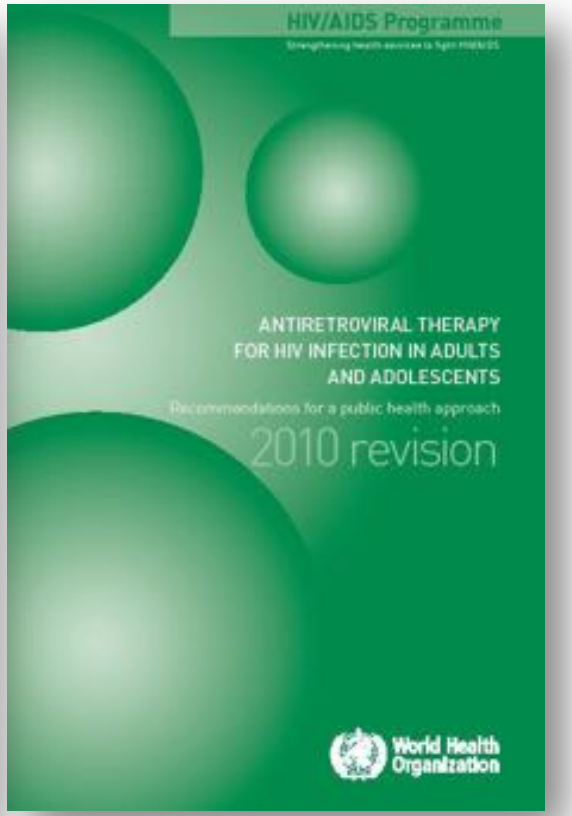
WHO's public health guidelines on ART: from "3 by 5 Initiative" to Universal Access



2002-2003



2006



2010

When to start ART: what is new since 2010 ?

- ***Strong evidence*** of the impact of ART on HIV transmission:
  - HPTN 052 study

- ***Emerging data*** on the impact of ART on HIV incidence at the population level

- ***Increasing evidence*** on clinical benefits of early ART initiation:
  - Observational studies showing **impact on HIV mortality and morbidity**
  - Scientific insights on HIV **immunopathogenesis** and on the effects of chronic **inflammation** associated with HIV infection

- **Better regimens**:
  - Better tolerable drugs
  - Better formulations
  - New classes

Increasing evidence that ART should be used earlier rather than later

Likely benefits of earlier initiation

– improves clinical benefits (AIDS & non-AIDS)

