New perspectives of HIV treatment
治療愛滋病毒感染的新觀點

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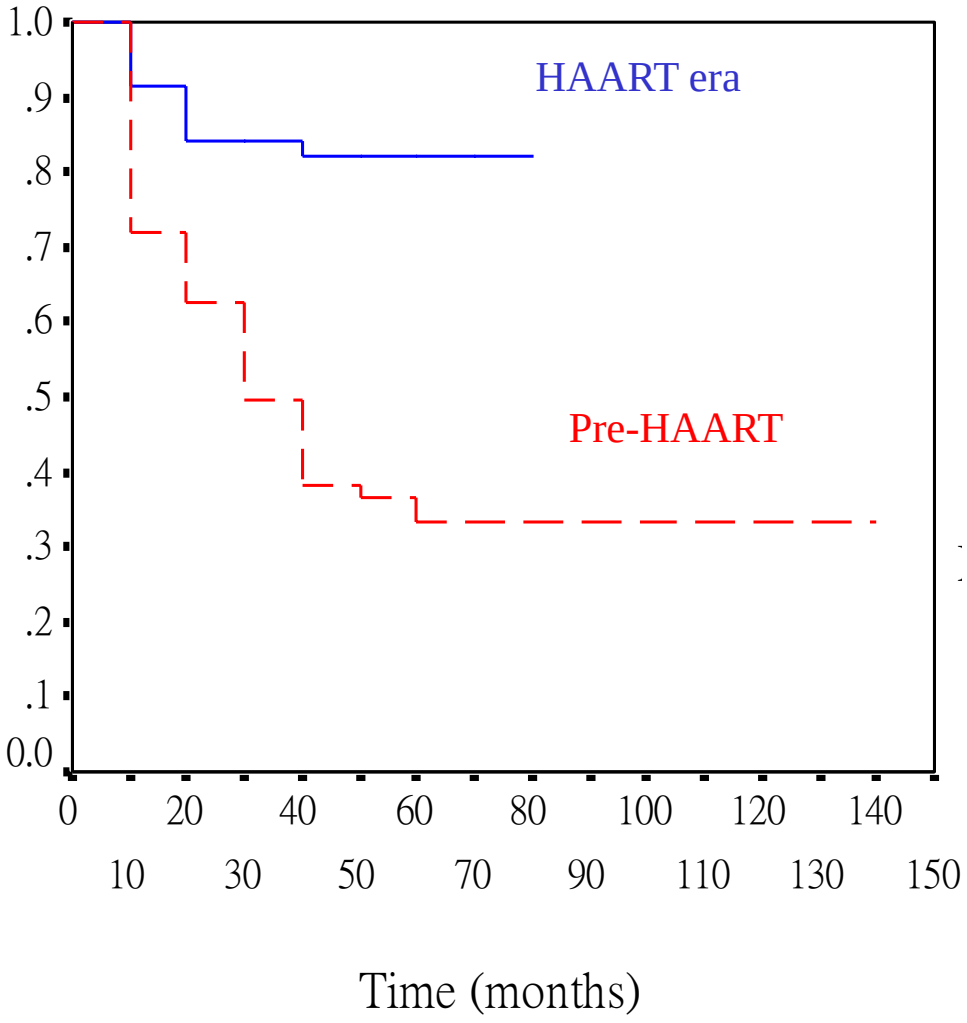
Timothy Brown, also known as "The Berlin Patient," is thought to be the only individual functionally cured of HIV

http://defeathiv.org/berlin/

HIV cure is *theoretically* possible but not yet a practicable strategy in the near future. In the meantime, treatment outcomes have progressively improved at individual level with positive implications for the population



Survival of HIV+ Chinese patients before and after HAART (highly active antiretroviral therapy)

Wong KH, Chan KCW, Lee SS, Chan MKT, Lee KCK. Delayed death and AIDS progression in an Asian cohort of advanced HIV disease patients in the HAART era. *XV International AIDS Conference 11-16 July 2004, Bangkok.*

AIDSMEDS
Your Ultimate Guide to HIV Care

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

- Combivir* (zidovudine + lamivudine, AZT + 3TC)
- Emtriva (emtricitabine, FTC)
- Epivir* (lamivudine, 3TC)
- Epzicom (Kivexa, abacavir + lamivudine, ABC + 3TC)
- Retrovir* (zidovudine, AZT, ZDV)
- Trizivir (abacavir + zidovudine + lamivudine, ABC + AZT + 3TC)
- Truvada (tenofovir DF + emtricitabine, TDF + FTC)
- Videx EC* & Videx* (didanosine, ddI)
- Viread (tenofovir disoproxil fumarate, TDF)
- Zerit* (stavudine, d4T)
- Ziagen* (abacavir, ABC)
- Amdoxovir (AMDX, DAPD)
- Tenofovir alafenamide fumarate (TAF)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Edurant (rilpivirine, RPV, TMC-278)
- Intelence (etravirine, ETR, TMC-125)
- Rescriptor (delavirdine, DLV)
- Sustiva (Stocrin, efavirenz, EFV)
- Viramune* and Viramune XR (nevirapine, NVP)
- Lersivirine (UK-453061)

Pharmacokinetic Enhancers

- Norvir (ritonavir, RTV)
- Tybost (cobicistat, GS-9350)

Protease Inhibitors (PIs)

- Aptivus (tipranavir, TPV)
- Crixivan (indinavir, IDV)
- Invirase (saquinavir, SQV)
- Kaletra (Aluvia, lopinavir/ritonavir, LPV/r)
- Lexiva (Telzir, fosamprenavir, FPV)
- Norvir (ritonavir, RTV)
- Prezista (darunavir, DRV)
- Reyataz (atazanavir, ATV)
- Viracept (nelfinavir, NFV)
- Prezcobix (Rezolsta, darunavir/cobicistat)
- Atazanavir + Cobicistat

Entry Inhibitors (including Fusion Inhibitors)

- Fuzeon (enfuvirtide, ENF, T-20)
- Selzentry (Celsentri, maraviroc, UK-427,857)
- Cenicriviroc (TBR-652, TAK-652)
- Ibalizumab (TNX-355)
- PRO 140

Integrase Inhibitors

- Isentress (raltegravir, MK-0518)
- Tivicay (dolutegravir, S/GSK-572)
- Vitekta (elvitegravir, GS-9137)

AIDSMEDS http://www.aidsmeds.com/ accessed on 14 October 2014

Entry inhibitor	Protease inhibitor	Integrase inhibitor	Reverse transcriptase inhibitor
Fusion inhibitor	No boosting		Nucleoside RTI
CCR5 antagonist	Boosting		Non-nucleoside NRTI

