SuPS3:Recent Progress in Basic and Clinical HIV Research:Outcomes from Asia and The Pacific

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SuPS3-02 The Journey: HIV/AIDS treatment and Prevention

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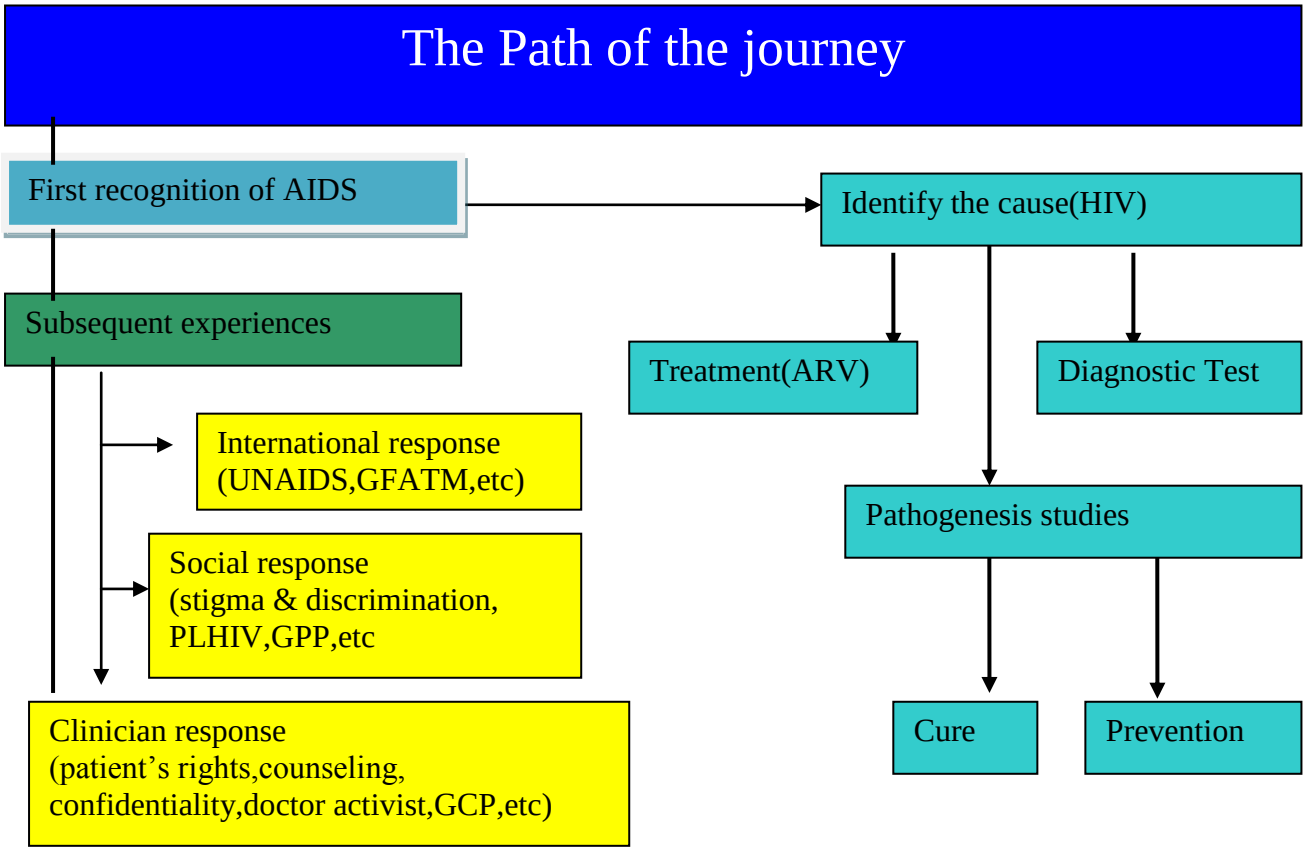


First official notice of a new disease, AIDS

- Gottlieb MS et al (Division of Clinical Immunology-Allergy,UCLA)
- Morbidity and Mortality weekly Teport of June 5, 1981
- Report of 5 young gay men in LA with Pneumocystis pneumonia (as well as CMV, candidiasis) with low T cell number and poor T cell responses
- 2011 marks the 30th Anniversary of AIDS

HIV Pathogenesis

- Undestanding the disease mechanism follows the discovery of the causative agent (HIV)
- CD4 T cell as main target for HIV
- CD4 molecule as the main receptor and chemokine receptors (CCR5, CXCR4) as co-receptors
- Virus causes CD4 cell depletion
- Opportunistic infections and co-infections
- Persistent and latent infection
- Chronic inflammation
- Host genetics

e.g., CCR5 Δ32 homozygous

The journey of HIV treatment

- From no treatment to monotherapy, dual therapy and triple therapy
- From only first-line to 2^{nd} , 3^{rd} ,4^{th} , etc. line
- From "salvage therapy" to suppressive therpy even in highly experienced patients
- From complex therapy to simplified therapy
- From limited access to universal access
- From treatment alone to treatment as (is) Prevention
- From untreatable to treatable disease and potentially curable

