National Centre for Infectious Diseases

Recommendations for the Use of Antiretroviral Therapy in Adults Living with HIV in Singapore

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Singapore HIV Congress | 30 November 2019

Overview

- Need for national ART recommendations
- Recommendations workgroup & process
- When to start?
- What to start?
- Switch strategies
- Monitoring while on ART

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NHIVP ROLES & FUNCTIONS

National Centre for Infectious Diseases

- Formulate national strategic approach to achieve UNAIDS 90-90-90 targets & beyond
  - ✓ Ending HIV in Singapore
  - ✓ 4th 90 – living well with HIV
- Consult & coordinate with key stakeholders across the continuum of HIV prevention, testing & treatment services
- Develop evidence-based guidelines & best practices on HIV prevention, testing & treatment
- Assess impact of international & locally conducted research on national policies
- Monitor epidemiological trends in national registries & inform solutions

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IMPORTANCE OF “GLOCALIZATION”

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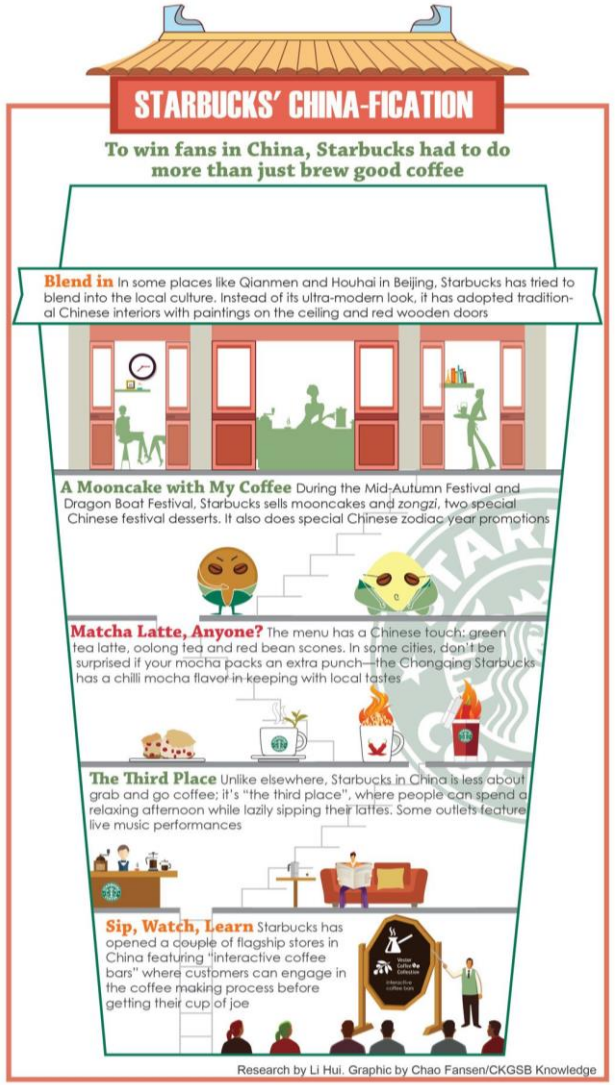
- International recommendations & benchmarks must be applied with local context in mind
- Of particular importance for ART:
  - Transmitted drug resistance trends
  - Health economics



RESULTS FOR HIV MOLECULAR SURVEILLANCE, 2013-2017

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HIV molecular surveillance	2013	2014	2015	2016	2017
Total number of samples tested	123	118	116	245	160
Recent infections (%)	17.1	17.8	22.4	20.4	23.8
Circulating subtypes (%)					
CRF01_AE	47.6	60.0	61.5	64.0	52.6
Subtype B	42.9	40.0	34.6	24.0	34.2
Transmitted Drug Resistance					
Any drug class (%)	3.3	3.4	7.0	3.7	3.1
NRTI (%)	2.4	1.7	0.9	0.8	1.3
NNRTI (%)	0.8	1.7	2.6	3.3	1.9
PI (%)	0	0	3.5	0.8	1.3

MOH, Communicable Diseases Surveillance 2017

ABACAVIR HSR (1)

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- HLA-B*5701 allele testing is recommended internationally to avoid hypersensitivity reactions (HSR)
- The frequency of the HLA-B*5701 allele in the population is a major factor governing the incidence & morbidity of HSR
- Allele frequencies in the three major ethnic groups in Singapore differ from international cohorts

Reducing hypersensitivity reactions with HLA-B*5701 genotyping before abacavir prescription: clinically useful but is it cost-effective in Singapore?