RECOMMENDED REGIMENS FOR INITIAL TREATMENT

2 NRTI + 1 NNRTI

2 NRTI + 1 PI (with or without boosting)

2 NRTI + 1 II

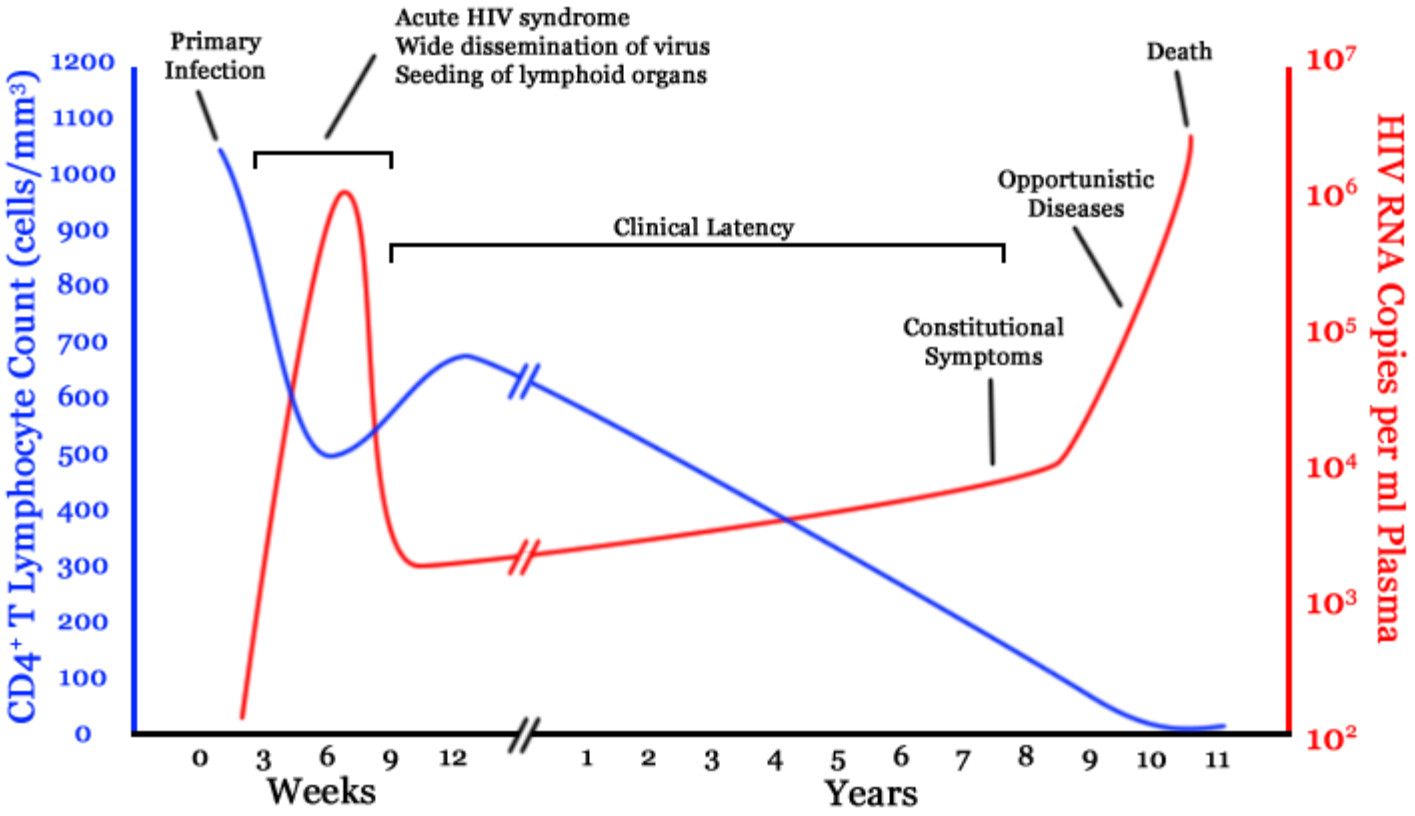
From DHHS guidelines

HAART
highly active antiretroviral therapy

Use 3 drugs from 2 groups only – effective, and preserve options

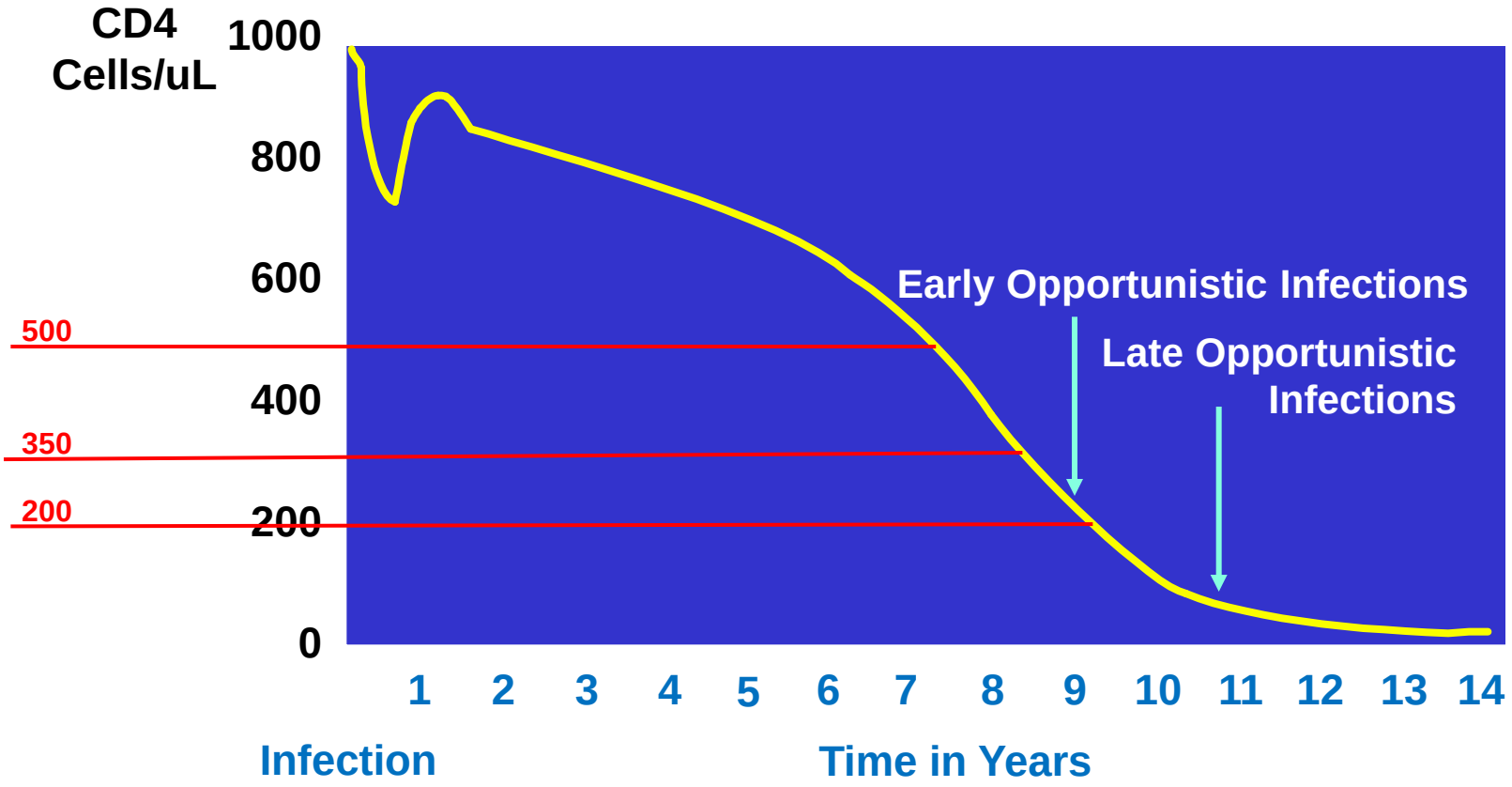
Who should receive treatment ?

Natural history of HIV/AIDS



http://en.wikipedia.org/wiki/Image:Hiv-timecourse.png

CD4 guided treatment strategy



AETC slide sets http://aidsetc.org/aidsetc?page=et-01-00

When should one be on HAART? (conventional strategy)

For chronic infection

- Symptomatic HIV infection
- Evidence of immune deficiency, e.g. CD4 < 350/uL
- Anticipated progression

Optimizing HIV treatment

Why optimize treatment

Can one size fit all ?