Evolution of when to start ARV

- A pendulum between early versus late treatment
- 1987 : treat the sick (late)
- 1998 :treat early (Hit hard, Hit early) hoping for HIV eradication
- 2003: More conservative (late) start due to the side-effects
- 2008: Earlier start due to safe & potent newer drugs and non-HIV complications with CD4 & virus
- 2011: Even earlier stat due to treatment as prevention (HPTN-052)
- It will never swing backward

Risk & benefit of early start

Potential benefits	Potential risks
Risk of HIV-associated complications that can sometimes occur at high CD4 e.g., TB, KS, peripheral neuropathy, HPV-associated malignancies, etc	Long-term adverse effects may reduce quality of life
Risk of serious non-OI conditions e.g., CVD, renal dis, liver dis, Cancers	Risk of serious toxicities(NVP in high CD4)
Higher chance to achieve near normal CD4	Development of drug resistance & risk of transmitting resistant virus
Lower rate of failure	Unknown durability of current available therapy
Fewer adverse effects	Limitation of future treatment options
Risk of HIV transmission	Healthcare infrastructure
	Cost

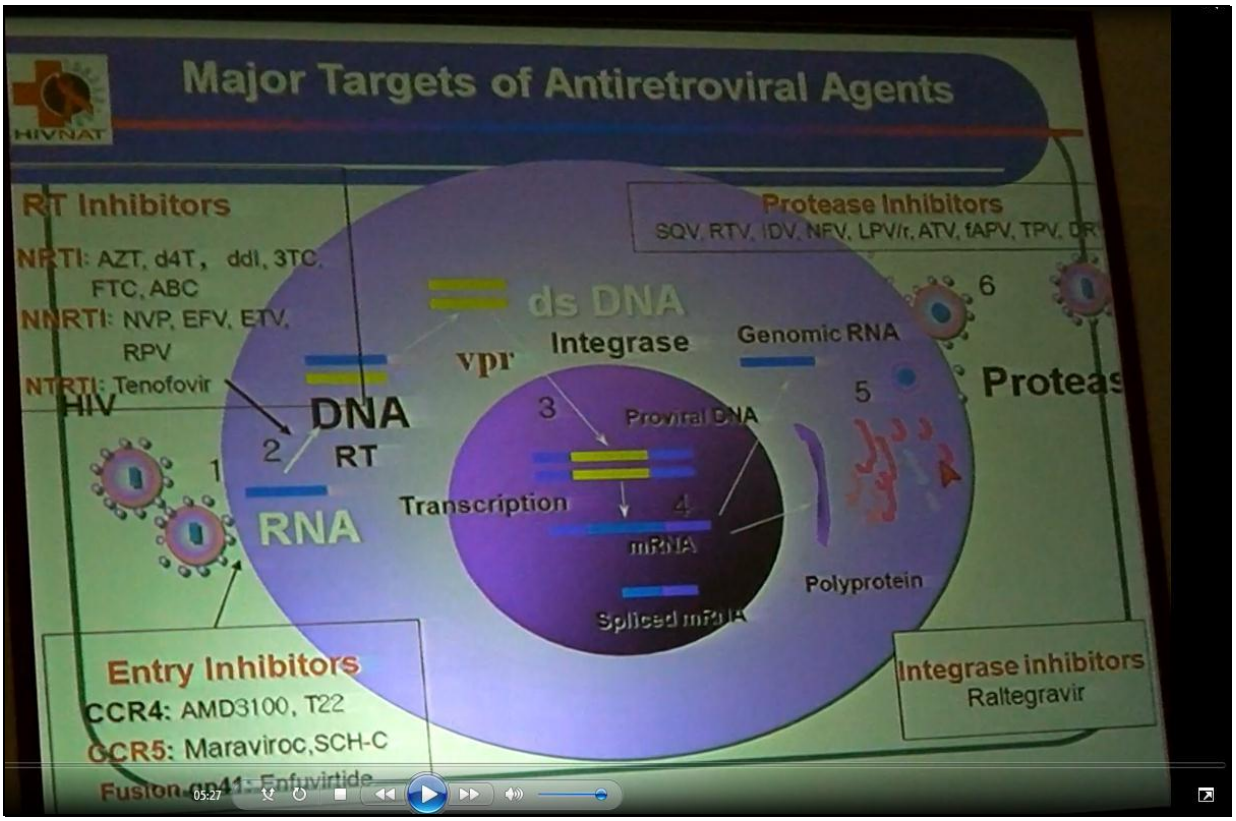
Changing guidelines for initiation of antiretroviral therapy in USA