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Kapoor et al, Pharmacogenetics and Genomics 2014

ABACAVIR HSR (2)

National Centre for Infectious Diseases

***HLA-B*5701* Genotyping for Abacavir Prescription: Re-Examination of its Cost-Effectiveness in Singapore**

Dear Editor,

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) that is used to control disease progression of human immunodeficiency viruses (HIV). It reduces the morbidity and mortality of HIV infections.[1] A serious side effect of abacavir is hypersensitivity reaction (HSR) which usually begins within 6 weeks of starting treatment and manifests as fever, malaise, nausea, vomiting and rashes. In severe cases, it results in multiple organ system failure.[2]

Patients with *HLA-B*5701* polymorphism are more likely to develop HSR.[3] Studies from several countries have demonstrated the efficacy of screening for this polymorphism prior to abacavir prescription.[4,5] A large-scale clinical trial has provided strong evidence to order *HLA-B*5701* genotyping prior to abacavir prescription and to avoid this drug in patients who carry the polymorphism.[6]

We need to assess the cost-effectiveness of screening tests such as *HLA-B*5701* genotyping even when they are shown to be clinically useful.[7] An assessment of the cost-effectiveness of *HLA-B*5701* genotyping before abacavir prescription was carried out in the local context.[8] The parameters used to assess the economic costs of the test include the additional cost of genotyping, prescription of expensive alternative antiretroviral therapy drugs in allele-positive patients, the burden of additional expenses and the loss of health that may be incurred after no such test was carried out. The report concluded that *HLA-B*5701* genotyping was not cost-effective in Singapore except for a specific subgroup of newly diagnosed Indian patients with early-stage HIV in whom tenofovir was contraindicated.

Since the publication of the results of that study, new information on *HLA-B*5701* genotyping has become available that includes the actual price of the test in Singapore, genotype frequency in a real cohort of patients and the actual costs of managing adverse reactions based on physicians' input. We attempted to ascertain whether refinement of data in the cost-effectiveness model would change the conclusions. To ensure consistency with our previous work, we retained the TreeAge model and same data where no new information was available.[8]

Materials and Methods

Our institutional review board verified that ethics review was not needed for this study. Patient data from Tan Tock Seng Hospital (TTSH) was anonymised. In TTSH, most infectious disease physicians order *HLA-B*5701* genotyping when they prescribe abacavir. The Clinical Immunology Laboratory in TTSH has been offering the test since 2015. Information on ethnicity and *HLA-B*5701* status of patients was provided by the laboratory without identifiers. The genotype frequency of Chinese (n = 758), Malay (n = 164) and Indian (n = 53) patients was 0.26%, 2.44% and 15.10%, respectively.

Patients were segmented according to early- and late-stage disease. Similar to the earlier study, late-stage HIV infection is defined as CD4 count <200/μL.[9] Each group was further divided based on tenofovir contraindications into 2 groups: 1) patients who contraindicated to tenofovir and were prescribed abacavir, and 2) patients who could be prescribed both abacavir and tenofovir. In the latter, 4 strategies were examined: 1) abacavir was assigned as first-line (without genotyping) treatment with tenofovir as second-line therapy; 2) abacavir was assigned as first-line (with genotyping) treatment with tenofovir as second-line therapy; 3) tenofovir was assigned as first-line treatment with abacavir as second-line (without genotyping) therapy; and 4) tenofovir was assigned as first-line treatment with abacavir as second-line (with genotyping) therapy. In patients whom tenofovir was contraindicated, 2 strategies were investigated: 1) abacavir was assigned as first-line treatment without genotyping, and 2) abacavir was assigned as first-line treatment with genotyping.

Zidovudine was assigned as next-in-line treatment followed by last-line therapy in both patient groups. All 3 NRTI, abacavir, tenofovir and zidovudine were used with lamivudine. The last line of treatment comprised personalised combination of stavudine, lamivudine, emtricitabine, atazanavir, lopinavir and ritonavir.

The treatment costs and cost structures shown in Table 1 were retrieved from the homepage of TTSH and after consultation with infectious disease physicians. Although we mirrored the cost calculations in the study by Kapoor and associates,[8] we have revised the cost structure to better reflect contemporary clinical practice.

The costs of treating side effects of abacavir, tenofovir and zidovudine were calculated using 2 categories of data: 1) public versus private fees for consultations and tests, and 2) inpatient treatment versus outpatient treatment. We have

- Genotyping was not cost-effective prior to abacavir use in early-stage HIV patients of all ethnicities
- However, genotyping was cost-effective for late-stage Malay and Indian HIV patients
- Conclusions drawn from pharmaco-economic analyses will vary across time because of the accumulation of new data, fluctuating test costs and drug prices

Goh et al, Ann Acad Med Singapore 2019

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WORKGROUP

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- Aim
  - Provide guidance to HIV care practitioners on the optimal use of ART for the treatment of HIV infection in adults and adolescents in Singapore
- Composition
  - Directors of HIV clinical programmes
  - Private ID practitioners who treat PLHIV
  - HIV pharmacists