- Avoid resistance
- Minimize side effects
- Reduce pill count
- Cut cost
- …. consider population effects of treatment

Combo – the way ahead

Multi-Class Combination Drugs


Atripla (efavirenz + tenofovir + emtricitabine)


Complera (Eviplera, rilpivirine + tenofovir + emtricitabine)


Stribild (formerly Quad) (elvitegravir + cobicistat + tenofovir + emtricitabine)

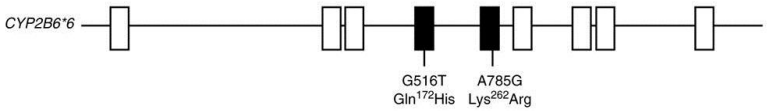

Triumeq (formerly Trii) (dolutegravir + abacavir + lamivudine)

Host genetics counts

Giving the right dose of the right drug to the right person at the right time

US guidelines
HLA-B*5701-positive patients should not be prescribed abacavir, because of a multiorgan clinical syndrome typically seen within the initial 6 weeks of treatment, reported in 5%–8% of patients

Abacavir (ABC) – NRTI in recommended regimens



Allelic variants of the human *CYP2B6* gene are associated with side effects and plasma levels

Efavirenz – NNRTI in recommended regimen, is metabolised through CYP2B6

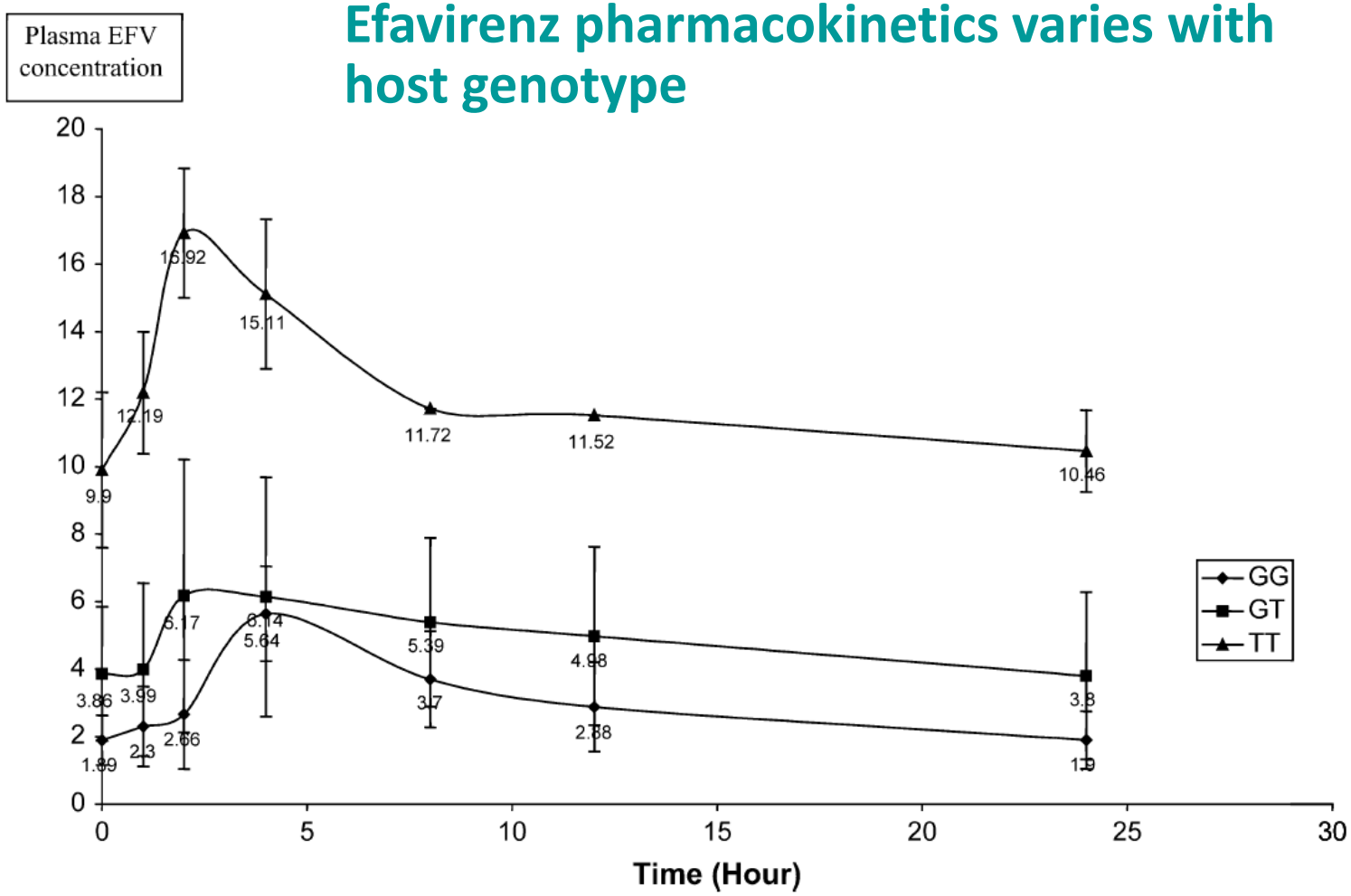
Lang T, et al. Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver.***Immunogenetics*** 2001;11:399-415

CYP2B6-G516T genotype frequency and mean efavirenz concentration

CYP2B6-G516T genotype	GG	GT	TT
Genotype frequency (%)	35 (57.3)	23 (37.7)	3 (4.9)
EFV concentration (mg/L) (mean ± SD)	2.53 ± 0.84	3.88 ± 1.17	11.43 ± 3.76

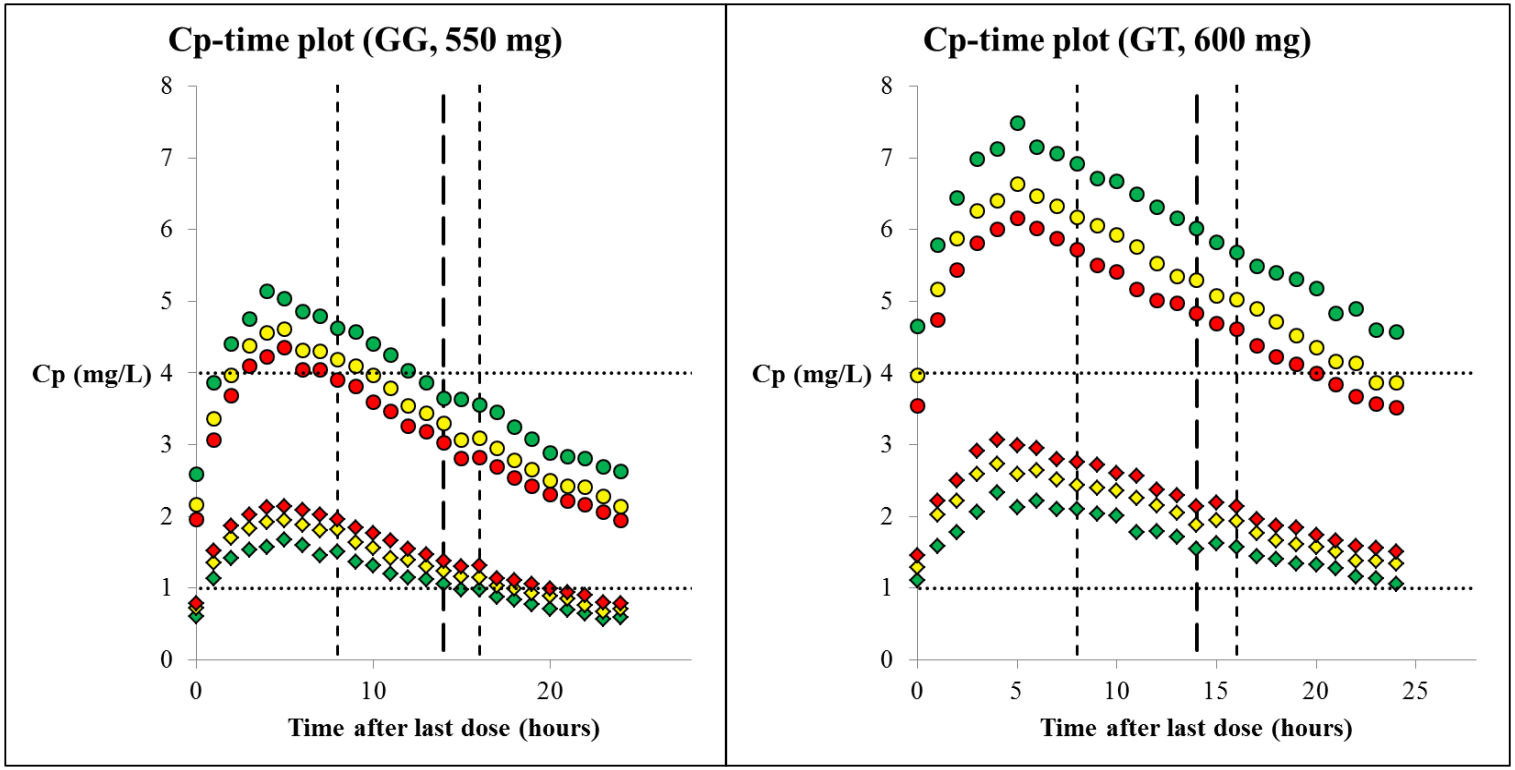
Naftalin CM, Chan KCW, Wong KH, Cheung SW, Chan RCY, Lee SS. CYP2B6-G516T genotype influences plasma efavirenz levels in a Hong Kong population allowing potential individualization of therapy. *HIV Med* 2014;15: 63-64.