– decreases risk of TB

– offers medium and long term cost-saving opportunities

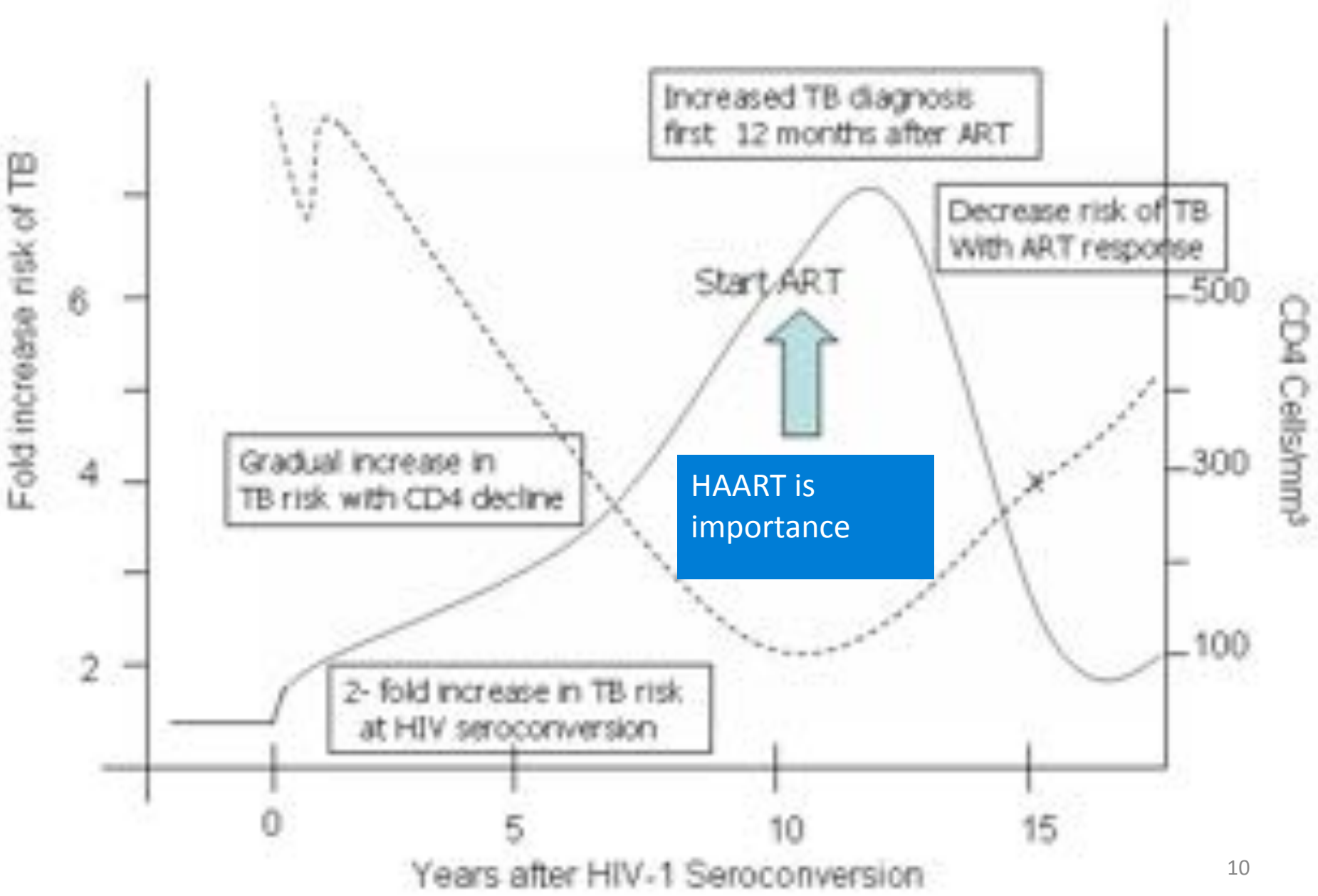
but

– could increase toxicities and risk of drug resistance

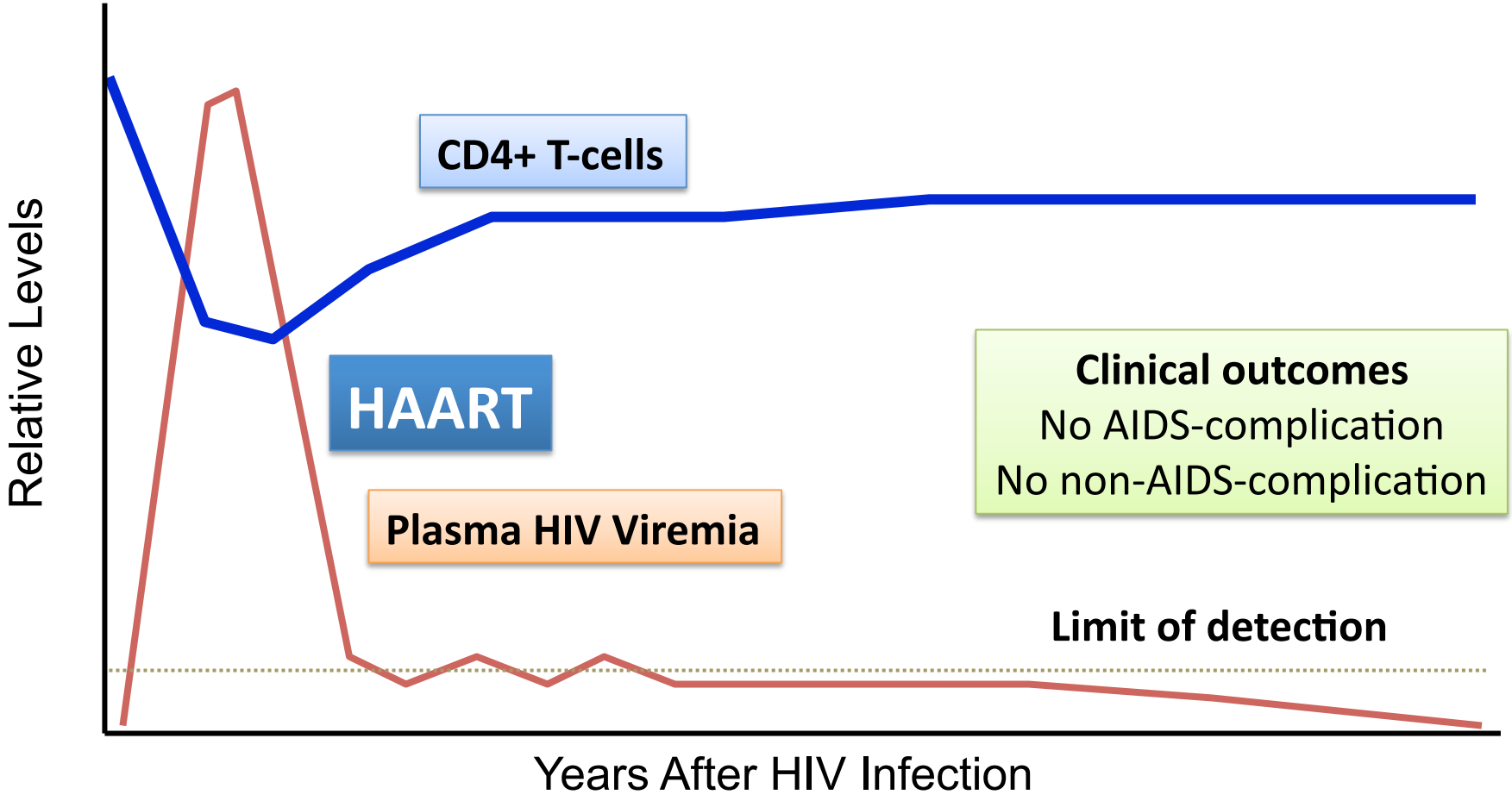
– increase up-front costs

– might limit preservation of treatment options

Risk of developing TB in HIV infected patients



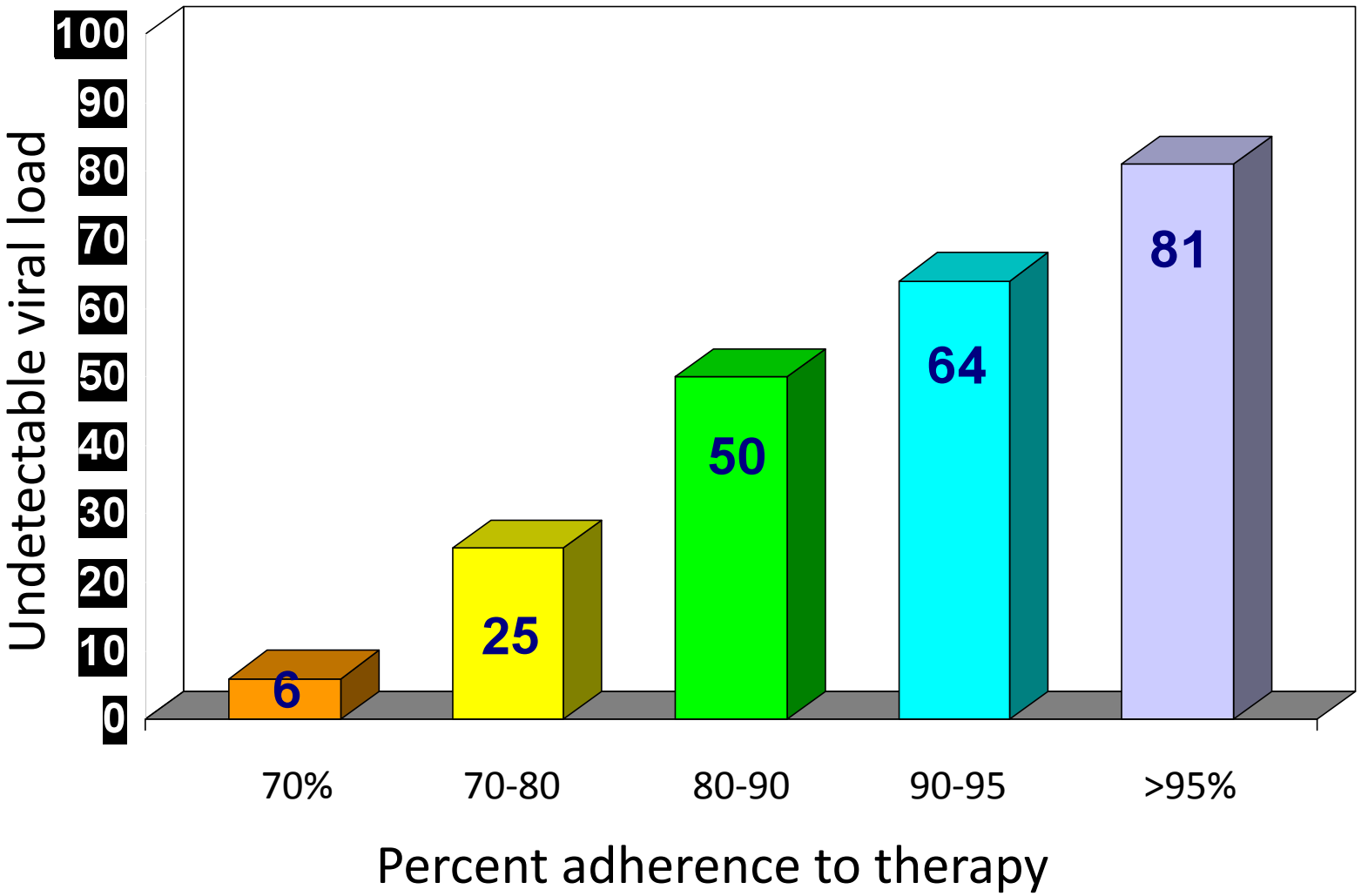
Current Ultimate Goal of HAART



Tools to Achieve Treatment Goals

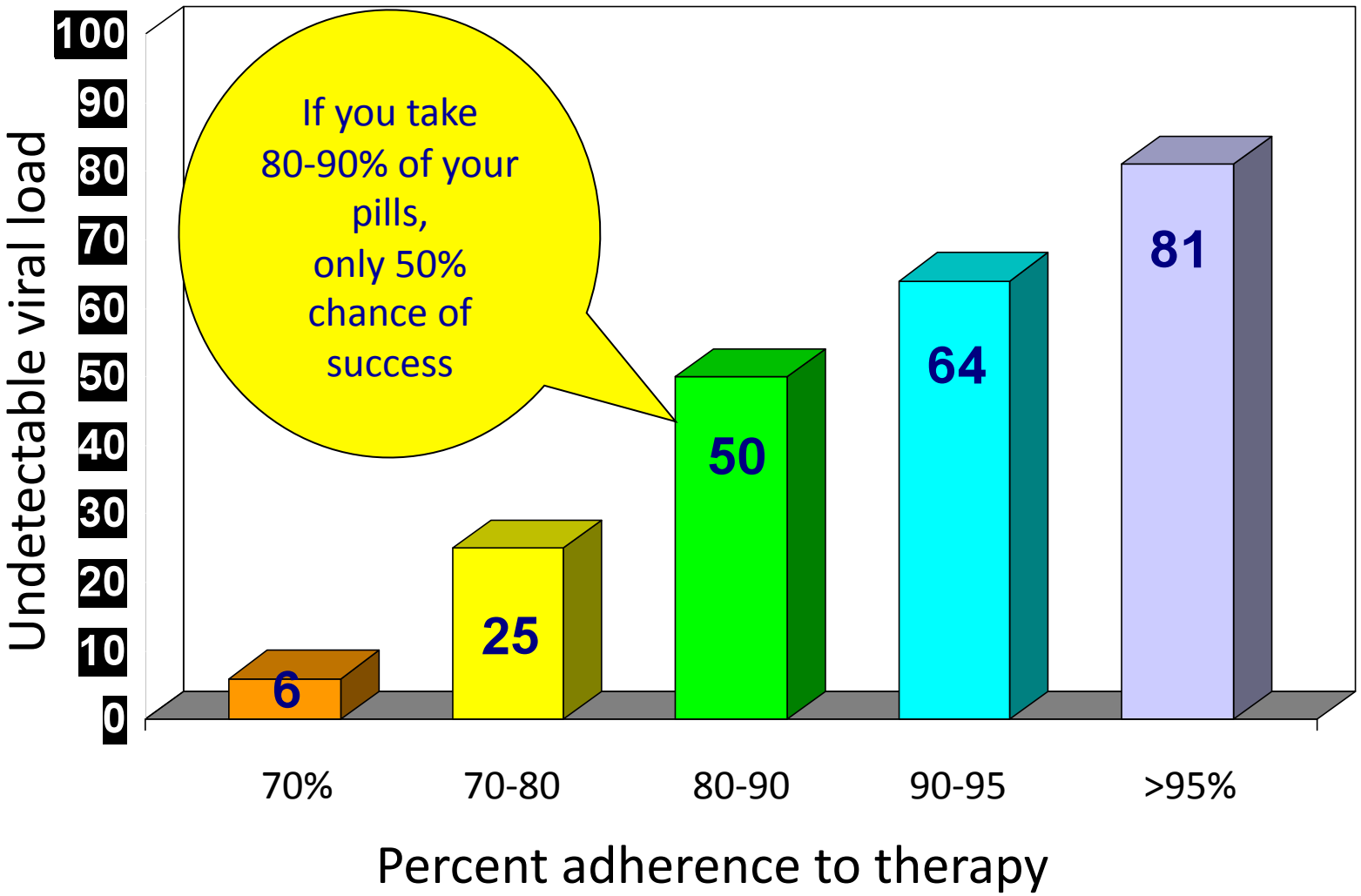
- Optimizing of ARV regimen : right drug for right person
- Maximizing adherence
  - compliance is very importance !!!!!
- Pretreatment resistance testing
- Discuss need for *regular follow up*
- People on ART still need to *use condoms*

Adherence versus Viral Load



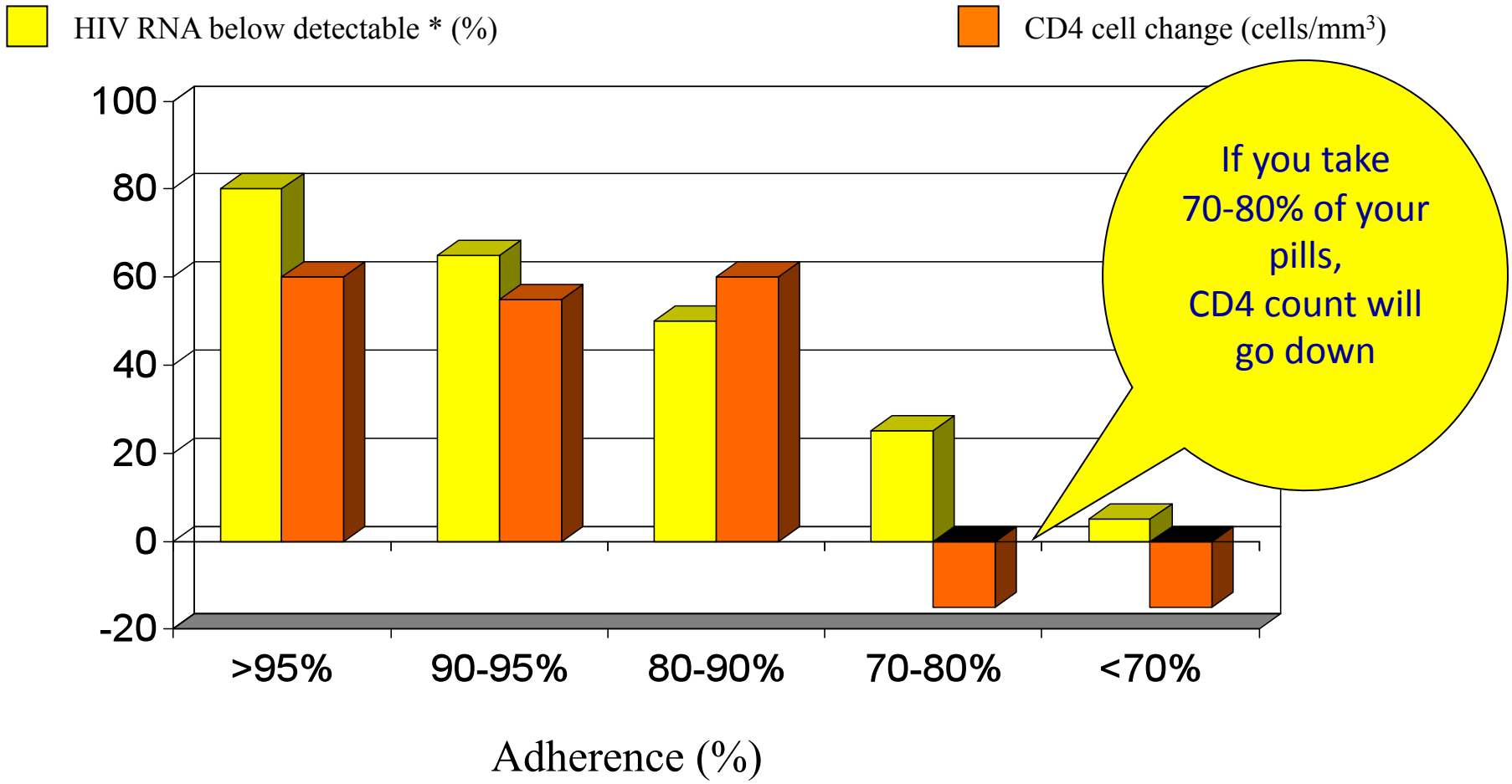
From Peterson et al, 6th Conf ROI abstr #92

Adherence versus Viral Load



From Peterson et al, 6th Conf ROI abstr #92

Adherence vs Response

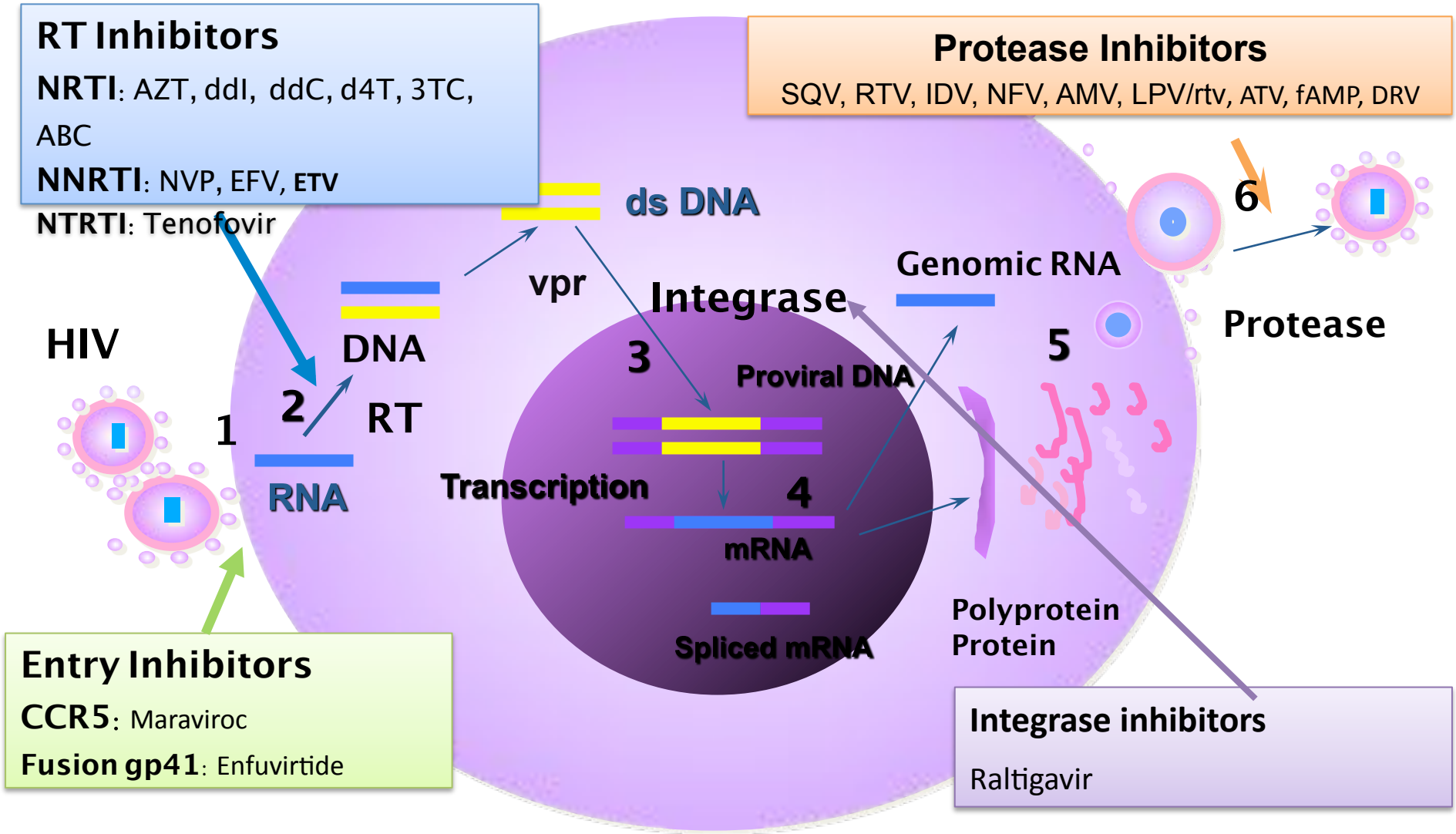


Important messages when starting ART

Patients should understand

- that ART is suppressive therapy
- that ART is life-long
- that near perfect adherence is necessary to prevent ART resistance
- that there are possibilities of side effects

Major Targets of Antiretroviral Agents



Classes of ARVs – clinical practice

NRTI	PI	NNRTI	Fusion inhibitors	Entry inhibitors	INSTI
Zidovudine	Saquinavir	**Nevirapine**	Enfuvirtide	Maraviroc	Raltegravir
Didanosine	**Ritonavir**	Delavirdine			
Stavudine	Indinavir	**Efavirenz**			
Lamivudine	Nelfinavir	Etravirine			
Abacavir	**Lopinavir/r**	Rilpivirine			
Tenofovir	**Atazanavir/r**				
Emtricitabine	Fosamprenavir				
	Tipranavir				
	Darunavir				