CD4	1998	2001	2006	2008	2009
>350	Offer if HIV-1 RNA> 20,000	Consider if HIV-1 RNA> 55,000	Consider if HIV-1 RNA>100,000	Consider in certain groups	Treat 350-500 consider for >500
200-350	Offer if HIV-1 RNA> 20,000	Offer,but controversy exists	Offer after discussion with patient	treat	treat
<200 or symptomatic	treat	treat	treat	treat	treat

Changing WHO guidelines for earlier initiation of ART in asymptomatic

CD4	2006	2009	>2012
>500	No	No	Possibly treat
350-500	No	No	May treat
200-350	No	Treat	Treat
<200	Treat	treat	treat

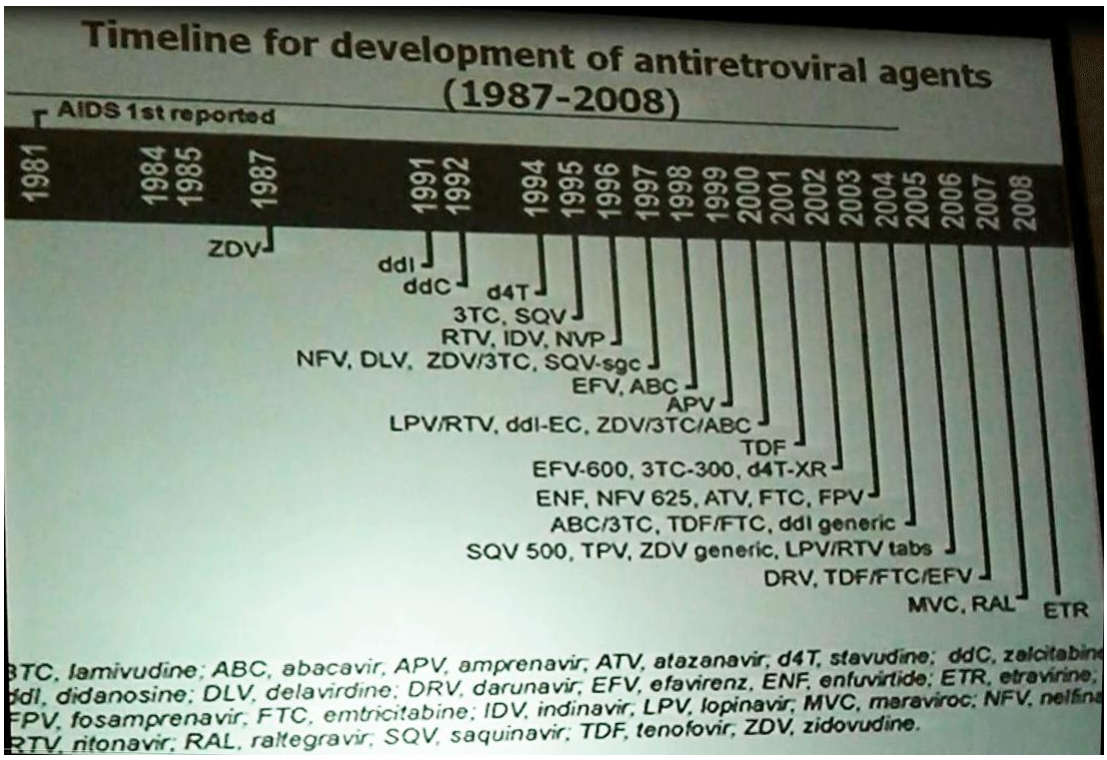
Major Targets of Antiretroviral Agents



Antiretroviral agents approved in the U.S. as of August 2011

Nucleoside RTI's	Non-Nucleoside RTI's	Protease Inhibitors
Zidovudine(ZDV)	Nevirapine(NVP)	Saquinavir(SQV)
Didanosine(ddI)	Delavirdine(DLV)	Ritonavir(RTV)
Zalcitabine(ddC)	Efavirenz(EFV)	Indinavir(IDV)
Stavudine(d4T)	Etravirine(ETV)	Nelfinavir(NFV)
Lamivudine(3TC)	Rilpinavir(RPV)	Amprenavir(APV)
Abacavir(ABC)	Nucleotide RTI Tenofovir DF(TDF)	Lopinavir/r(LPV/r)
Emtricitabine(FTC)	Integrase inhibitors	Atazanavir(ATV)
		Fosamprenavir(Fos-APV)
		Tipranavir(TPV)
		Darunavir (DRV)
		Entry Inhibitor Enfuvirtide(T-20)

Timeline for development of antiretroviral agents(1987 – 2008)



Recent ARV development: 2010-2011

- Many drugs were recently discontinued during phase II/III development e.g., apricatibine & amdoxivir (NRTI, 2010), vicroviroc (CCR5RI, 2010), bivirimat (MI, 2010)
- Many have been recently approved e.g., rilpivirine(NNTTI,2011), Viramune XR (2011), Complera(ODFDC of RPV/TDF/FTC)
- Many are on phase III trials in 2011 e.g., dolutegravir & elvitegravir(II), cobicistat(PK booster), ELV/CBS/FTC/TDF(Quad)