Efavirenz pharmacokinetics varies with host genotype



To KW, Liu ST, Cheung SW, Chan DPC, Chan RCY, Lee SS. Pharmacokinetics of Plasma efavirenz and CYP2B6 polymorphism in southern Chinese *Ther Drug Monit* 2009;31(4):527-530.

Population PK study



Optimal doses
GG 500mg
GT 350mg
TT 100mg

…. the road to personalized treatment

Protease inhibitors	ATV SQV NFV RTV IDV LPV TPV DRV
Non nucleoside reverse transcriptase inhibitors	NVP EFV ETV RPV
Integrase inhibitors	RGV
Nucleoside reverse transcriptase inhibitor	ZDV 3TC ABC
Anti-mycobacterial	RFB

TDM

TDM available as a free supplemental service to HIV clinics in Hong Kong

Therapeutic drug monitoring by HPLC

SS Lee & Denise Chan. TDM lab information 2014 Hong Kong

Research angles

for HIV treatment optimization

Therapeutic drug monitoring as a supplemental service

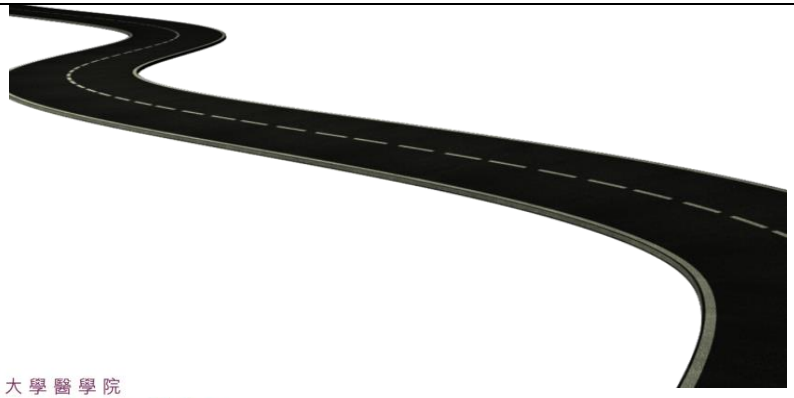
CYP polymorphism and impacts on treatment focusing on efavirenz, an NNRTI

Pharmacokinetic enhancement – mouse model

Metabolic complications – avoiding complications

Renal complications – tenofovir

Host genetic screening – APO genes and Protease Inhibitors



- **Improve adherence**
- **Uphold safety**
- **Enhance access**
- **Increase choice**

Population perspectives of HIV treatment

HPTN052

THE STUDY. Multicentre recruitment of 1763 heterosexual serodiscordant couples in which the HIV +ve partner had a CD4 cell count between 350 and 550 cells/uL (ineligible for treatment at that juncture). About half from Africa. They were randomized to (A) start treatment immediately, or (B) defer treatment until their CD4 counts fell into the range 250 to 200.

MAIN RESULTS: A total of 39 individuals became infected during a median follow-up period of 1.7 years. (incidence 1.2 per 100 person-years)

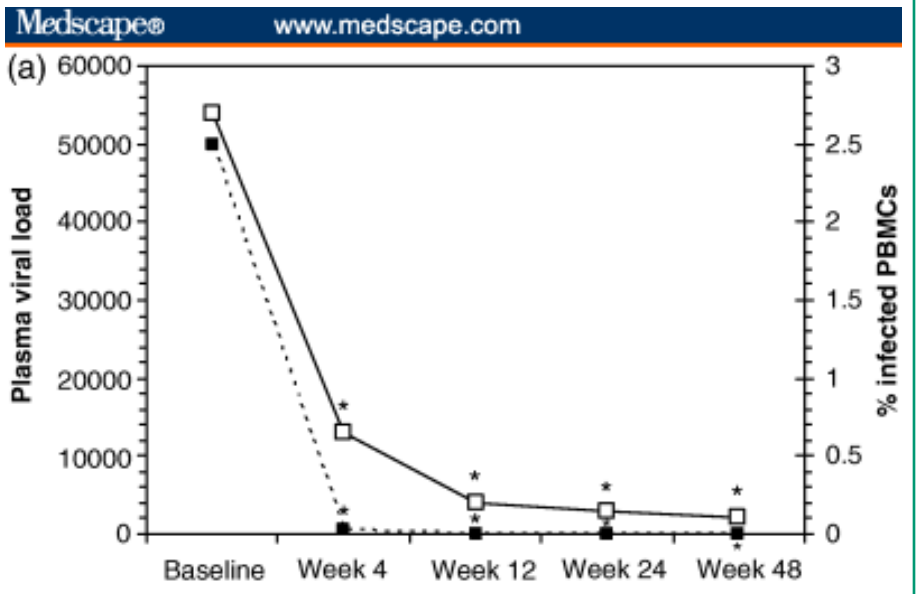
Immediate-treatment arm – 4
Deferred-treatment arm – 35 .

28 were virologically linked; 11 cases of transmission were unlinked, that is, attributable to sex outside the primary relationship. Only 1 of the 28 belonged to the immediate-treatment arm.

A majority of transmission events were estimated to have occurred when the index partner had a CD4 count above 350 cells/uL

Final multivariate analysis showed that baseline viral load was the strongest predictor of transmission in both groups.

http://www.sciencemag.org/content/334/6063.cover-expansion



L Al-Harthi et al. Evaluation of the Impact of Highly Active Antiretroviral Therapy on Immune Recovery in Antiretroviral Naive Patients. *HIV Medicine*. 2004;5(1)