When to Start ART

When to start ART in Adults & Adolescents

Myanmar National Guideline 2011

- HIV positive **asymptomatic** ARV naïve individuals – CD4 $\leq$ 350/mm^3

- HIV positive **symptomatic** ARV naïve individuals – WHO stage 2 if CD4 $\leq$ 350/mm^3

or WHO stage 3 or 4 irrespective of CD4 count

Starting ART in specific situations

- HIV positive **pregnant women** with CD4 ≤ 350/mm3 irrespective of clinical symptoms or WHO clinical stage 3 or 4 irrespective of CD4 count

- **HIV/TB co-infection** ARV naïve individuals –presence of active TB if CD4 ≤ 500/mm3 (MDR TB, ART regardless of CD4 count)

- **HIV/HBV co-infection** – individuals who require treatment for their HBV infection regardless of CD4 count

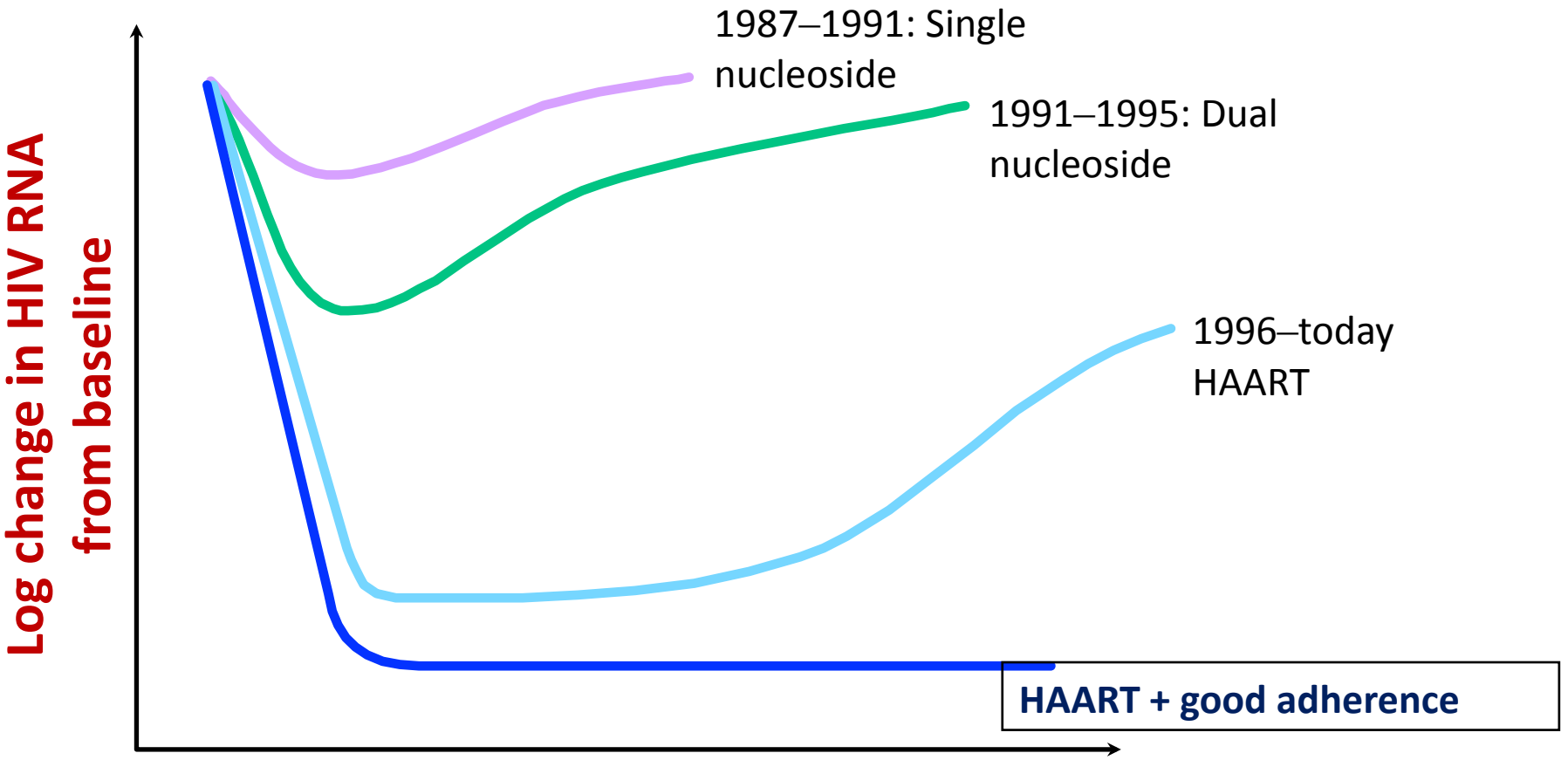
When to start ART (WHO 2013)

- **Threshold moved to ≤ 500 CD4** NEW
- **Priority for reaching all HIV+ symptomatic persons and those with CD4 ≤ 350**
- **More CD4-independent situations for ART initiation (in addition to HIV/TB co-infection and HBV advanced liver disease):**
  - HIV serodiscordant couples NEW
  - Pregnancy NEW

GL are a "tool" for countries to produce their own guidelines:
they will adapt the new threshold(s) with operational / programmatic local context

WHAT ART REGIMEN TO START

Why always use three drugs



First Line Antiretroviral Drugs in Myanmar
(2011 National guideline)

3 drug combinations should always be used for antiretroviral therapy.

1. **AZT +3TC + EFV (*)**
2. **AZT +3TC+ NVP (*)**
3. **TDF +3TC/FTC + EFV (*)**
4. **TDF +3TC/FTC + NVP**
5. **d4T*+3TC/EFV**
6. **d4T*+3TC+NVP**

(*) Preferred First Line ART regimen

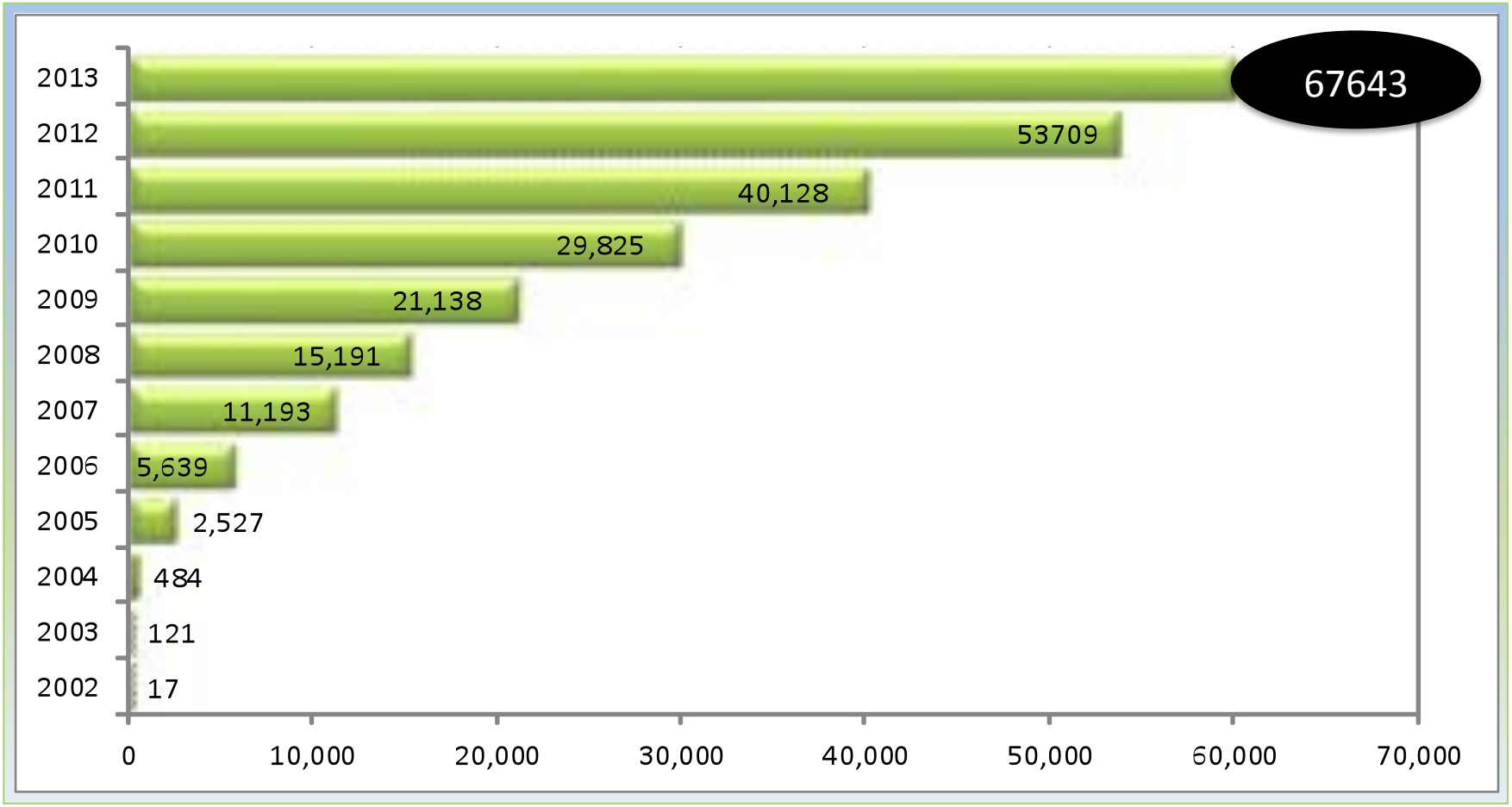
First Line Antiretroviral for 2014 in Myanmar(new patient)

3 drug combinations should always be used for antiretroviral therapy.

No	ART Regimen	Recommended Regimen %	Remark
1	**TDF +3TC (FTC) + EFV**	77%	**Preferred first line regimen**
2	**AZT +3TC + EFV**	11%	**Alternative first line regimen**
3	**AZT +3TC+NVP**	5%	
4	ABC+3TC+EFV	7%	

(d4T* is phasing out gradually and will not be available beyond 2015)

Number of PLHIV receiving ART



67,643 on ART for 2013… reports being compiled for final figures

HOW TO MONITOR AND WHEN TO SWITCH

Monitoring ART in those at higher risk of adverse effects

ARV drug	Major toxicity	High-risk situations
d4T	Lipodystrophy, neuropathy, lactic acidosis	Age > 40 yr, CD4 < 200/mm3, BW > 75 kg, INH or ddI use
AZT	Anaemia, neutropenia	Anaemia at baseline, CD4 < 200/mm3, BW < 50 kg
TDF	Renal dysfunction	Underlying renal disease, age > 40 yr, BW < 50 kg, diabetes, hypertension, PI or nephrotoxic drugs
EFV	Teratogenicity Psychiatric illness	First trimester of pregnancy Depression or psychiatric illness
NVP	Hepatotoxicity	HCV and HBV coinfection

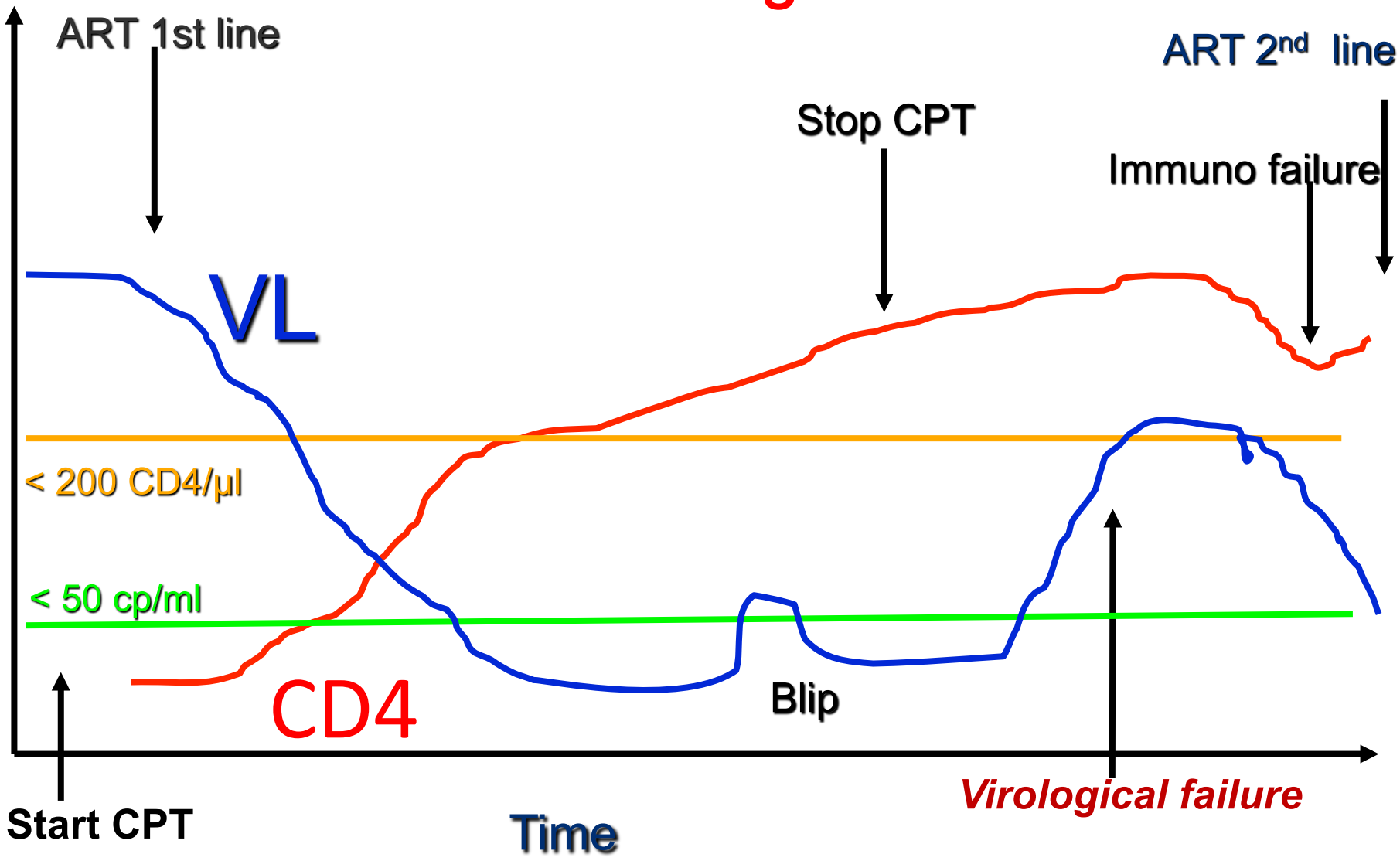
Monitoring

CBC, CD4	Every 4-6 months
HIV viral load	Every 6-12 months
FBS, lipid profile, UA, Electrolyte	Every 6-12 months
SGOT, SGPT, Cr	Every 6 months
HBsAg, Anti-HCV	At beginning
CXR	At beginning
Pap smear	At beginning and annually