****Number of new ARV is increasing as well as the price ****

Preferred first-line ART in developed and developing countries

ART	Past	Present	Future
N(t)NRTI	AZT/3TC,d4T/3TC ,ABC/3TC	TDF/FTC,ABC/3TC	TDF/FTC
	AZT/3TC,d4T/3TC	AZT/3TC, TDF/FTC	TDF/FTC
NNRTI	NVP,EFV	EFV	EFV
	NVP,EFV	EFV,NVP	EFV
PI	IDV,SQV,NLV	ATV/r,DRV/R,LPV/r	DRV/r,ATV/r
	IDV,SQV,NLV	LPV/r	LPV/r,ATV/r,?DRV/r
Others	None	RAL	RAL, MVC
	None	None	?RAL

Current 2nd & 3rd line ART

Countries	Second line	Third line
Developed	Guided by resistance testing/tropism testing	Guided by resistance testing/tropism testing
Developing	TDF/3TC(FTC) +LPV/r	RAL + DRV/r

Treatment beyond ART

- HIV & ARV-related complications: OI,metabolic syndromes & premature aging
- Immune activation and inflammation(causing various HIV-related morbidities): Trials with activation inhibitor(chloroquine),inflammation inhibitor(statins, anti-IL 6),immunosuppressive and antimitotic drug(cyclosporine, hydroxycarbamide)
- HIV cure(functional vs. eradication)

A long journey of universal access to ART

2000: XIII IAC in Durban calls for"Access to All"
2001: UNGASS Declaration of Commitment on HIV/AIDS
2002: Global Fund to Fight AIDS,TB and Malaria
2003: Launch of PEPFAR & WHO/UNAIDS "3 by 5" initiative
2007: 3 million people on ART reached, only 2 years late
2010: Update WHO ART guidelines for earlier ART initiation
- WHO/UNAIDS treatment 2.0
- 6.6 million people on ART by 2010

2011: • Controlled trial (HPTN-052) demonstrated that ART can prevent sexual transmission of HIV to discordant couples, I'e., treatment is (as) prevention
•High Level Meeting(Jund)recommits 15 million on ART by 2015

HIV treatment & care in Asia:Overview

- -Asia as awhole has a better healthcare infrastructure than Africa.BUT
- -Asia has the same level of ART converage as Afica(31% vs. 37%)although most generic ARV and its raw material are produced inAsia and the total number of patients who need ART is several magnitudes lower in Asia
- -Number of patients on ART increased from 160,000 in 2005 to 720,000 in 2009 but this accounts for only 31% of those who were in need except Camvodia, Thailand & PNG
- -In addition, PMTCT coverage in Asia is much lower than Africa(32% vs. 54%)
- -Most rreatment programs in Asia depend on external funding except Thailand, China, India

Challenges of HIV treatment & care in Asia-Pacific

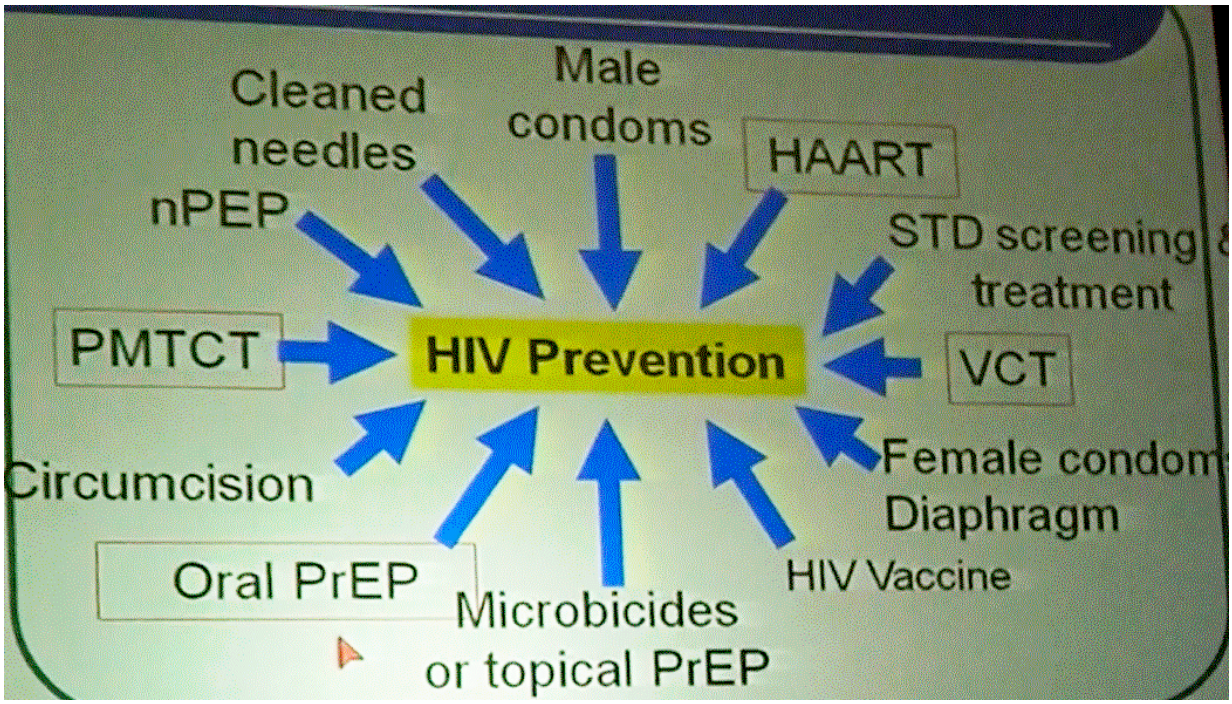
- Wider of universal access
- Earlier treatment at least to meet the new WHO Treatment Guidelines
  - How to get patients diagnosed early and shorter time from diagnosis to care?
  - Cost of drugs esp.2nd & 3rd line drugs and lab.Monitoring(VL,DR)
  - Manpower shortage:Task shifting
- Long-term care:STD, reproductive health, HIV and age-related
- Metabolic complications & malignancies
- Policy commitment on Treatment as preention in order to come up with more national budget on treatment & care
- Adherence to care, drug resistance & its transmission
- Psychosocial barriers to care e.g., homophobia, stigma
- Test every one and treat every one early (Test &treat)