http://www.medscape.com/viewarticle/467766_3

With HIV treatment

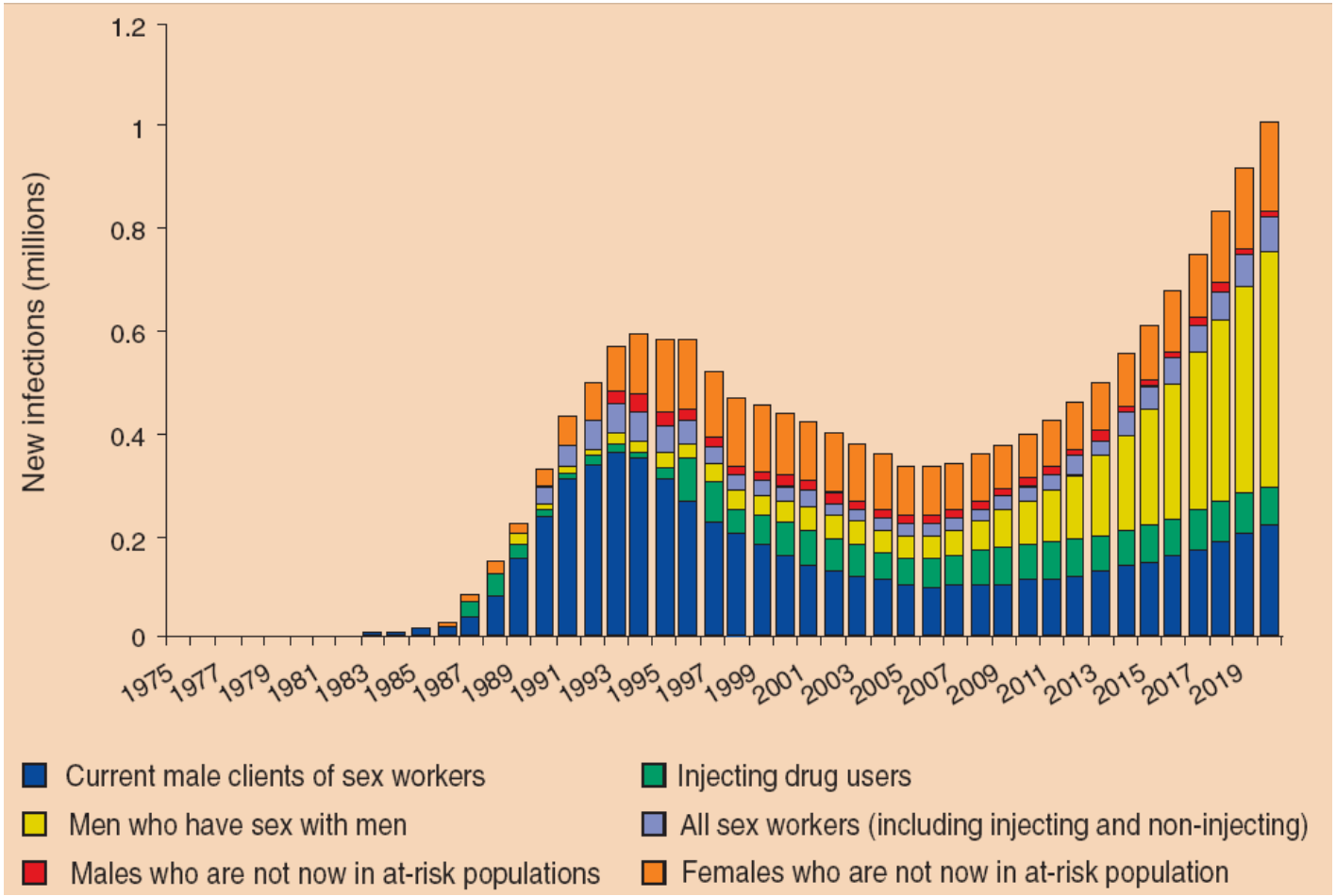
↓ viral load of treated patients

Assuming good coverage

↓ **viral load in the population**

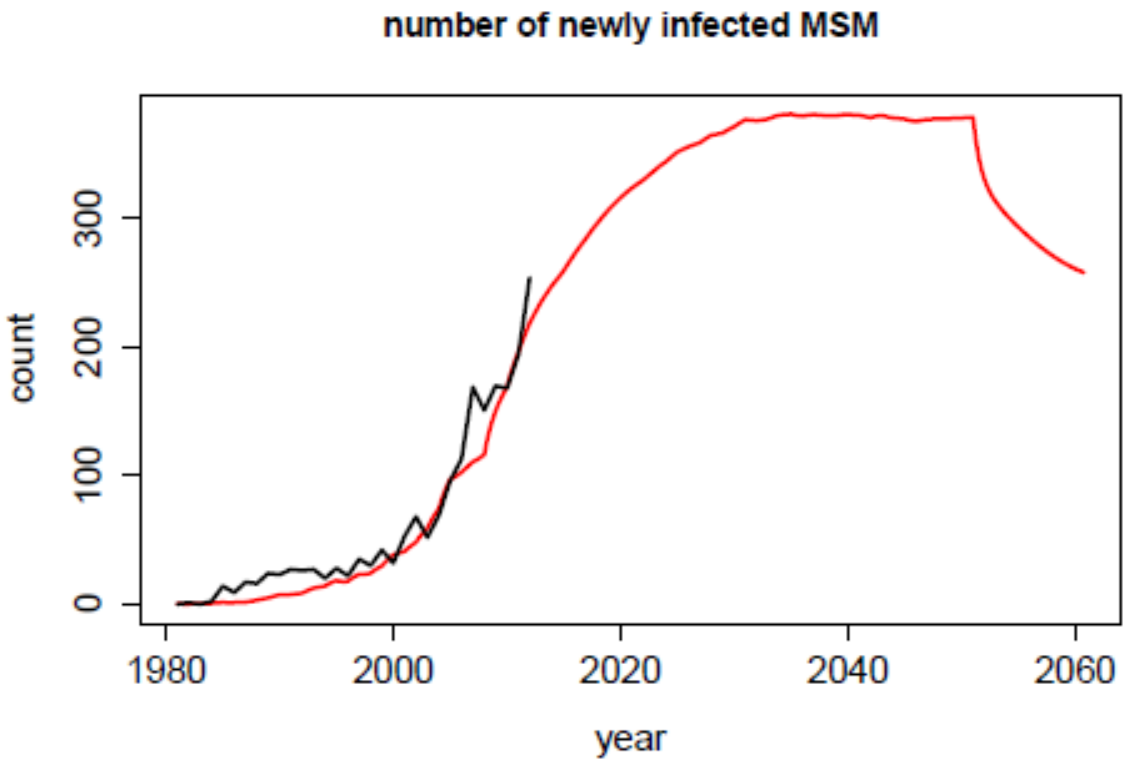
MSM remains a main subpopulation hard-hit by HIV

Annual new HIV infections in adults by population group a decline from early prevention successes, an increase from current failures



UNAIDS. Redefining AIDS in Asia – report of the Commission on AIDS in Asia. New Delhi: OUP, 2008