Recommendations: Monitoring for ART Response

RECOMMENDATION	STRENGTH
Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure	***Strong recommendation, low-quality evidence*** NEW
If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure	***Strong recommendation, moderate-quality evidence***

Evolution of CD4 Count and Viral Load after Starting ART



ART switching criteria for failure

Failure	Definition
Clinical failure	New or recurrent WHO stage 4 conditions
Immunological failure	Fall of CD4 to baseline or below or 50% fall from on-treatment peak or persistent CD4<100
Virological failure	Plasma viral load > 1000 copies/ml

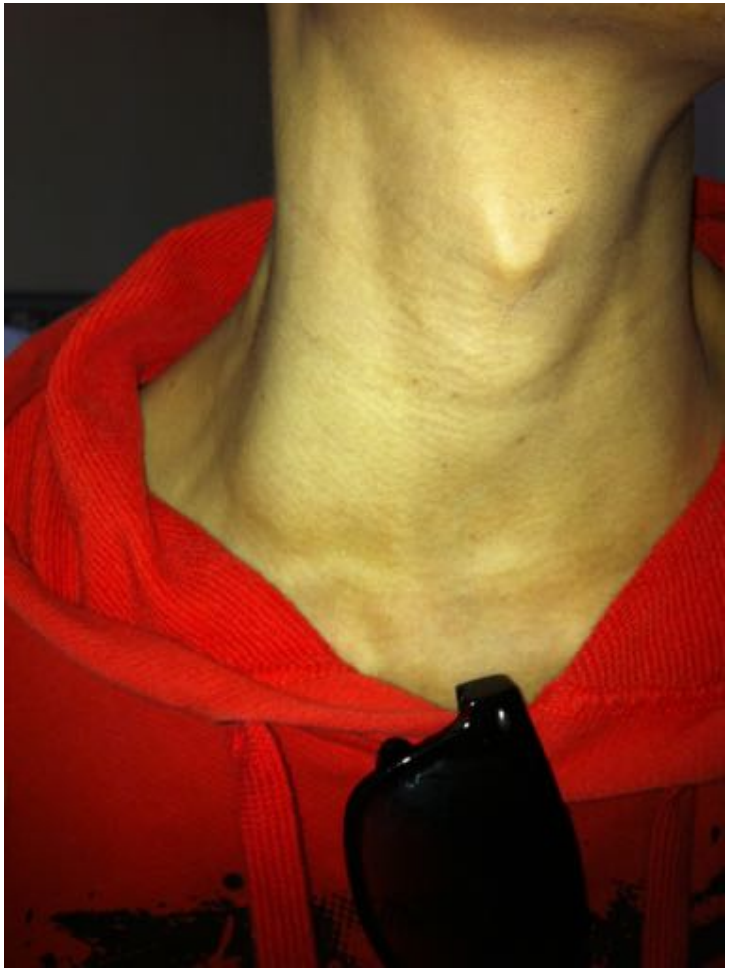
WHAT ART TO SWITCH TO

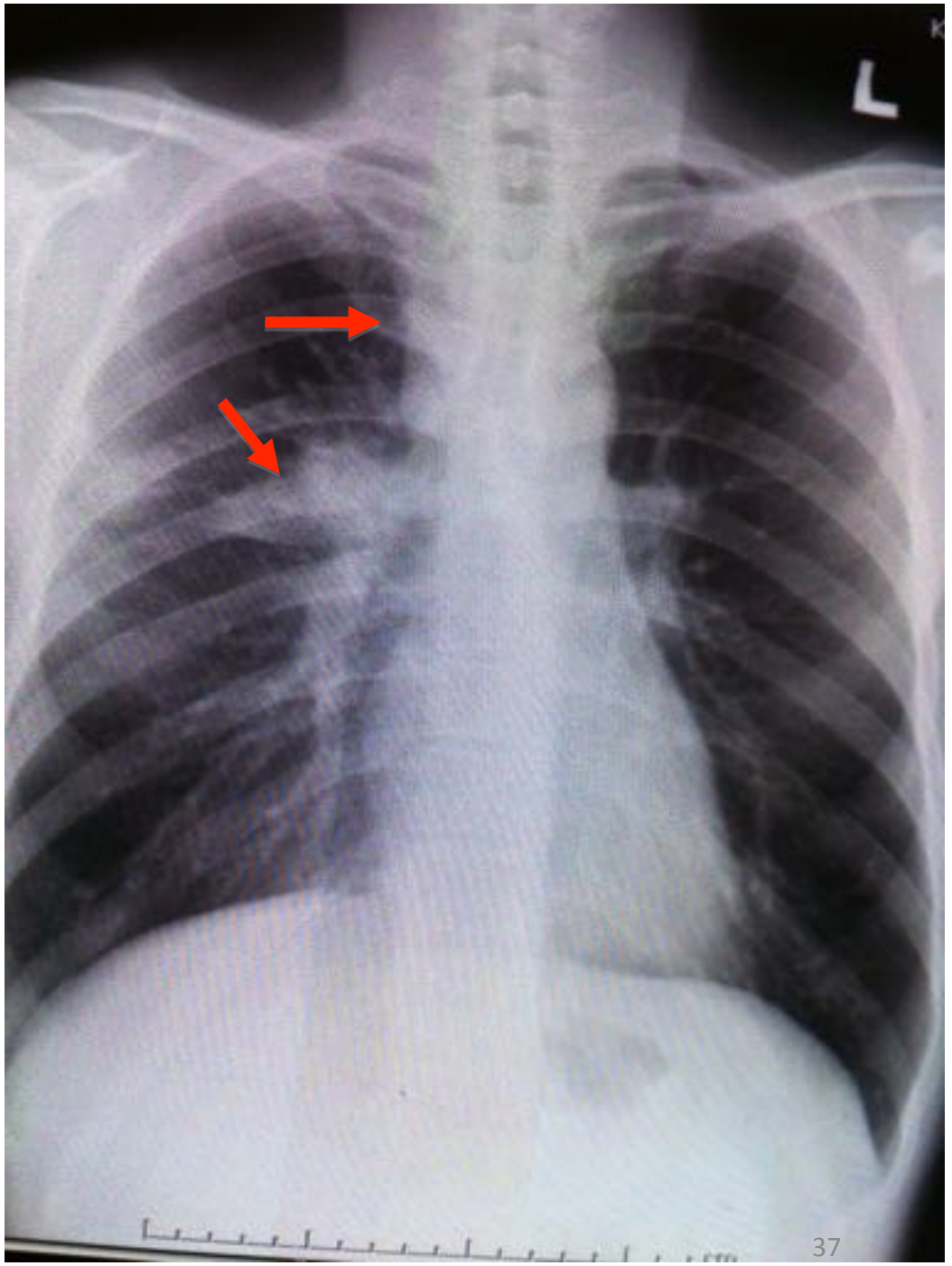
Summary of changes to recommendations: What ART to Switch to

TARGET POPULATION	WHAT TO SWITCH IN ADULTS (PREFERRED REGIMENS)			
	2010 ART GUIDELINES		2013 ART GUIDELINES	STRENGTH & QUALITY OF EVIDENCE
HIV+ ADULTS AND ADOLESCENTS	If d4T or AZT used in first-line	TDF + 3TC (or FTC) + ATV/r or LPV/r	**No change**	***strong, moderate-quality evidence***
	If TDF used in first-line	AZT + 3TC + ATV/r or LPV/r	**No change**	***strong, moderate-quality evidence***
HIV+ PREGNANT WOMEN	Same regimens recommended for adults		**No change**	***strong, moderate-quality evidence***
HIV/TB CO-INFECTION	If rifabutin available	Same regimens as recommended for adults	**No change**	***strong, moderate-quality evidence***
	If rifabutin not available	NRTI backbone plus LPV/r or SQV/r with adjusted dose of RTV (i.e., LPV/r 400mg/400mg BID or SQV/r 400mg/400mg BID)	**No change**	***strong, moderate-quality evidence***
HIV/HBV CO-INFECTION	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)		**No change**	***strong, moderate-quality evidence***

Major opportunistic infections

1. Mycobacterium tuberculosis
2. Pneumocystis jeroveci pneumonia
3. Cerebral toxoplasmosis
4. Cryptococcosis
5. Systemic penicilliosis




L

Optimal Timing to initiate HAART in Patients with Active OIs

Active OIs	When to start	Remarks
Tuberculosis	**CD4 <50**[1,2] Within 2 weeks of the Diagnosis **CD4 higher** Within 8 weeks of the Diagnosis	**TB meningitis**[3]: is less certain Treatment at 2 wks had more severe AEs than at 8 wks of TB Rx
Cryptococcosis	Less certain	Early Rx (3 days) was associated with 2.85x risk of death vs 10 weeks[4]
Other OIs	Within 2 weeks after OI diagnosis	

[1]Abdool Karim SS, et al. NEJM. 2011;365:1492- 1501; [2]Blanc FX, et al. NEJM 2011;365(16): 1471-1481.
[3]To¨ ro¨ k ME, et al. CID. 2011;52:1374-1383; [4]Makadzange AT, et al. CID. 2010; 50:1532-1538. And IAS-USA 2012 JAMA

ARV Toxicities

- Initial problems tolerating therapy
- Hypersensitivity reactions
- Immune-reconstitution related
- Chronic toxicities
- Drug-drug interactions

Guiding principles in the management of ARV drug toxicity

1. Determine the seriousness of the toxicity
2. Evaluate whether the toxicity is attributable to ARV or non-ARV drug(s)
3. Consider other disease processes (e.g. viral hepatitis if jaundice)
4. Manage the adverse event according to severity

Guiding principles in the management of ARV drug toxicity: In general:

Grade 4 (severe life-threatening reactions)

- Immediately discontinue all ARV drugs until the patient is **stabilized**
- symptomatic and supportive therapy
- Introduce ARV drugs using a modified regimen when the patient is **stabilized**

Grade 3 (severe reactions)

- Substitute the offending drug without stopping ART

Guiding principles in the management of ARV drug toxicity (continue)

Grade 2 (moderate reactions)

- Consider continuation of ART as long as feasible
- If the patient does not improve on symptomatic therapy, consider single-drug substitution