HIV prevention is easy(ABC) but needs

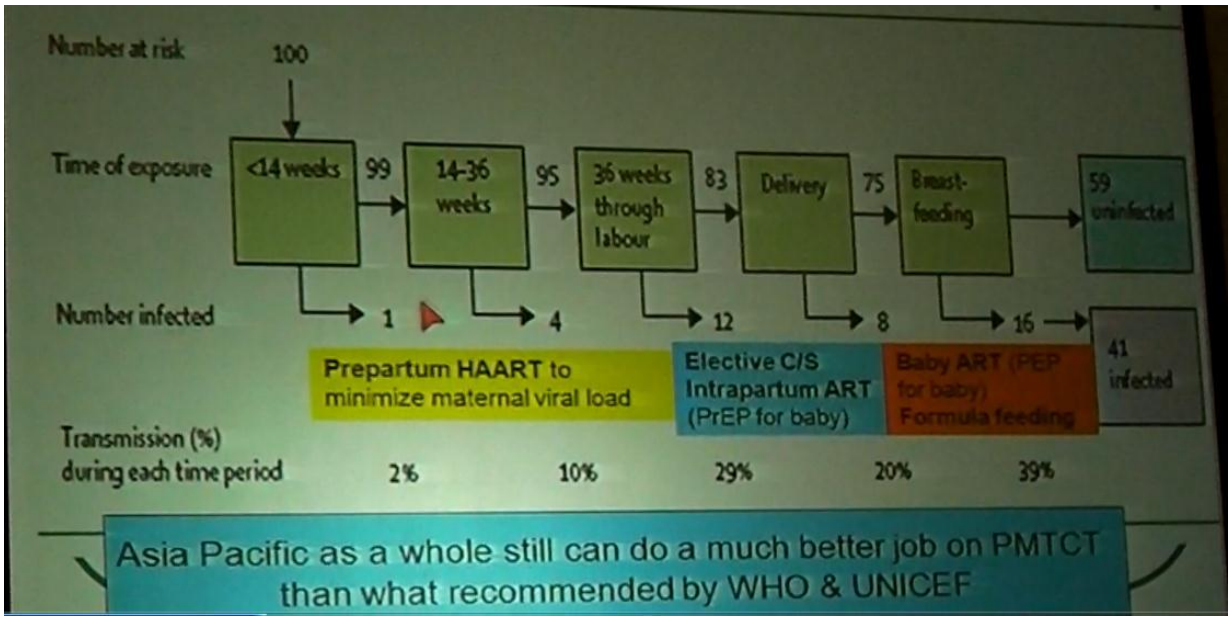
- -Knowledge
- -consciousness
- -attitude
- -commitment
- -behavioral change
- -policy
- -financial and manpower support
- -sustainability