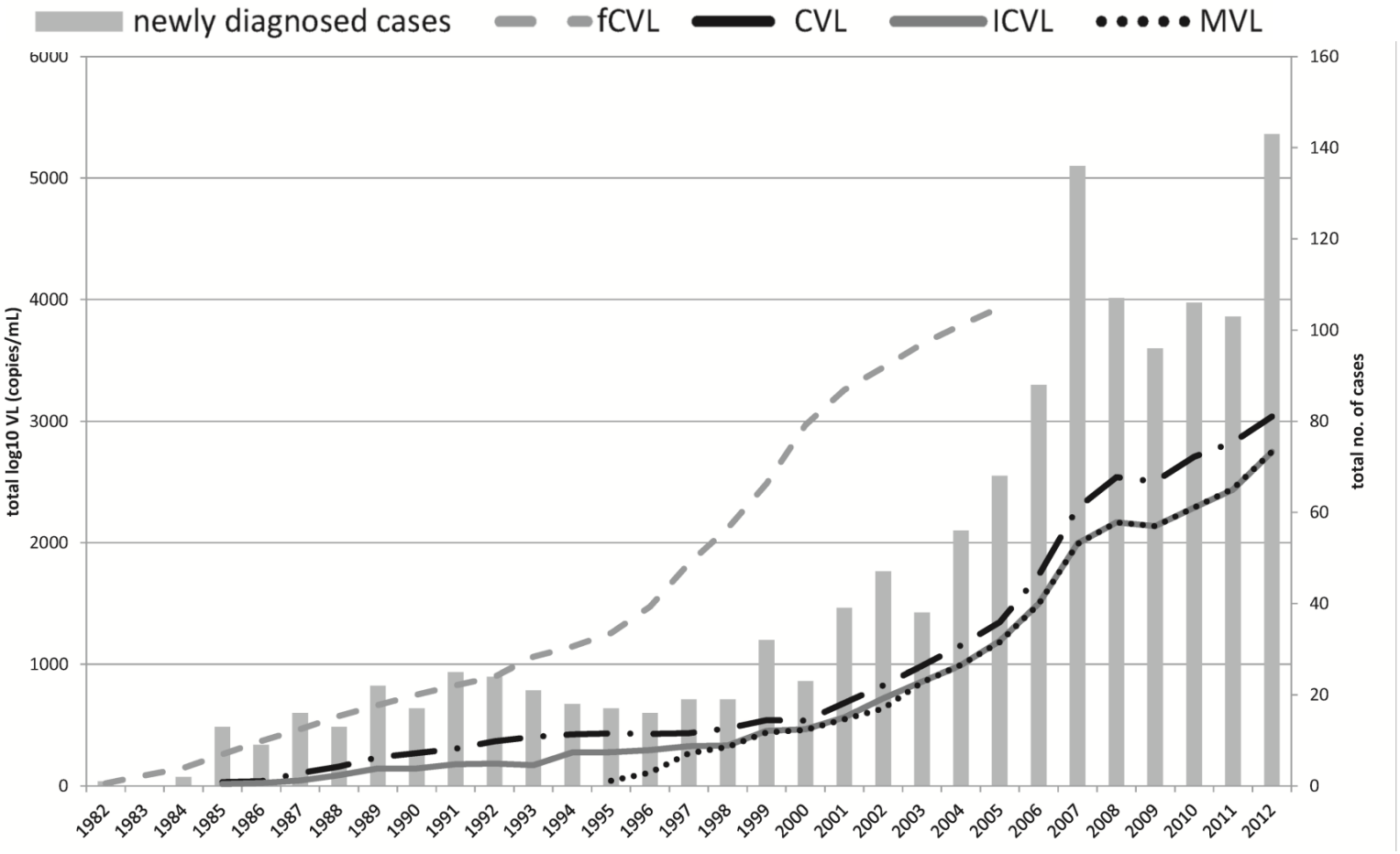
HIV epidemiology in MSM



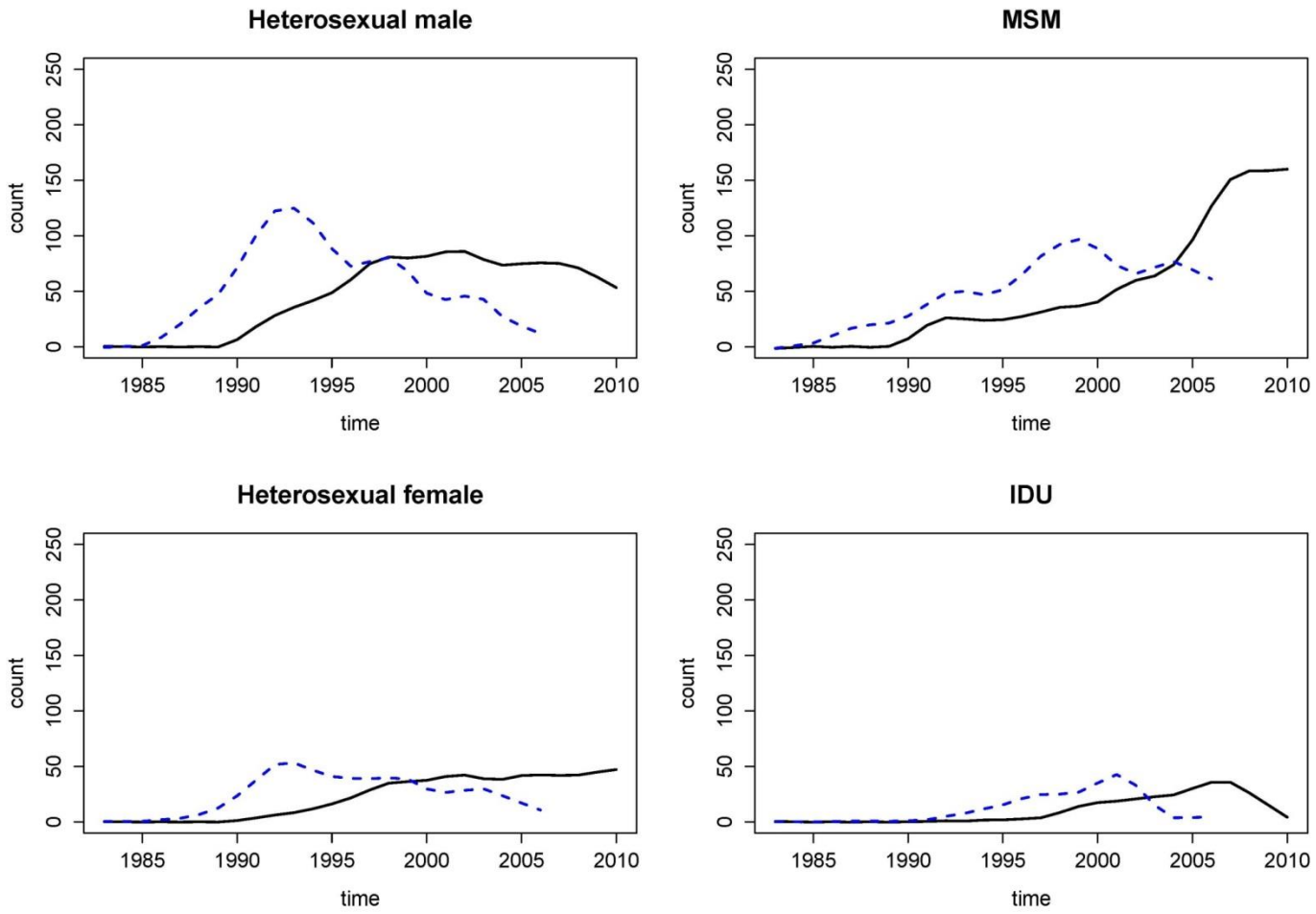
Impacts of

- Effective treatment on transmission
- Connectivity changes after receiving care
- Reduction of risk behaviours after diagnosis

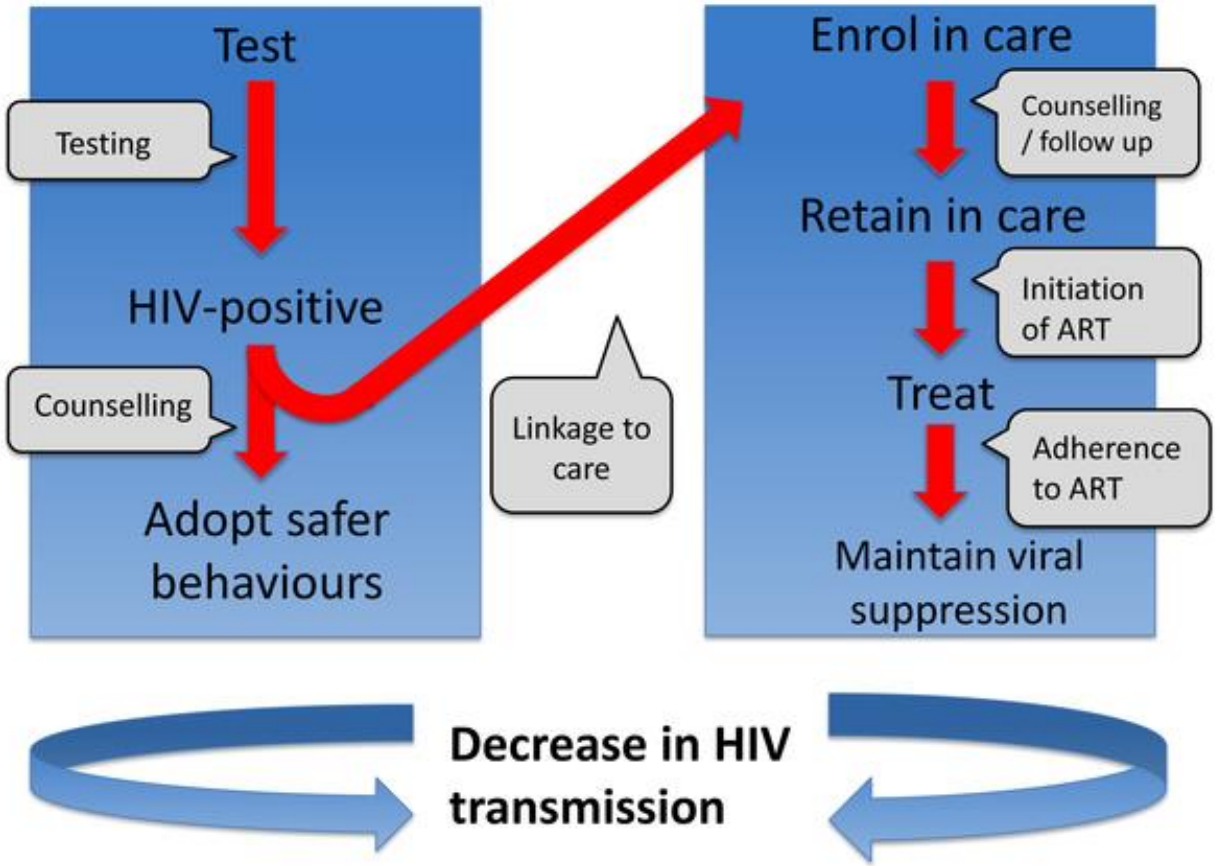
Viral load measures of MSM at population levels – Hong Kong example



Including undiagnosed HIV+ individuals
– Hong Kong example



What else are needed to reduce onward transmission from someone infected with HIV.