PROCESS

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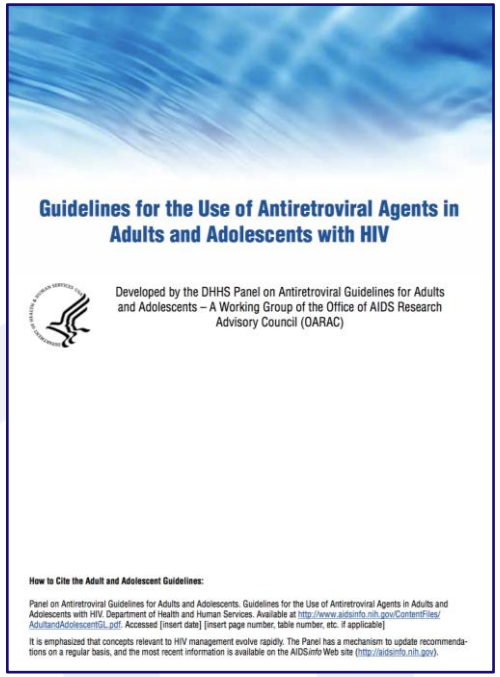
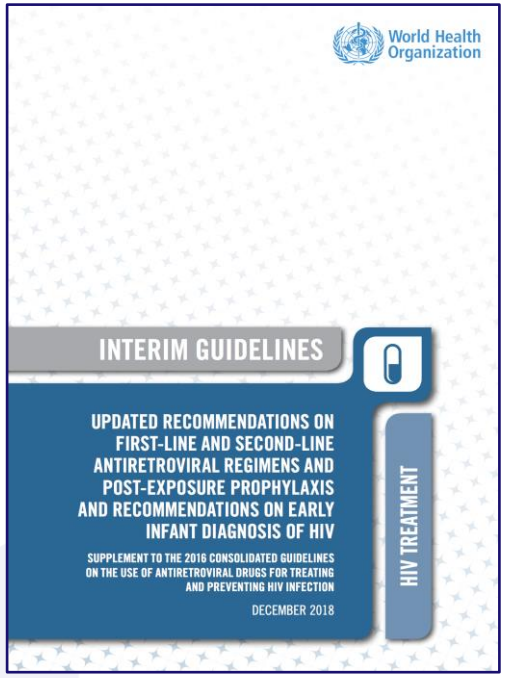
1) Review of select benchmark international guidelines





2) Adaptation to Singapore context

✓ Inclusion of interim local studies & data such as transmitted resistance trends, cost-effectiveness

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WHEN TO START (1)

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- ART regardless of CD4 count
  - Two landmark RCTs (TEMPRANO & START) showed reduced mortality & morbidity when patients who had CD4 counts > 500 were randomised to immediate vs delayed initiation
- "Rapid" ART
  - Starting ART within 1 week - 1 month of presentation slows disease progression, reduces the size of the viral reservoir & risk of treatment failure, and improves immune recovery
  - Same Day?
- ART to prevent HIV transmission
  - U = U

TEMPRANO, NEJM 2015
START, NEJM 2015
Mateo-Urdiales et al, Cochrane Database of Systematic Reviews 2019
Cao et al, Clin Infect Dis 2016
Zhao Y et al, Clin Infect Dis 2019
Ananworanich et al, EBioMedicine 2016

WHEN TO START (2)

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- We recommend that ART should be started in all people living with HIV infection within 2 weeks of presentation
- ART may be delayed in certain situations
  - Clinical: presence of certain opportunistic infections
    - CMV retinitis
    - Cryptococcal meningitis
    - TB meningitis or CD4 > 50
  - Psychosocial: patient readiness
    - Education
    - Adherence
    - Cost

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TENOFOVIR-BASED REGIMENS

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NRTI Backbone	3rd Drug		Singapore	DHHS 2019	WHO 2018
TFV (TDF or TAF)[#] + FTC or 3TC	NNRTI	EFV 400			
		EFV 600			
		RPV	Only if: - CD4 >200 - VL <100,000 c/ml		
	PI	DRV/r			
		ATV/r			
		LPV/r			
	INSTI	DTG	Only if: - Hep B co-infected - HLA B5701 +		
		BIC	Not available	TAF/FTC/BIC	
		RAL			

[#] To be avoided in patients with CrCl <60 mL/min/1.73m^2

ABACAVIR-BASED REGIMENS

National Centre for Infectious Diseases

NRTI Backbone	3rd Drug		Singapore	DHHS 2019	WHO 2018
ABC* + 3TC	NNRTI	EFV 400	Only if: - VL <100,000 c/ml		
		EFV 600	Only if: - VL <100,000 c/ml		
		RPV	Only if: - CD4 >200 - VL <100,000 c/ml		
	PI	DRV/r			
		ATV/r	Only if: - CD4 >200 - VL <100,000 c/ml		
		LPV/r			
	INSTI	DTG			
		BIC	Not available		
		RAL			