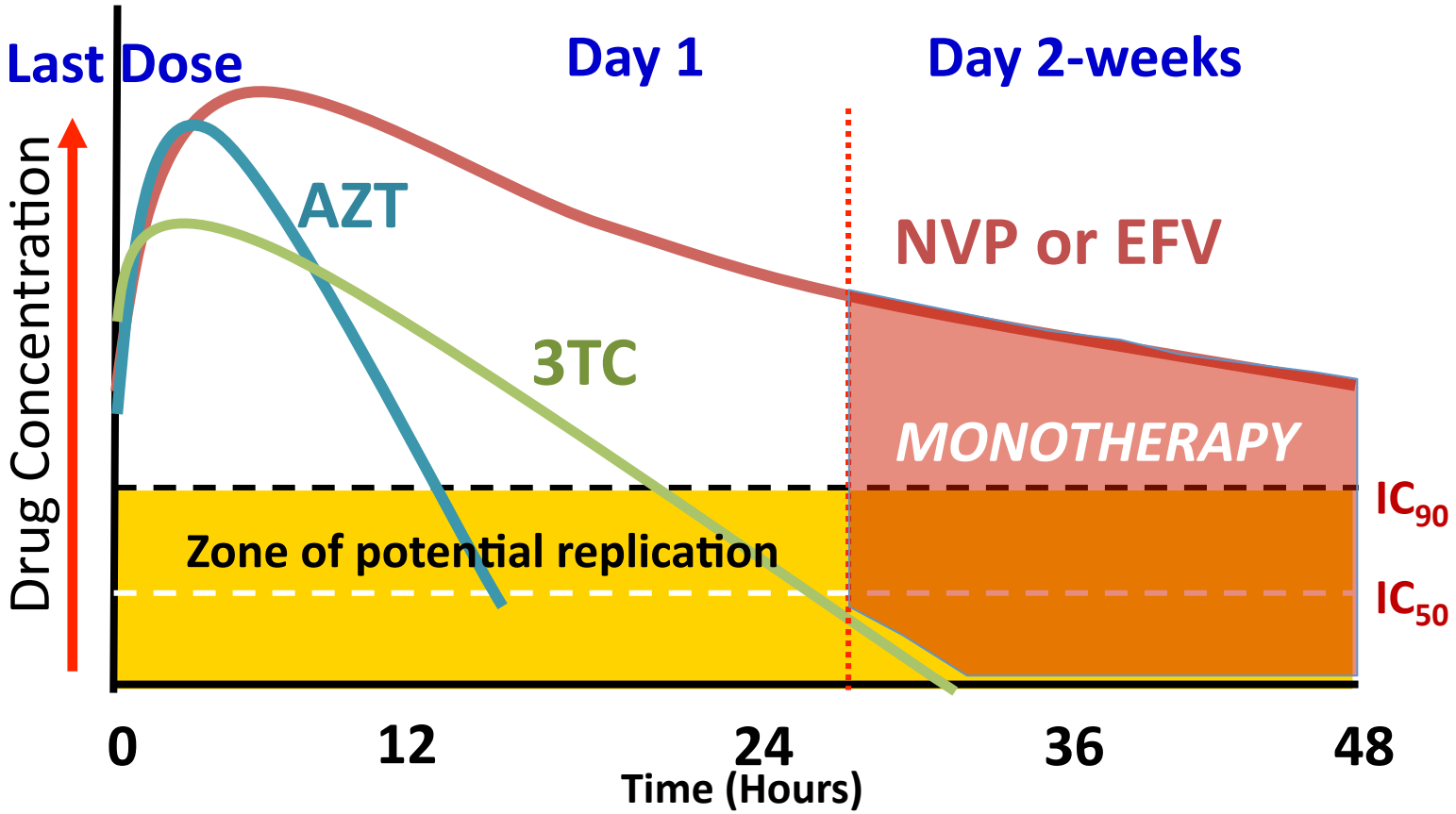
Grade 1 (mild reactions)

- do not require changes in ART
- Stress the maintenance of adherence despite toxicity for mild and moderate reactions

Single-drug switching for toxicity

- AZT intolerance (anaemia)
  ⇒ **TDF** OR **d4T**
- d4T intolerance (neuropathy)
  ⇒ **AZT OR TDF**
- Nevirapine intolerance (rash)
  ⇒ **efavirenz**
- Efavirenz intolerance (CNS toxicity)
  ⇒ **Nevirapine**

Potential Concern When Stopping Drugs With Different Half-lives



S. Taylor et al. 11th CROI Abs 131

Clinical care options 2004

Discontinuation of ARV due to toxicity

- If ARVs are discontinued , stop all ARVs simultaneously unless the regimen includes an NNRTI
- Long half-life of NNRTI may lead to effective monotherapy
- Stop NNRTI and continue other ARVs(2 NRTIS) for at least 7 days (optimal time is not known) before discontinuing all, or substitute PI for NNRTI for a period before stopping all
- to avoid NNRTI resistance

Cotrimoxazole Preventive Therapy (CPT)

WHO Guideline

- In resource limited setting
- Start at CD4 ≤ 350 / μl, all symptomatic individuals including pregnant women (WHO clinical stages2, 3 or 4)

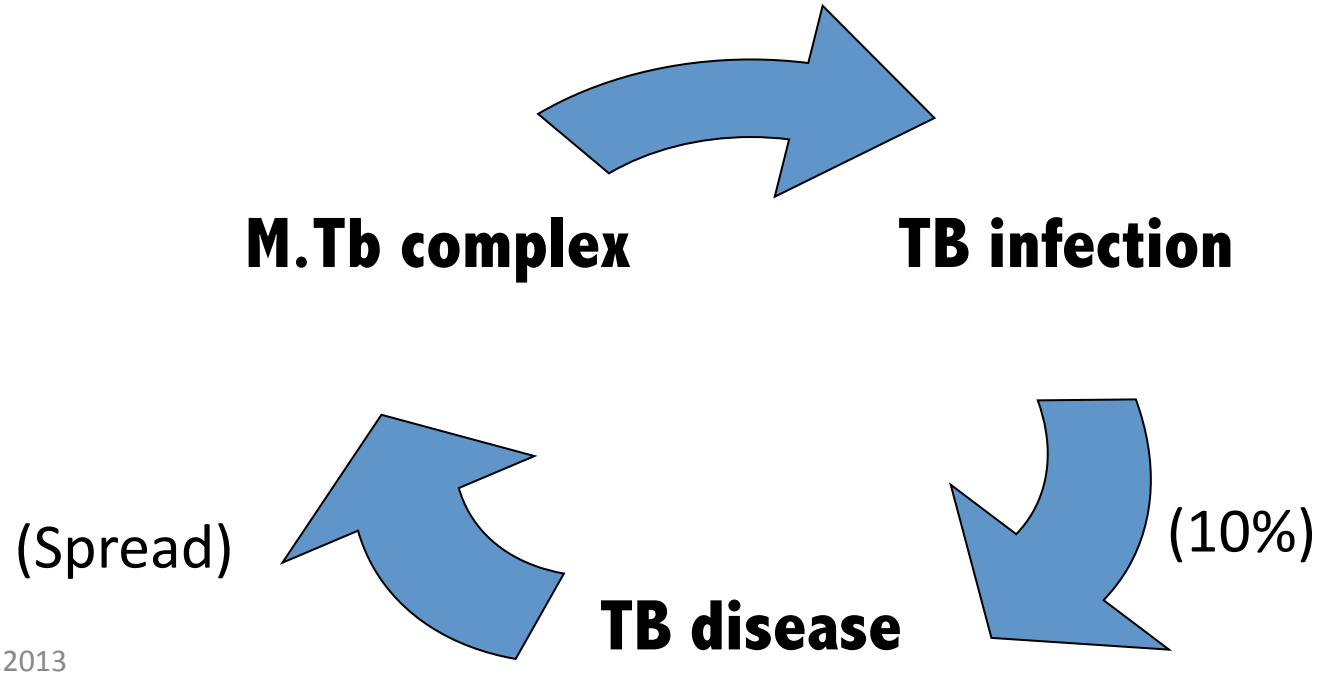
- Prevent the PCP, Cerebral Toxoplasmosis
- Also prevent the bacterial diarrhoea & chest infection, malaria

- Skin reaction is the commonest side effect

Human Tuberculosis

- Infection with M.tb complex.
- 2 clinical states- (1) TB infection.

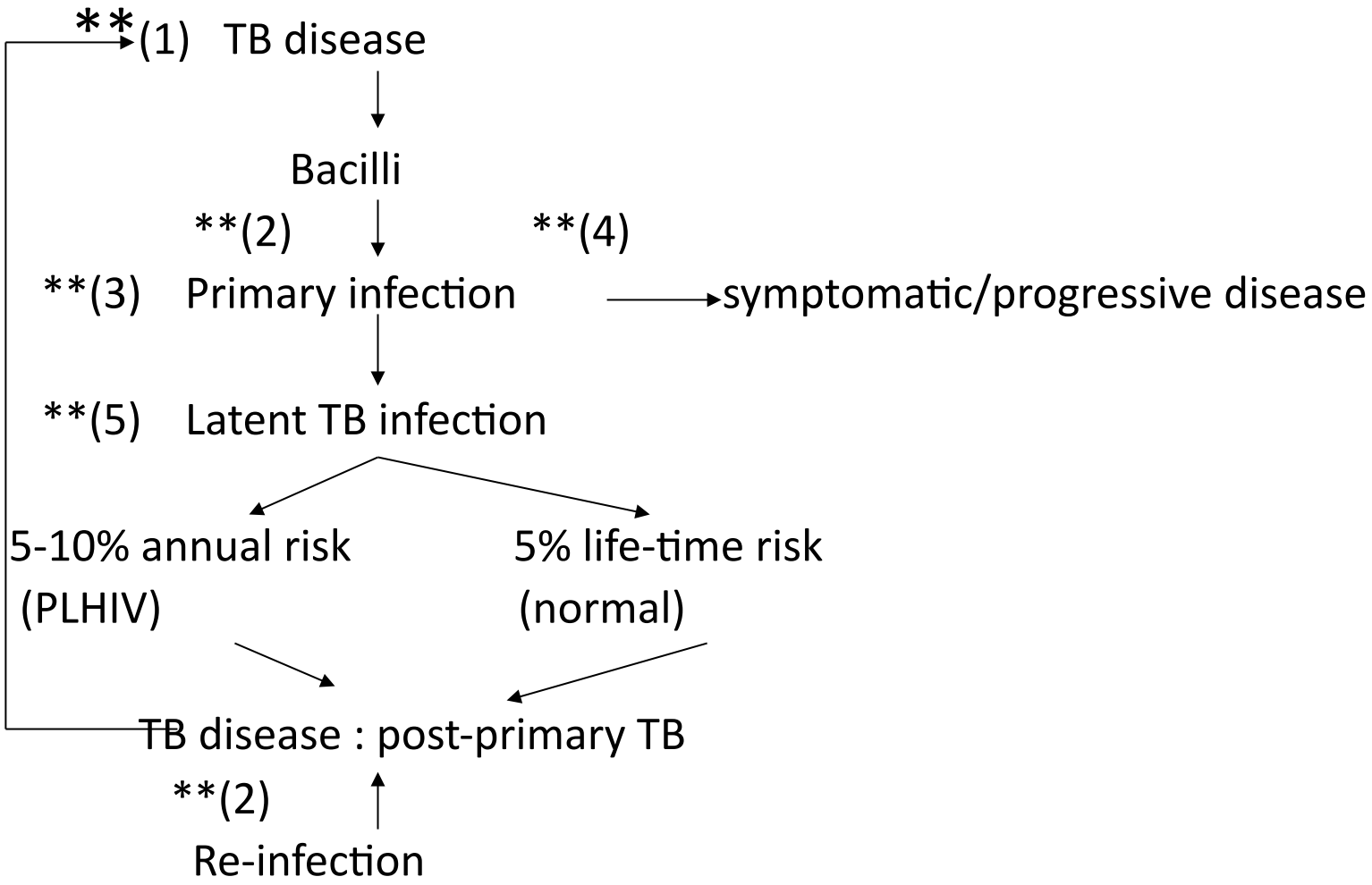
  (2) TB disease (active TB)



TB Risk with HIV Infection

- Exceptionally high rate of reactivation of latent infection (7-10% per year)
- Rapid progression to TB following new infection
- Increased risk begins soon after HIV infection and increases as immunosuppression increases
- Increased risk is reduced but not eliminated by antiretroviral treatment
- Increased potential for reinfection after successful treatment for TB

Natural Course of TB Infection and interventions**



Preventing HIV-associated TB

Exposure

Primary prophylaxis

infection

Latent TB infection

TB preventive therapy: treatment of LTBI

Disease

Restore protective immunity: ART

Treatment of Latent Tuberculosis Infection (LTBI)

Isoniazid Preventive Therapy (IPT)

Isoniazid Prophylaxis Therapy (IPT)

- WHO has recommended at least 6 months of isoniazid prophylaxis therapy (IPT) for PLHA-Children and adults and those receiving ART
- Reduce the risk of developing TB by 33%
- Active TB can be excluded by the use of a simplified screening algorithm that relies on four clinical symptoms.
- symptoms of current cough, fever, weight loss or night sweats

IPT (Cont'd)

- dose of 300 mg/day for 6-9 months
- INH resistance is not significantly associated with providing IPT
- is being evaluated by the NTP in a pilot project in 9 townships for introducing it on a wider scale

Mandalay General Hospital

ART Supply Programme & HIV Care

Dr Mar Mar Aye
(MGH)

MU I OPD – Started in May 2005

- **Tuesday and Friday (Morning)**

MU II OPD – Started in April 2007

- **Monday and Thursday (Morning)**

MU III OPD(TB/HIV) – Started in August 2009

- **Wednesday and Friday (Evening)**

Pre-ART OPD – Started in March 2011

- **Thursday (Evening)**

➢ NAP Team Leaders attend OPD regularly

Human Resources in medical units OPD

- One physician, one Assistant surgeon and at least 4 HIV coordinators - attend to the IHC OPD
- 2 nurses & one manual worker of medical ward - drug dispensing
- PLWHA - 3 volunteers - help registration, patient flow
- One expert patient – for discussion, providing information, solving social problems of patients, etc