**From self, partner, community, government, international technical and funding organizations*

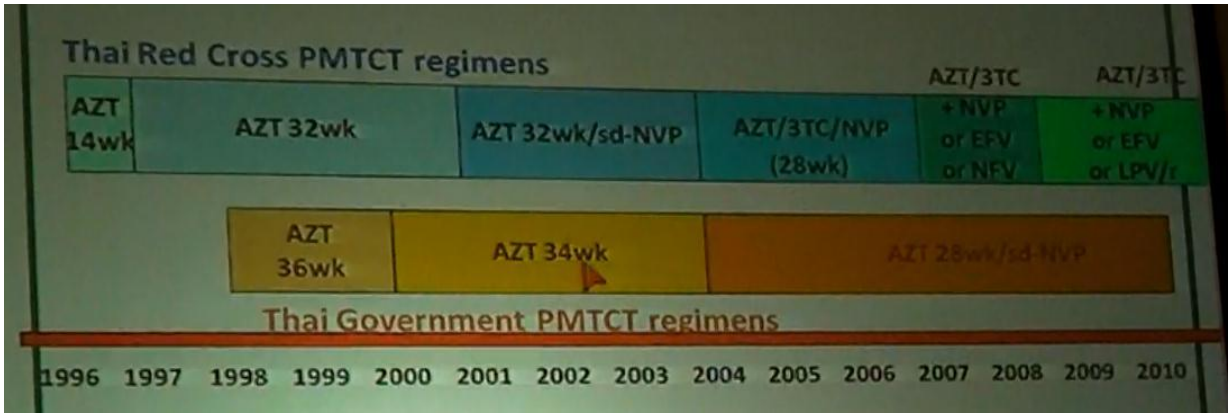
HIV Prevention Methods



Timing of HIV transmission to infant and PMTCT



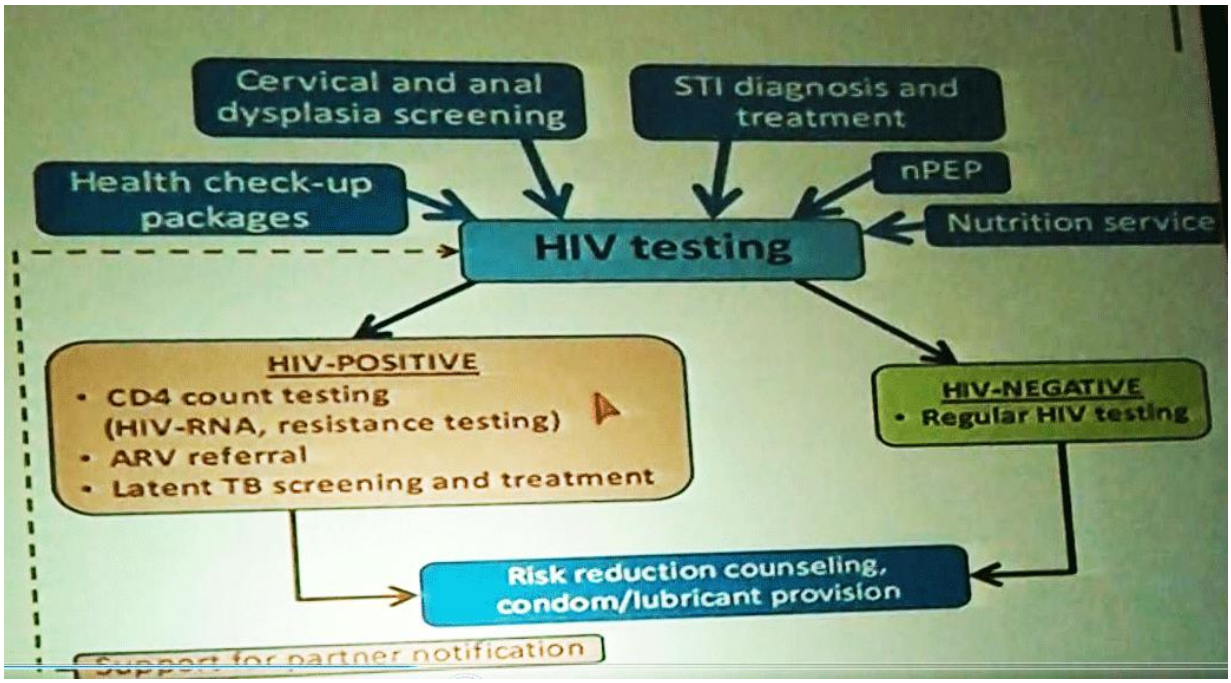
The Journey of PMTCT in Thailand



Voluntary counseling and testing (VCT) for HIV

- Rationale: an effective (and cost-effective) component of prevention approaches which promotes sexual and behavioral change to reduce HIV transmission once the HIV status is known
- Uptake of conventional (passive) VCT is low
- Provider initiated counseling and testing(PICT):
- improving VCT uptake and linkage of HIV positive persons into care
- destigmatize HIV by offering HIV testing to all regardless of risk level
- Couples VCT
- porvides a supportive environment which couples(either concordant or discordant) can make joint decision in accessing testing and can support each other should one or both become HIV positive.
- Mobile VCT

Provider- initiated counseling and testing for HIV at the TRC-AC



PICT for MSM at the TRC-AC

Provider-initiated testing and counseling for HIV in the Thai Red cross MSM sexual Health Clinic