PLOS | MEDICINE

Wilson DP (2012) HIV Treatment as Prevention: Natural Experiments Highlight Limits of Antiretroviral Treatment as HIV Prevention. *PLoS Med* 9(7): e1001231. doi:10.1371/journal.pmed.1001231
http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001231

Change underway…….

Panel's Recommendations

• Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression.
  ◦ The strength of and evidence for this recommendation vary by pretreatment CD4 T lymphocyte (CD4) cell count: CD4 count <350 cells/mm^3 **(AI)**; CD4 count 350 to 500 cells/mm^3 **(AII)**; CD4 count >500 cells/mm^3 **(BIII)**.
• ART is also recommended for HIV-infected individuals to prevent of transmission of HIV.
  ◦ The strength of and evidence for this recommendation vary by transmission risks: perinatal transmission **(AI)**; heterosexual transmission **(AI)**; other transmission risk groups **(AIII)**.
• Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

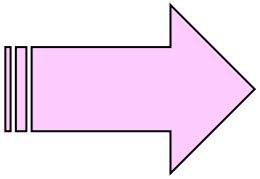
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. **Updated 2014**

When should one be on HAART?

For chronic infection

- Symptomatic HIV infection
- Evidence of immune deficiency
- Anticipated progression



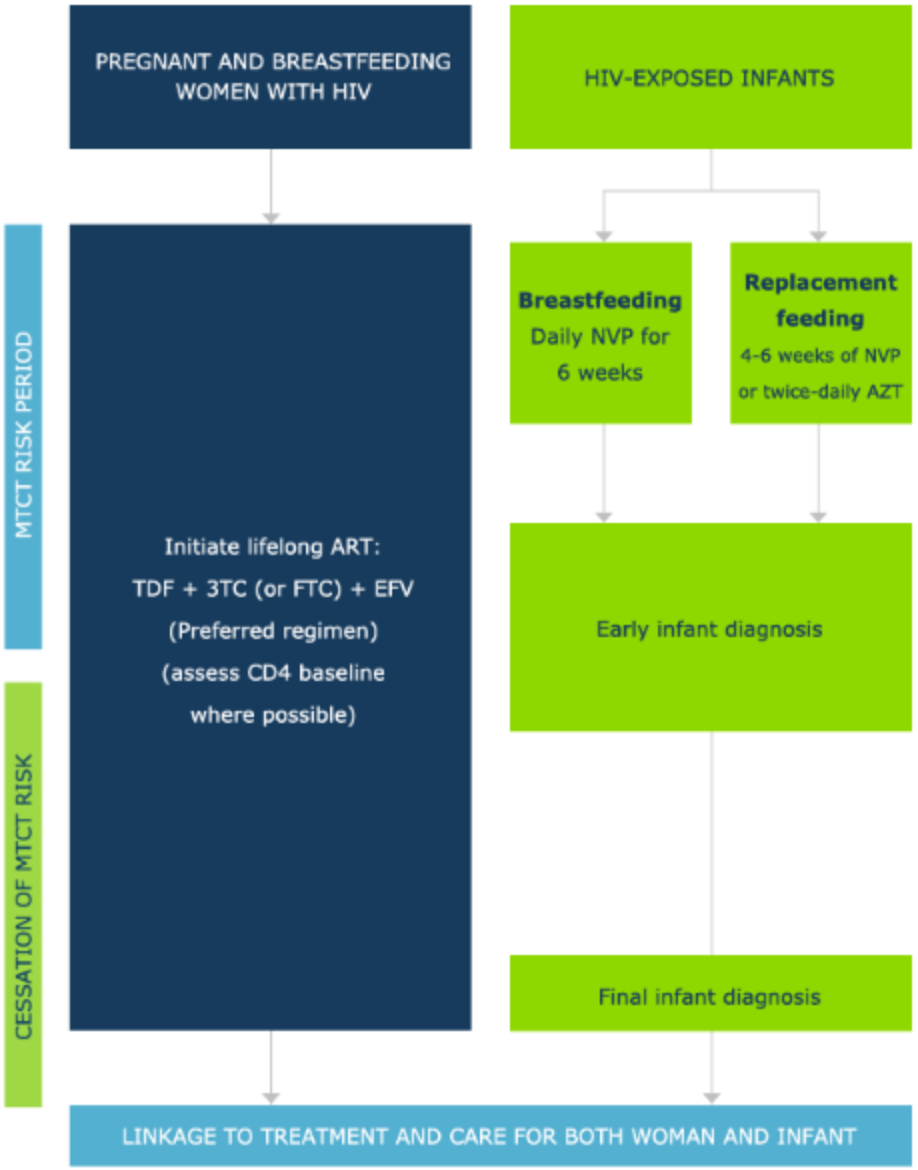
Expanded strategy

- **To reduce the risk of disease progression, irrespective of CD4 count** (i.e. severity of immune deficiency)
- **To prevent transmission**
  - From mother to baby
  - After exposure, e.g. occupational (post-exposure prophylaxis)
  - Pre-exposure prophylaxis

PMTCT

Prevention of mother-to-child transmission

WHO recommendations Option B+



WHO. 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. http://www.who.int/hiv/en/

PEP

post-exposure prophylaxis

- Clinical assessment of exposure
- Eligibility assessment for HIV post-exposure prophylaxis
- HIV testing of exposed people and source if possible
- Provision of first aid in case of broken skin or other wound

- Risk of HIV
- Risks and benefits of HIV post-exposure prophylaxis
- Side effects
- Enhanced adherence counselling if post-exposure prophylaxis to be prescribed
- Specific support in case of sexual assault

- Post-exposure prophylaxis should be initiated as early as possible following exposure
- 28-day prescription of recommended age-appropriate ARV drugs
- Drug information
- Assessment of underlying comorbidities and possible drug-drug interactions

- HIV test at 3 months after exposure
- Link to HIV treatment if possible
- Provision of prevention intervention as appropriate

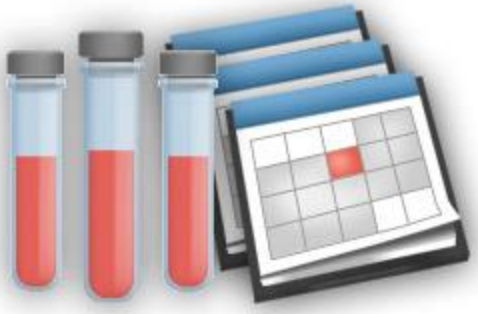
WHO. Guidelines on PEP and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children – recommendations for a public health approach . (*supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*) December 2014 http://www.who.int/hiv/en/

PrEP

pre-exposure prophylaxis

Daily oral PrEP with the fixed-dose combination of tenofovir (TDF) 300 mg and emtricitabine (FTC) 200 mg has been shown to be safe and effective in reducing the risk of sexual HIV acquisition in adults

PrEP IS A NEW HIV PREVENTION METHOD IN WHICH PEOPLE WHO DO NOT HAVE HIV INFECTION TAKE A PILL DAILY TO REDUCE THEIR RISK OF BECOMING INFECTED.



ONLY PEOPLE WHO ARE HIV-NEGATIVE SHOULD USE PrEP. AN HIV TEST IS REQUIRED BEFORE STARTING PrEP AND THEN EVERY 3 MONTHS WHILE TAKING PrEP.

PrEP CAN ONLY BE PRESCRIBED BY A HEALTH CARE PROVIDER AND MUST BE TAKEN AS DIRECTED TO WORK.