DA Counseling and defaulter tracing

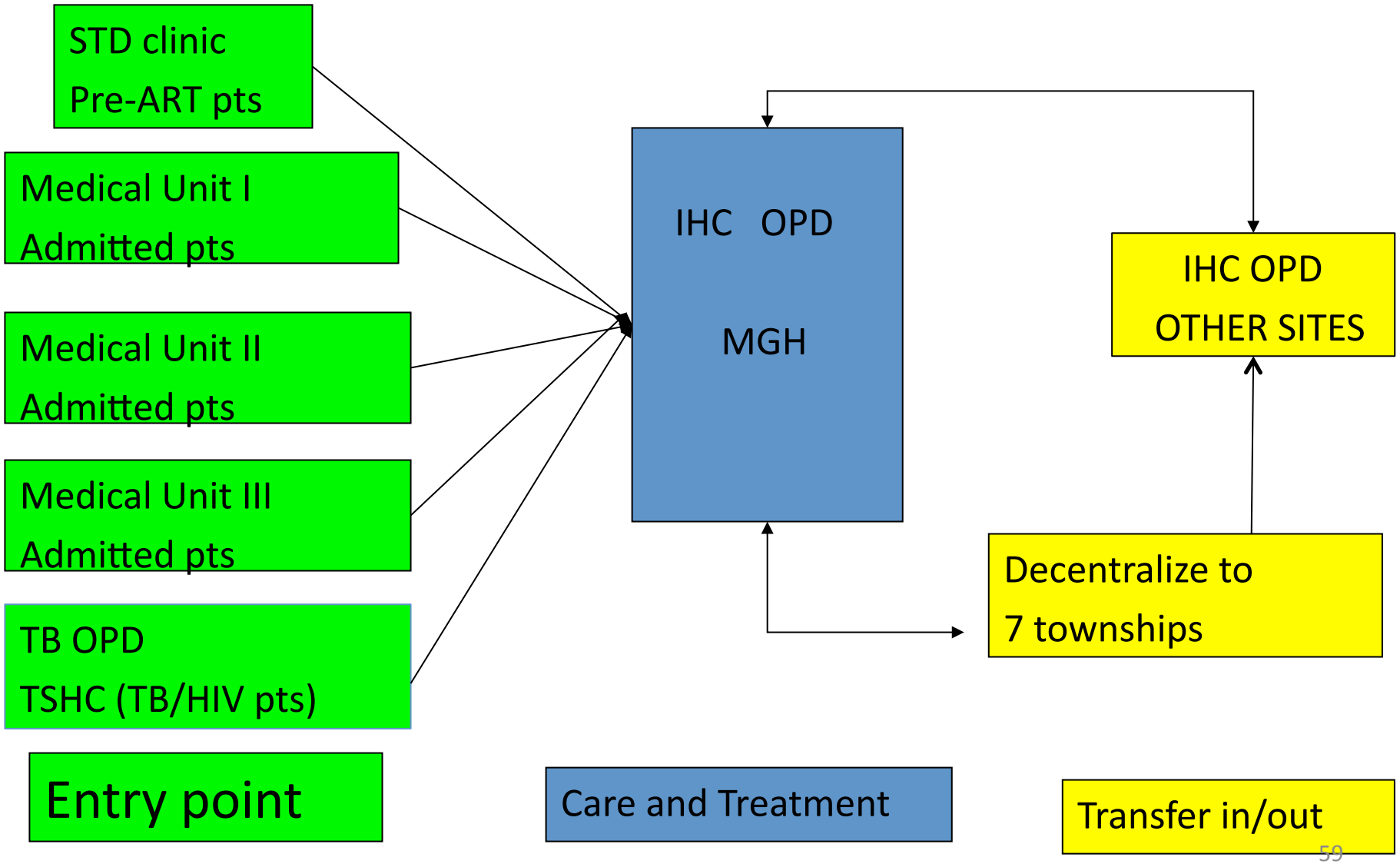
- Drug adherence counseling three sessions was provided by the **medical social workers** from MGH as well as from the VD/STD clinic

Drug Delivery system

- Two Nurses from medical units are distributed the ARVs/ OI drugs and investigation request form to the patients at the day of OPD

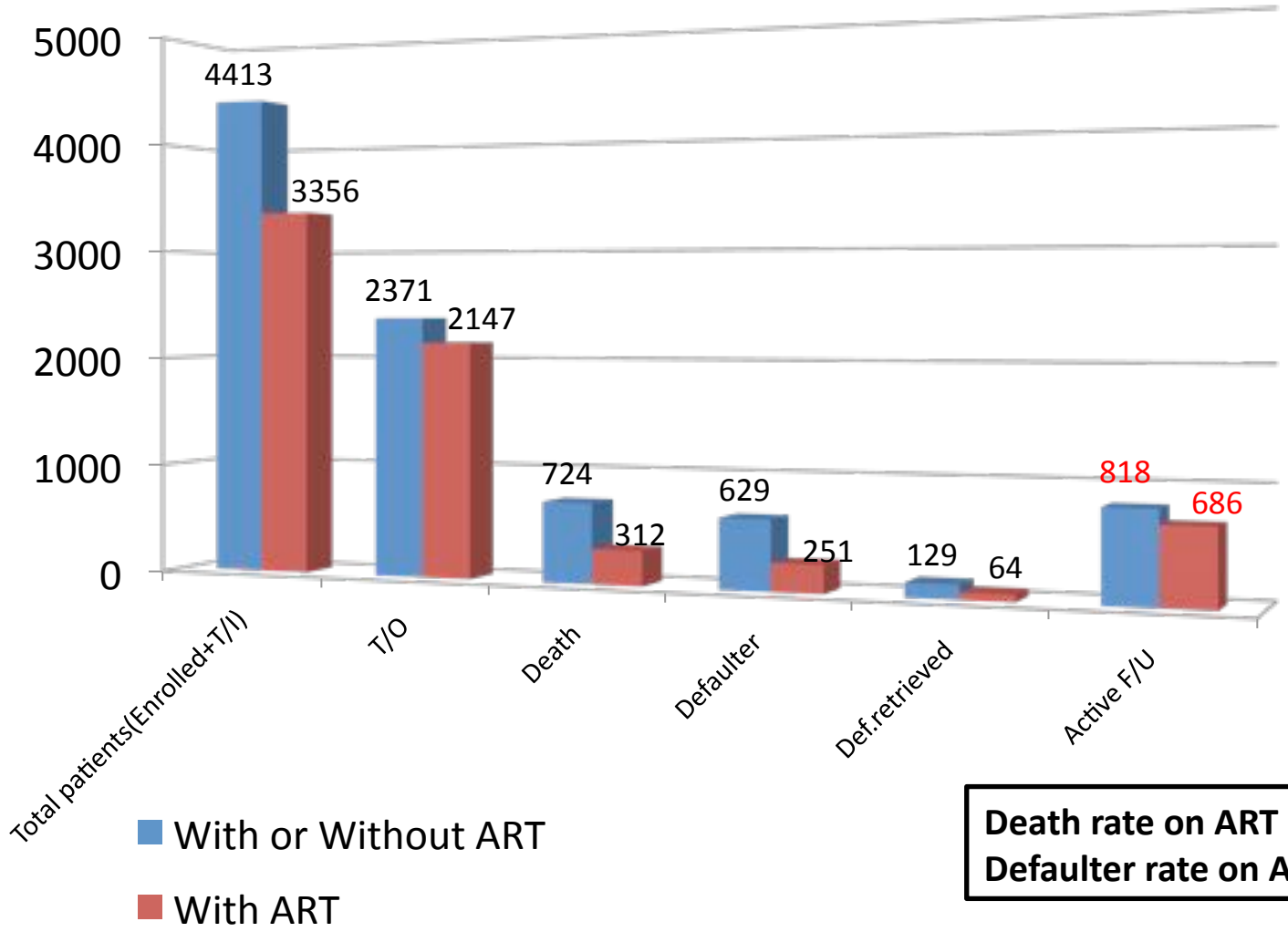
- At the end of every month, the nurses provide the monthly drug report of the ward to the MS MGH as well as to the Union