*Among 1,429 MSM clients in 2009

*52% known HIV+ve

*35% known HIV-ve and 13% unkonw HIV status

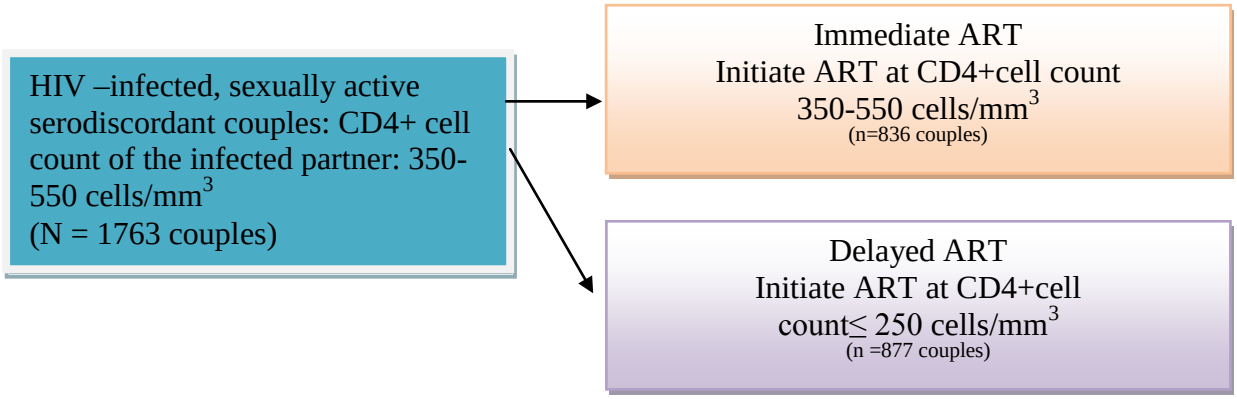
Previous HIV status	STI MSM clients		Anai Pap MSM clients	
	HIV-ve	Unknown	HIV-ve	Unknown
Acceptance of HIV testing	34%	98%	77%	85%
% tested + ve for HIV	8%	13%	13%	33%

Results of recent randomized controlled HIV prevention trials

- RV144(2009): 16,000 Thais receiving ALVAC(canary poxvector) primed/AIDSVAX gp 120B/E boosted resulted in 31% reduction in HIV acquisition
- CAPRISA 004(2010): 1% TDF gel microbicide gave 36% protection
- iPrEx(2010): Daily TDF/FTC in MSM : 42% efficacy(N=2,499)
- HPTN 052 (2011): HAART given early (CD4=350-550) resulted in 96% reduction in HIV transmission to their discordant couples as compared to late initiation (CD<250): Treatment as Prevention
- TDF2(2011) Daily TDF/FTC given to 1,218 heterosexual men and women in Botswana resulted in 63% reduction in HIV acquisition
- Partners PrEP(2011): Daily TDF of TDF/FTC given to 4,758 HIV-negative men and women resulted in 62-73% reduction in acquiring HIV from their infected partners

Is such level of efficacy justified "routine use" outside trials?