US DHHS. AIDS.gov http://www.aids.gov/hiv-aids-basics/prevention/reduce-your-risk/pre-exposure-prophylaxis/

	Men Who Have Sex with Men	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection	HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work	HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work In high-prevalence area or network	HIV-positive injecting partner Sharing injection equipment Recent drug treatment (but currently injecting)

US Public Health Service. Pre-exposure prophylaxis for the prevention of HIV infection in the United States – 2014: a clinical practice guideline http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf

WHO. Consolidated guidelines on HIV prevention, Dx, Tx & care for key populations. 2014 http://www.who.int/hiv/pub/guidelines/keypopulations/en

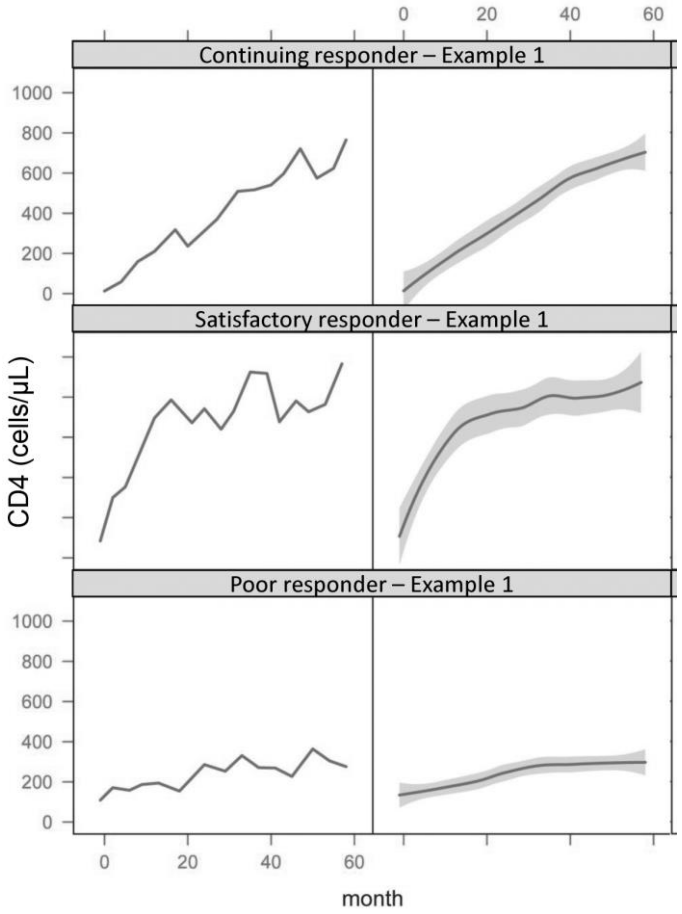
ALL KEY POPULATION GROUPS

Where serodiscordant couples can be identified and where additional HIV prevention choices for them are needed, daily oral PrEP (specifically tenofovir or the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention for the uninfected partner *(conditional recommendation, high quality of evidence) (74).*

MEN WHO HAVE SEX WITH MEN

Among men who have sex with men, PrEP is recommended as an additional HIV prevention choice within a comprehensive HIV prevention package *(strong recommendation, high quality of evidence).*

CD4 trajectories after treatment



CD4 trajectory

Smoothed curve with 95% CI

CD4 count can be monitored at 3- to 6-month intervals after initiation of treatment

Strategy change

CD4 guided → viral load guided

GLOBAL REPORT

– UNAIDS report on the global AIDS epidemic 2013.
http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/unaids_global_report_2013_en.pdf

35 million

At the end of 2013, 35 million people were living with HIV.

28 million

Over 28 million people are eligible for antiretroviral therapy, under WHO 2013 consolidated ARV guidelines.

11.7 million

At the end of 2013, 11.7 million people had access to antiretroviral therapy in low- and middle-income countries.

WHO. http://www.who.int/hiv/en/

Preface
Foreword
Foreword
Project Team
Acknowledgements
List of Reviewers / Authors

A. BASICS OF HIV MEDICINE

1. Virology and immunology
2. Epidemiology
3. Diagnoses, classification and staging of HIV disease
4. Psychosocial needs of HIV patients

B. PUBLIC HEALTH MANAGEMENT

5. HIV testing strategies and programmes
6. Public health surveillance
7. Prevention targeting the HIV positives

C. CLINICAL HIV MANAGEMENT

8. The primary care perspectives of HIV management
9. Antiretroviral therapy
10. Managing treatment failure
11. Adherence to HAART
12. Investigations for optimizing HIV treatment
13. An HIV traveller
14. Metabolic problems and cardiovascular complications
15. HIV-associated neurocognitive disorders (HAND)
16. Immune reconstitution inflammatory syndrome
17. Dermatologic manifestations in HIV disease

D. OPPORTUNISTIC & CONCURRENT INFECTIONS

18. Candidiasis in HIV
19. Cytomegalovirus diseases
20. Cryptococcosis
21. *Mycobacterium avium* complex infection
22. Tuberculosis in HIV/AIDS
23. *Penicillium marneffei*
24. *Pneumocystis* pneumonia
25. Progressive multifocal leukoencephalopathy
26. Toxoplasmosis
27. HIV and hepatitis co-infections
28. Sexually transmitted infections (STI) in HIV/AIDS

E. NEOPLASIA

29. Kaposi's sarcoma
30. HIV-associated lymphoma
31. Malignancies in HIV patients

F. SPECIAL SETTINGS & THE COMMUNITY

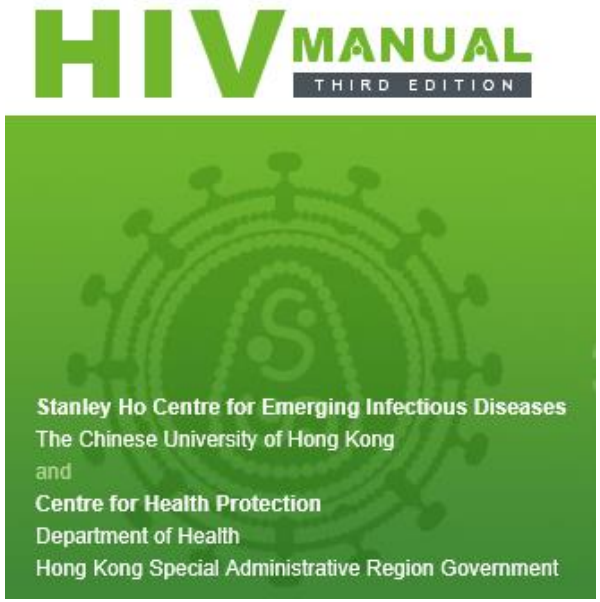
32. Women and HIV positive pregnancy
33. HIV infection in infants and children
34. HIV and health care workers

APPENDICES

I. Interactive tables on antiretrovirals
II. Collection of recommended guidelines
III. HIV services in Hong Kong
IV. Information sources on internet
V. HIV report form
VI. Abbreviations

ANTI-HIV MED

Available on the App Store
GET IT ON Google play



http://www.hivmanual.hk

HIV MANUAL
THIRD EDITION

Stanley Ho Centre for Emerging Infectious Diseases
The Chinese University of Hong Kong
and
Centre for Health Protection
Department of Health
Hong Kong Special Administrative Region Government

Updates to the Manual and Anti-HIV Med would be announced on the Facebook page

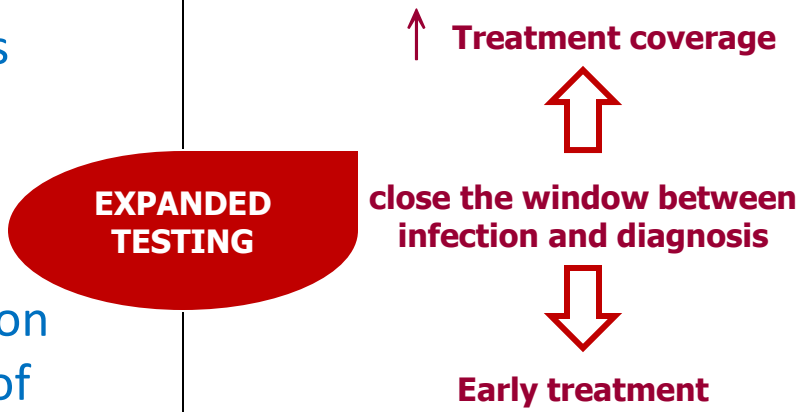
Available on the App Store

GET IT ON Google play

www.hivmanual.hk

To conclude:

- HIV is still incurable, but effectively managed
- One size does not fit all. Local protocols are needed to make safe, simple and affordable regimens available and accessible.
- Effective treatment minimizes population viral load, which can lead to reduction of transmission risk.
- The swing from a behavioural model to a biomedical model for HIV prevention



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