Patients flow in Mandalay General Hospital



Outcome of MU I ART clinic

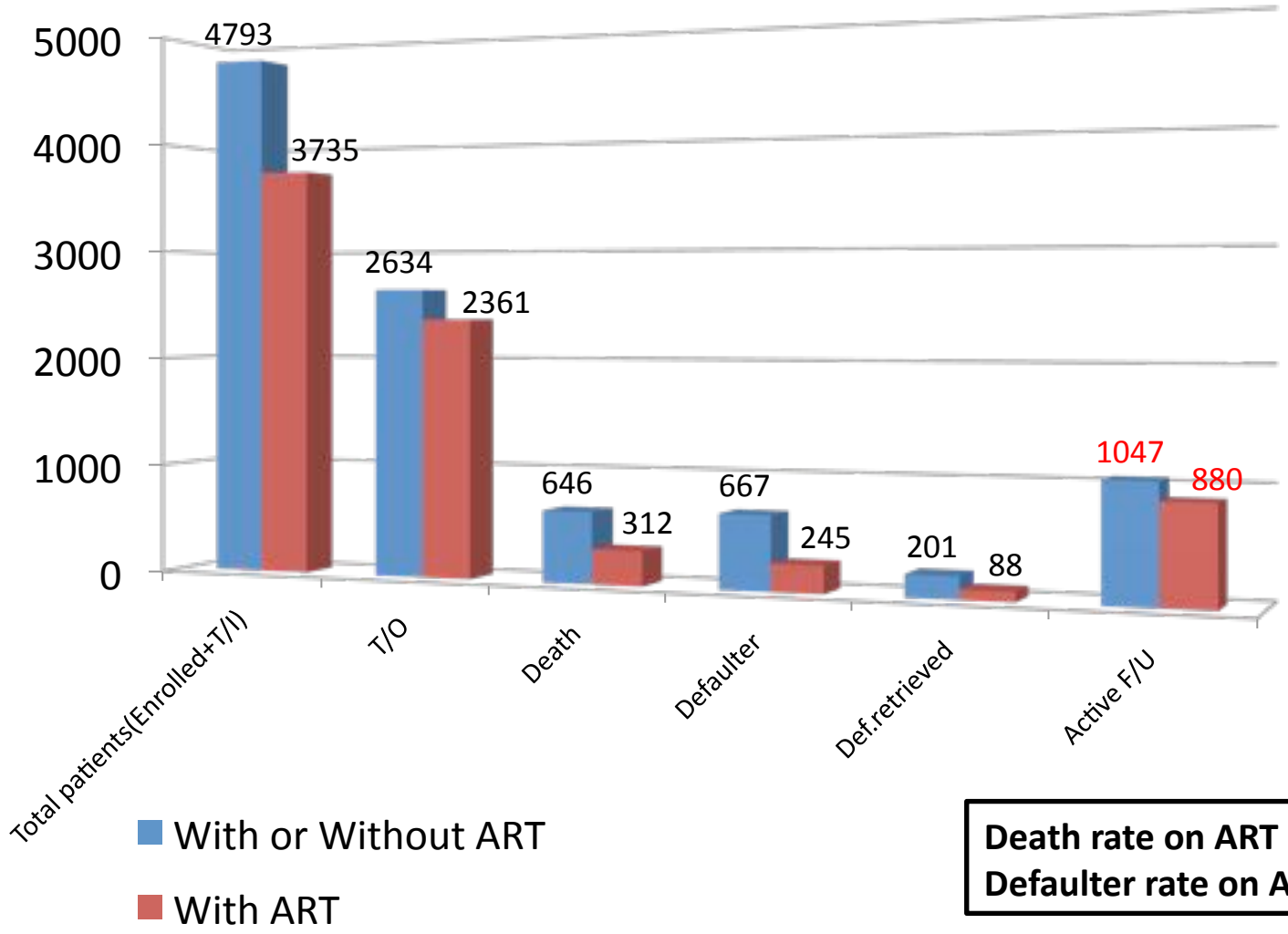
as of September-2014



Death rate on ART : 9 %
Defaulter rate on ART : 5.6 %

Outcome of MU II ART clinic

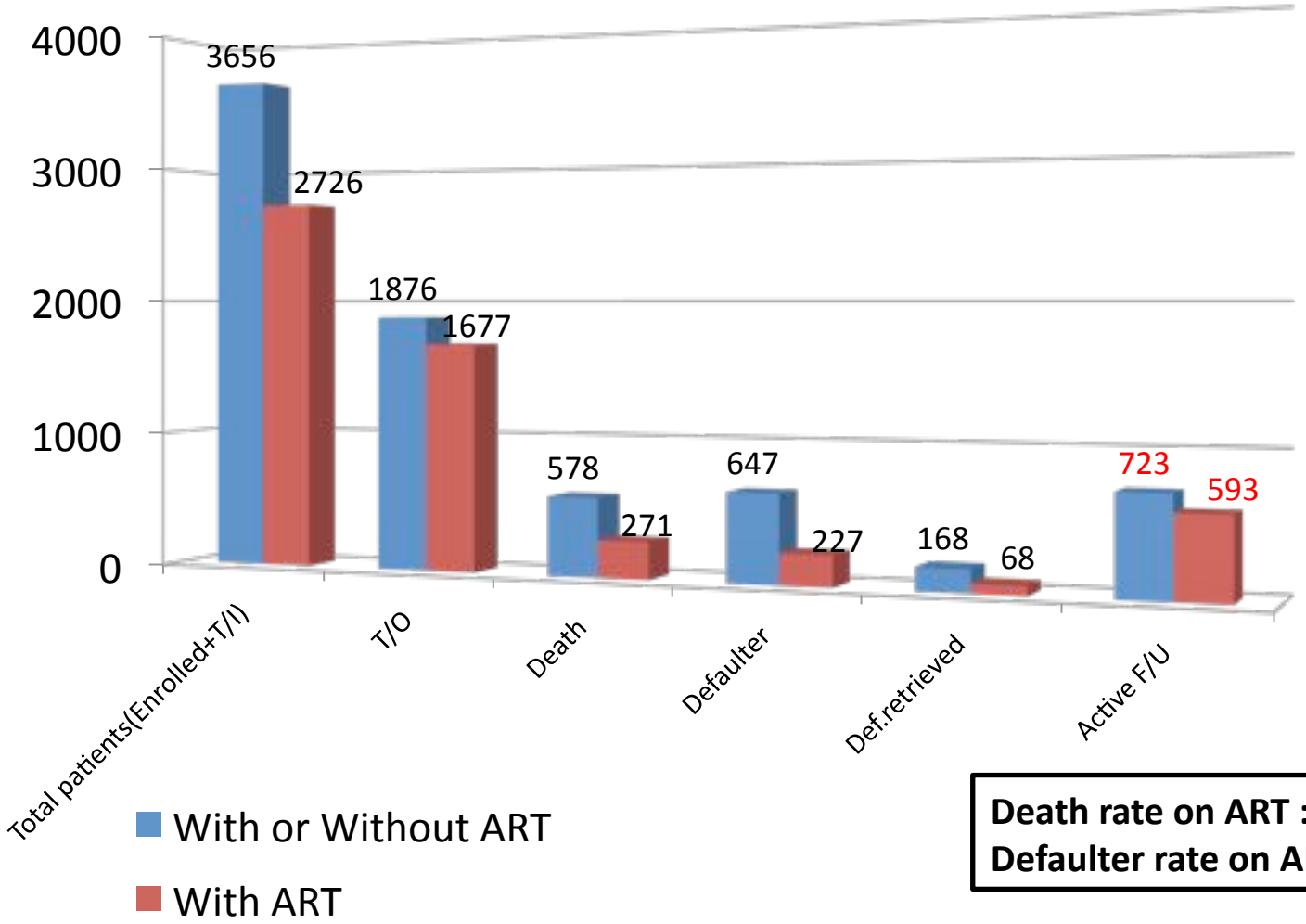
as of September-2014



Death rate on ART : 8 %
Defaulter rate on ART : 4.2 %

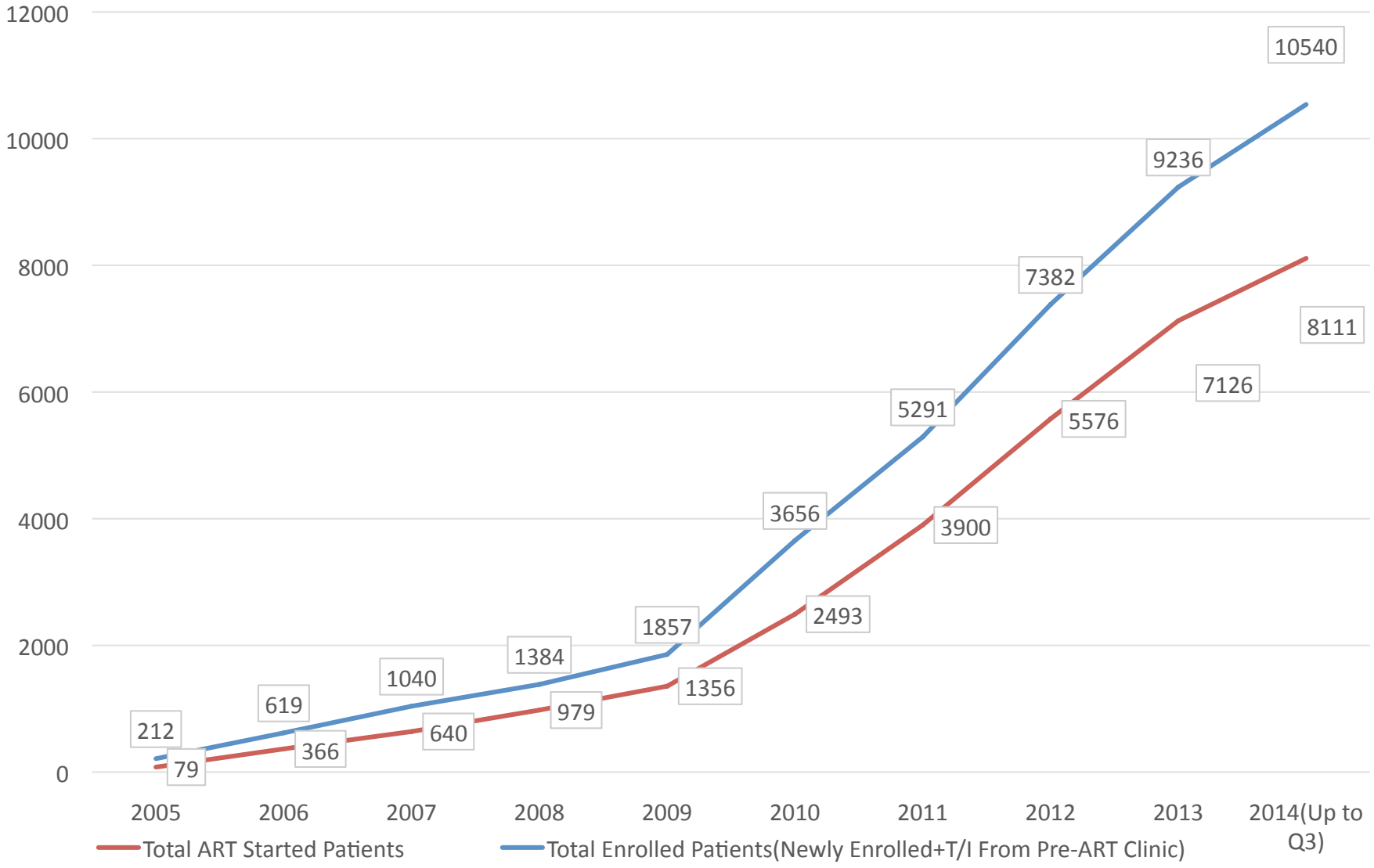
Outcome of MU III ART clinic

as of September-2014

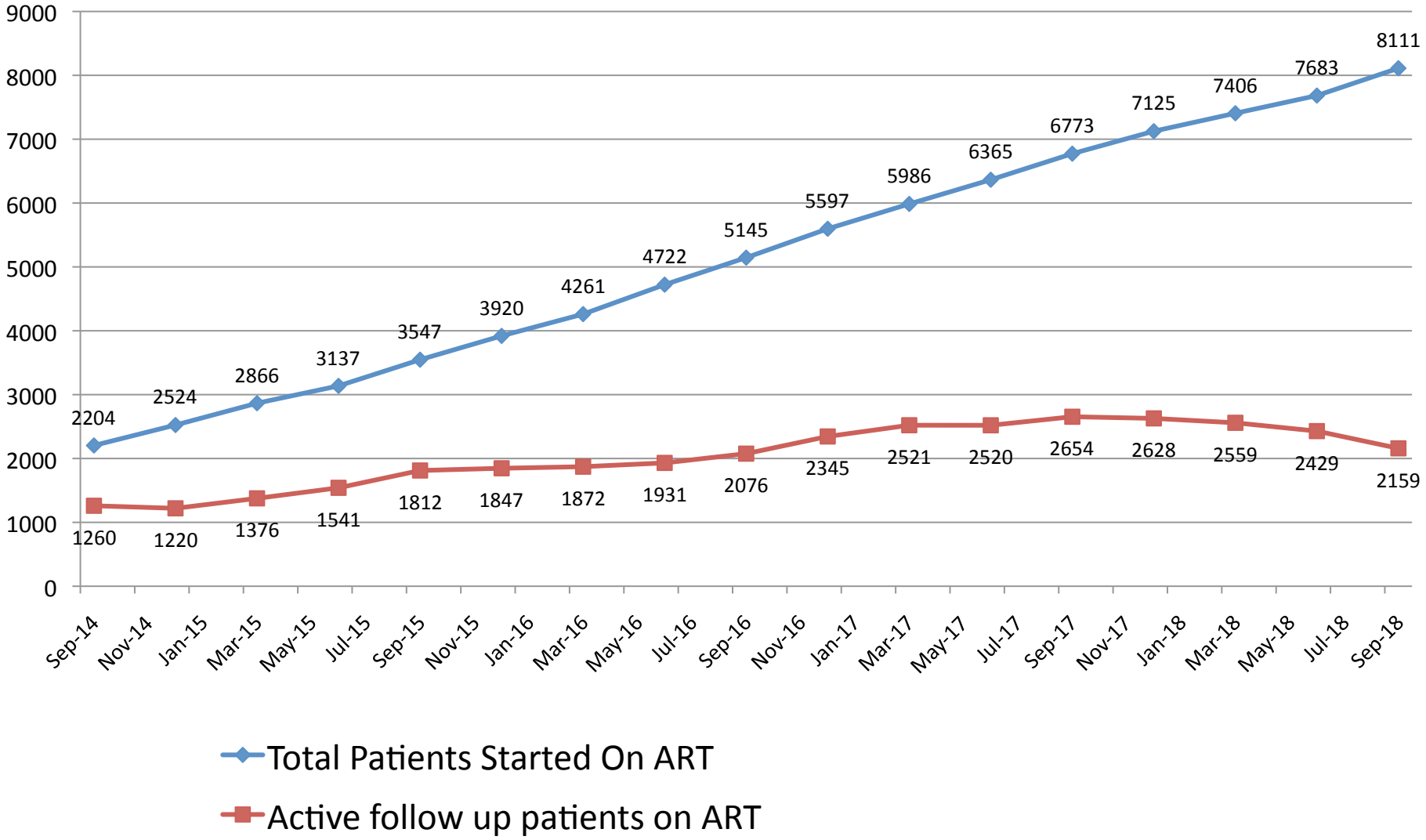


Death rate on ART : 10 %
Defaulter rate on ART : 5.8 %

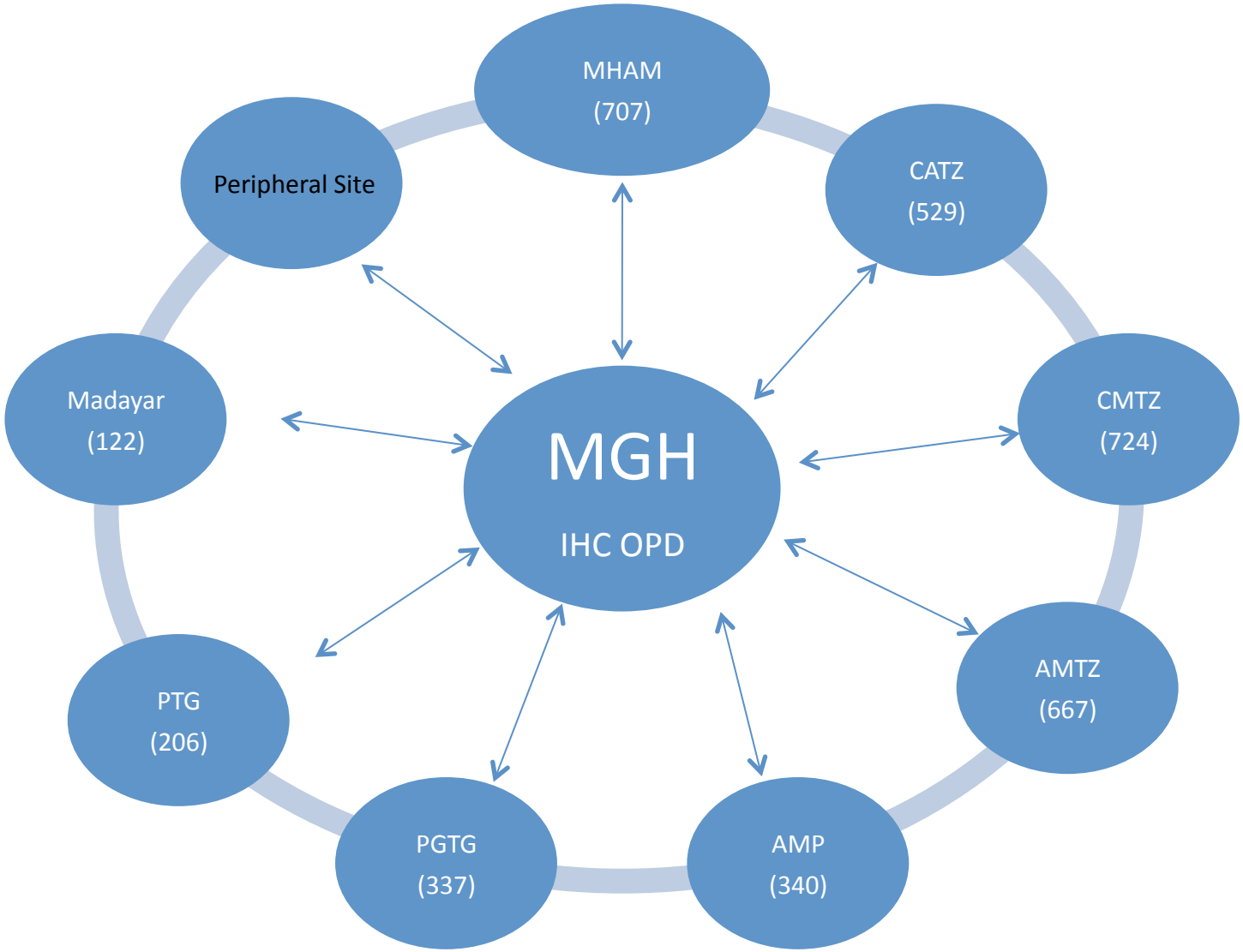
Cumulative numbers of Patients Enrolled and Patients started on ART up to 2014(3rd Quarter) MU I, MU II, MU III