HPTN 052: Immediate vs delayed ART in serodiscordant couples

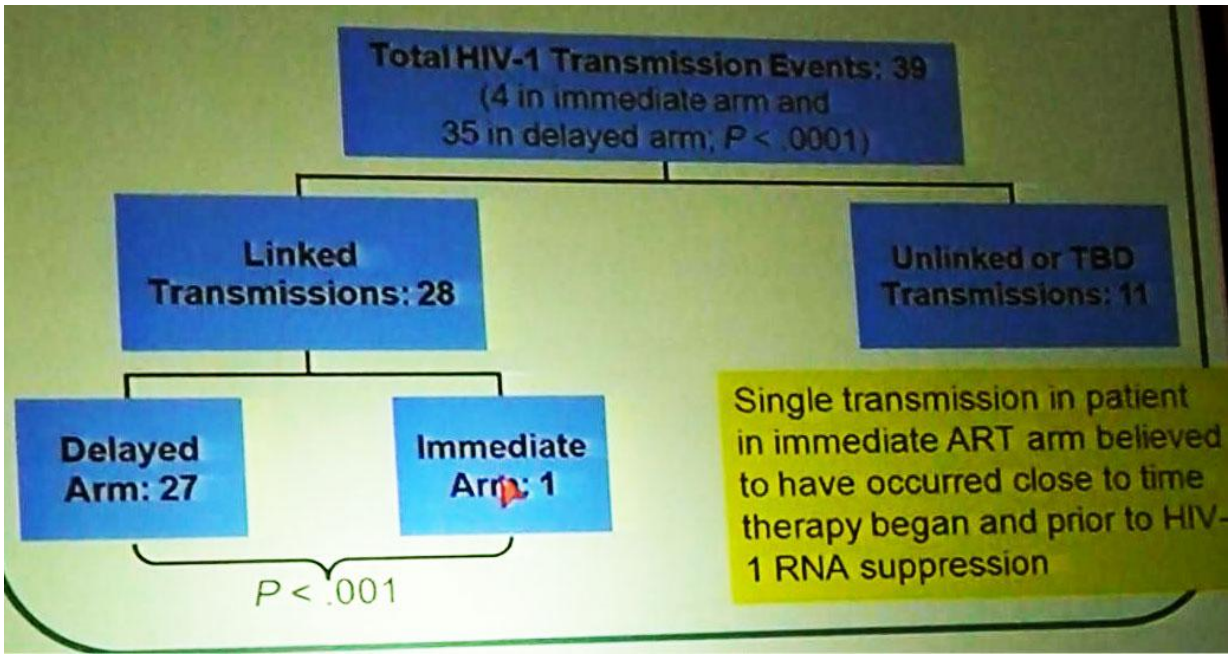


**Based on 2 consecutive values ≤250 cells/mm^3*

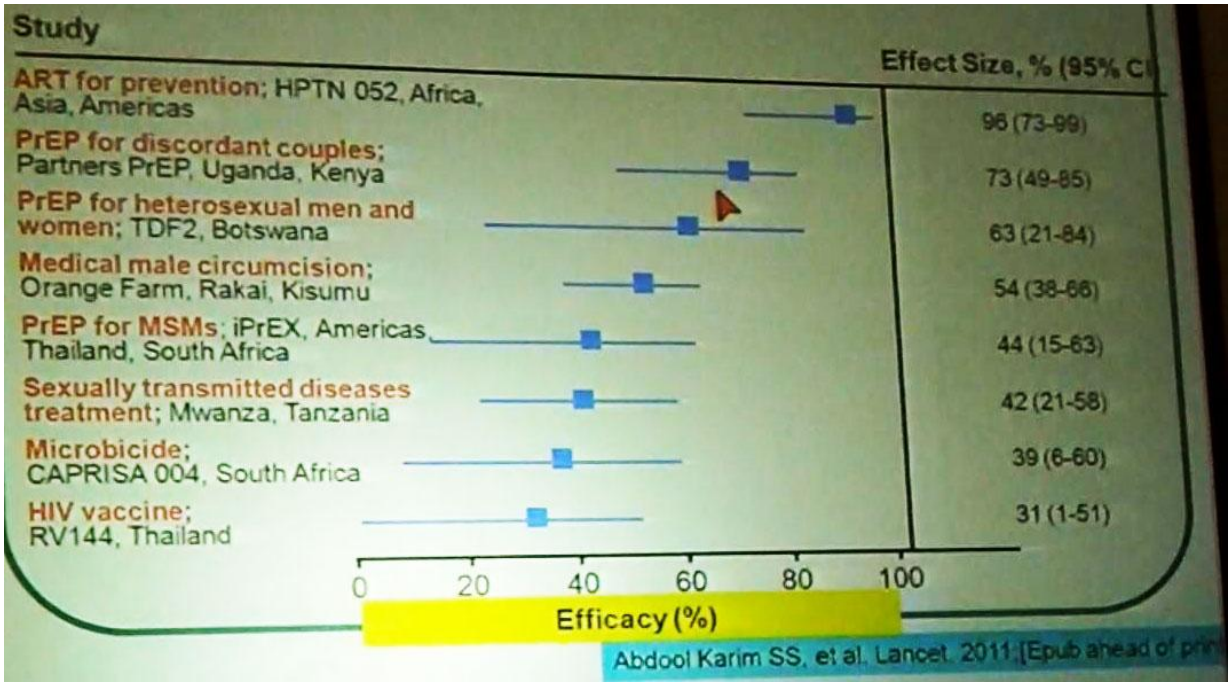
- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints:WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and us of condoms

**** DSMB recommended release of results as soon as possible following April 28,2011 review follow-up continues but all HIV-infected partners offered ART after release of results*

HPTN 052: HIV Transmission reduced by 96% in serodiscordant couples



Efficacy of HIV prevention strategies from randomized clinical trials



What are the concerns with PrEP?

- A high demand that may not be met
- Efficacy in IDU has not yet been shown
- PrEP should never be used as 1st line defense against HIV(i.e., always + condom and other proven prevention methods)
- HIV testing is needed before using PrEP and should be regularly tested
- Adherence and safety monitoring needed
- Ethical concern among conservative tax payers, thus making national & international policy of PrEP provision difficult
- Should it be used in place of Placebo in all future HIV prevention trials?

By-products of the HIV journey(beyond prevention & treatment)

- Healthcare workers: understand human rights, confidentiality, communication skill(counseling), cost concern, GCP, operational research, and may become doctor activists
- Society and community:anxiety & denial, stigma & discrimination, volunteers, NGO, CBO, self-help group)PLHIV group)
- -International community: generation of UNAIDS, UNITAID,GFTM,PEPFAR, Medicine patent pool, etc.
- -This journey will never end