Total Patients ever started On ART Vs Active Follow up Patients on ART per year up to 2014(3rd Quarter) MU I, MU II, MU III

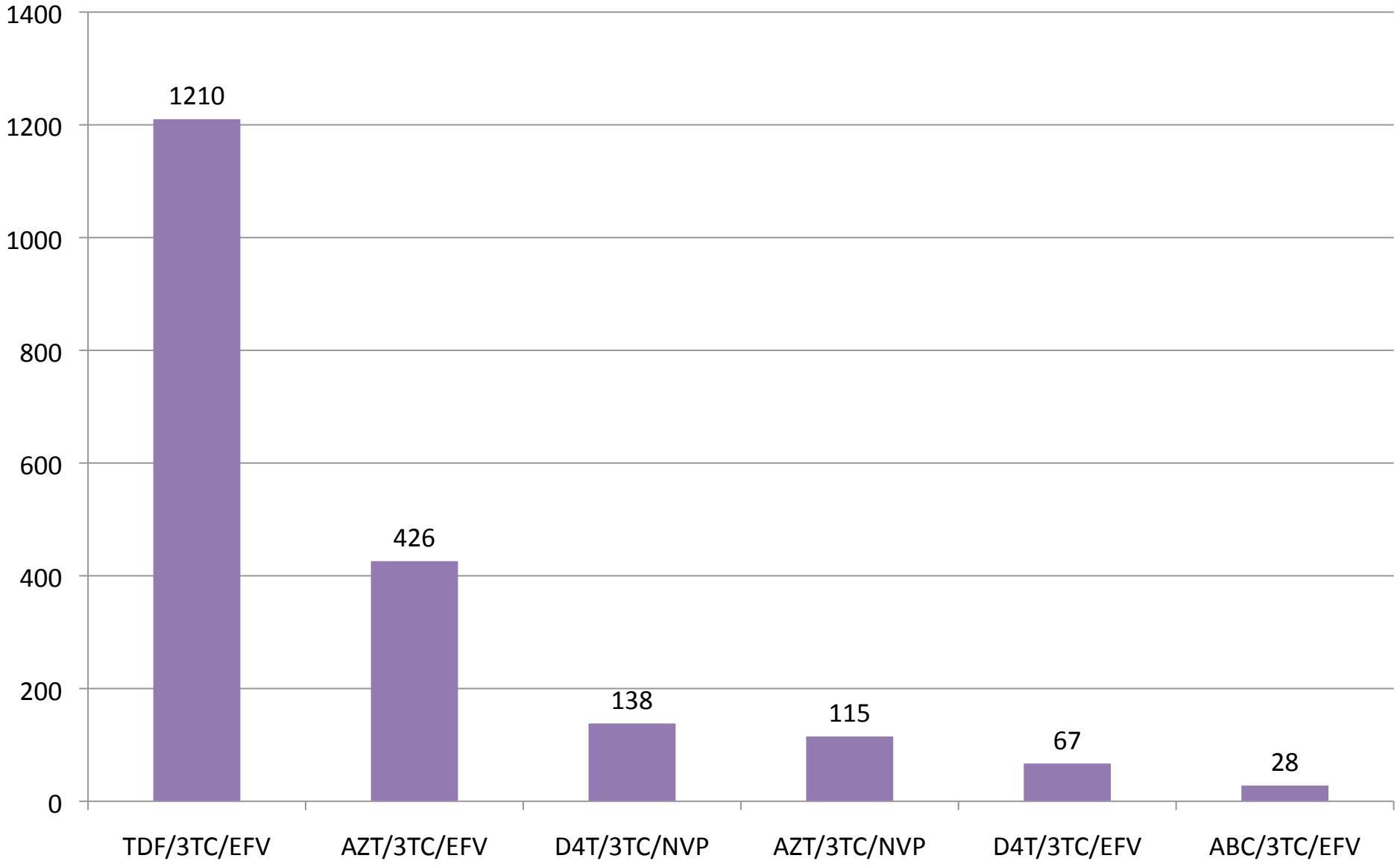


DECENTRALIZATION(UP TO SEPT-2014)

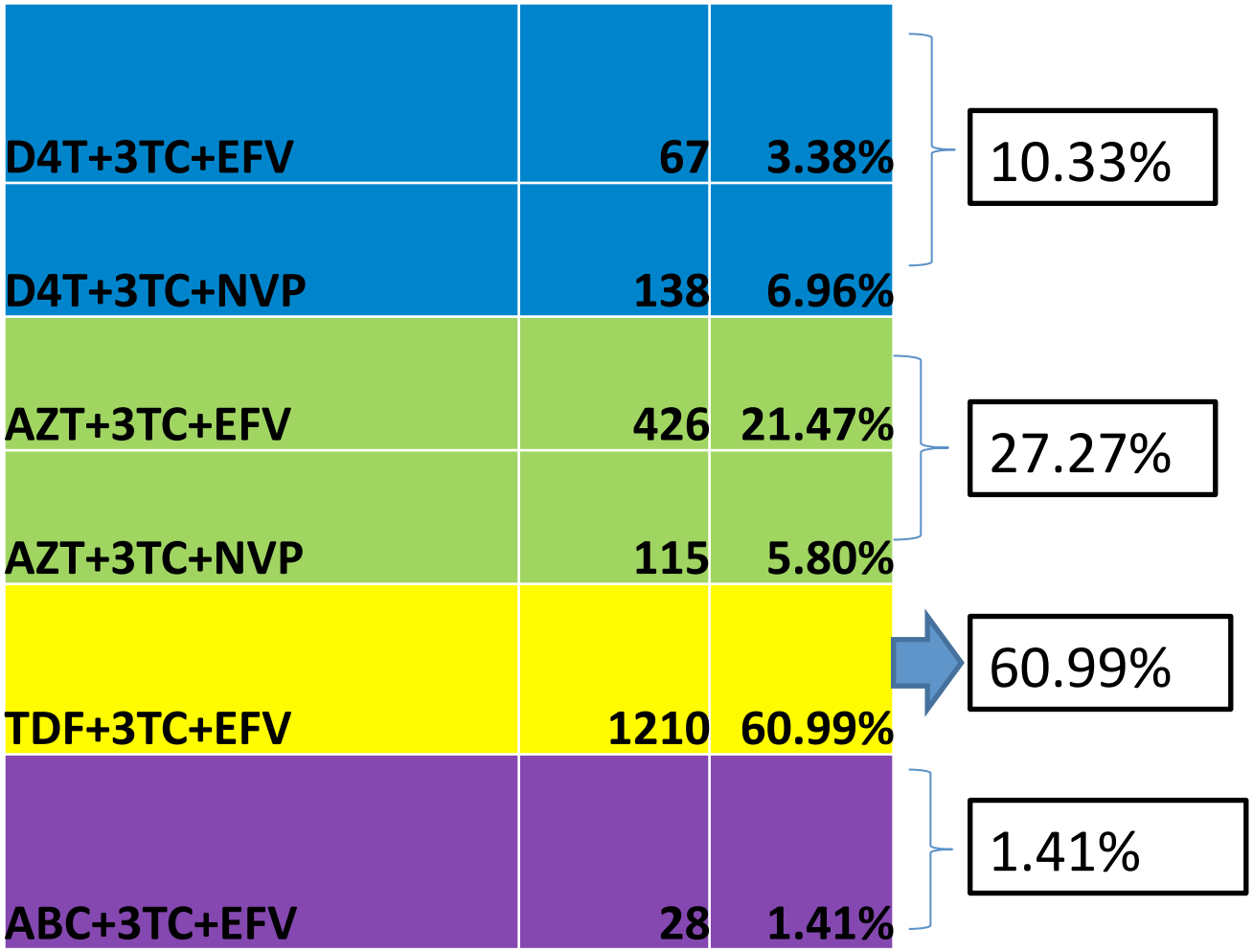


Current Regimens – first line ART
In Adult ART clinic(Active follow up)

First Line :1984(91.89%)
Second Line: 175(8.1%)

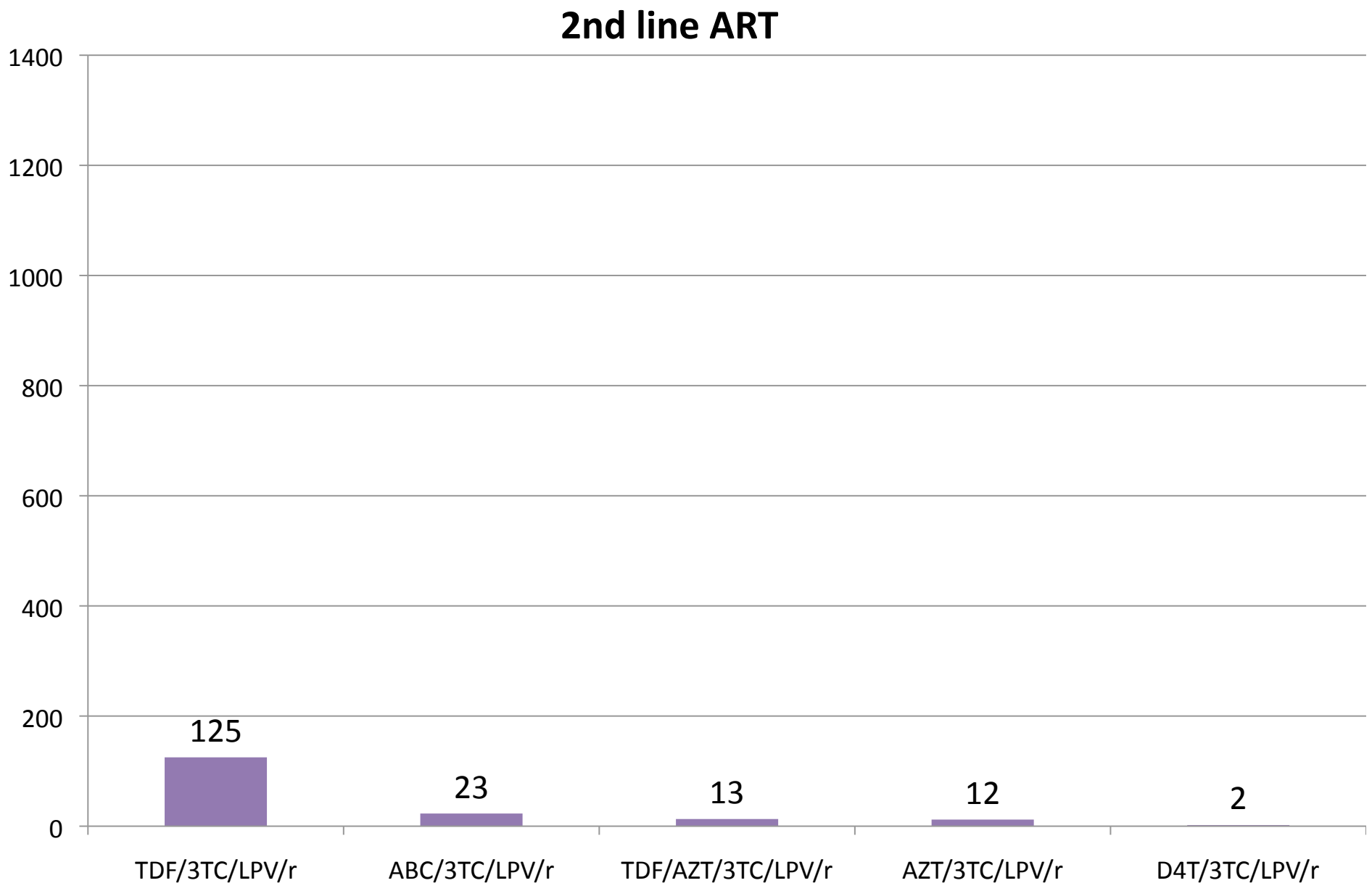


Present first line adult regimens for active follow up patients used in MGH IHC Clinic as of September 2014



Current Regimens – second line ART
In Adult ART clinic(Active follow up)

First Line :1984(91.89%)
Second Line: 175(8.1%)



Challenges

- Increasing enrolled patients
- Financial and transportation problems of patients from other township
- Difficulties in defaulter tracing
  - due to incomplete or wrong address and poor awareness about importance of continuous HIV care
- As for drug dispensing site , OPD responsible nurses are always changing
- Shortage of OI drugs
  - eg. Pyrimethamine, sulphadiazine, gancyclovir, foscarnet, dapsone

    antifungal drugs


Thank you

Thank you

For further information please contact :

Jean-Marc Debricon
CEO
jm@greenshootsfoundation.org
Mobile: +44 7595 600 766

Green Shoots Foundation
P.O. Box 63678
London, SW11 9BD
UK

UK charity number 1138412 US 501(c)(3) registered

General enquiries: info@greenshootsfoundation.org
Website: www.greenshootsfoundation.org

GreenShoots
FOUNDATION