* To be avoided in patients with high cardiovascular risks; HLA-B*5701 screening would only be cost-effective in late-stage Malay and Indian ethnicities

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SWITCHING BACKBONE

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INITIAL DRUG	REASON TO SWITCH	SWITCH TO	IF	WHEN TO SWITCH
TDF/FTC →	Documented Side Effects: - Nephropathy - Osteoporosis	ABC/3TC	If cost is a major concern	
	Reduce risk of future side effects with prolonged use		If no significant cardiac risk	≥ 6 months stable
AZT/3TC →	Documented Side Effects: - Anaemia - Mitochondrial toxicities	ABC/3TC		
	Improve Adherence - Reduce dosing frequency			≥ 6 months stable
ABC/3TC →	Cardiac Risk	TDF/FTC		

SWITCHING 3RD DRUG (1)

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INITIAL DRUG	REASON TO SWITCH	SWITCH TO	IF	WHEN TO SWITCH
EFV 600 ➔	Documented NPSE	EFV 400 (recommended) or DRV/r (alternative)	VL >100K or CD4 <200	
	Documented NPSE	RPV	VL <100K or CD4 >200	
	Improved SE Profile or QoL Enhancement (shift work, etc)	RPV	VL ND and CD4 >200	≥ 6 months stable
		INSTI (DTG)		
EFV 400 ➔	Documented NPSE	RPV	VL <100K or CD4 >200	
	Improved SE Profile or QoL Enhancement (shift work, etc)	RPV	VL ND and CD4 >200	≥ 6 months stable
		INSTI (DTG)		

SWITCHING 3RD DRUG (2)

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INITIAL DRUG	REASON TO SWITCH	SWITCH TO	IF	WHEN TO SWITCH
ATV/r →	Unacceptable Jaundice or Kidney or GB stones	EFV 400 (caution → lower barrier to resistance)	(VL >100K or CD4 <200) AND no NPSE	
	Unacceptable Jaundice or Kidney or GB stones	DRV/r	(VL >100K or CD4<200) AND (NPSE or Chronic PPI Use)	
	Simplify Regimen	RPV (caution → lower barrier to resistance)	VL ND and CD4 >200	≥ 6 months stable
	Simplify Regimen	INSTI (DTG)		
DRV/r →	Simplify Regimen	EFV 400	(VL ND and CD4 >200) AND Chronic PPI Use	≥ 6 months stable
	Simplify Regimen	RPV	(VL ND and CD4 >200) AND NPSE	
	Simplify Regimen	DTG		
Any 3rd Drug →	Drug-Drug Interactions	INSTI (DTG)	Specific situations likely to result in significant DDI e.g. TB treatment, chemotherapy	

SWITCHING FROM OLDER FIXED-DOSE COMBINATIONS

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INITIAL DRUG	REASON TO SWITCH	SWITCH TO	IF	WHEN TO SWITCH
AZT/3TC/NVP (Z250) ➔ - **AZT 300mg / 3TC 150mg / NVP 200mg** - **Dosed 1 tab 12h**	Documented Side Effects: - Anaemia - Mitochondrial toxicities	ABC/3TC/RPV OR ABC/3TC/NVP XR	HLA-B*5701 Negative (depending on ethnicity)	
d4T/3TC/NVP (S30/S40) ➔ - **d4T 30mg OR 40mg / 3TC 150 mg / NVP 200mg** - **Dosed 1 tab 12h**	Improve Adherence: - Reduce dosing frequency		VL ND and CD4 >200	≥ 6 months stable

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MONITORING RECOMMENDATIONS (1)

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Investigation	Frequency of testing							
	Entry into care	ART initiation/ change	2-12 weeks after ART initiation/ change	Every 3-6 months	Every 6 months	Every 12 months	Clinically Indicated	Treatment failure
CD4 count	√	√ (only at initiation)		√ During first 2 years of ART or if viremia develops or CD4 <300cells/mm^3 Or If treatment is delayed		√ After 2 years of ART with consistently suppressed viral load * Optional once CD4 recovery has occurred & no clinical decisions need to be made for OI prophylaxis	√	√
HIV VL	√	√	√ If VL is detectable at 2-8 weeks, repeat every 4-8 weeks until viral load <200 c/mL, and thereafter, every 3-6 months	√ For the first 2 years of treatment	√ For stable patients if VL is ND for one year or more & no adherence concerns		√	√
HLA-B*5701		√ If considering ABC (in late stage Malay & Indian patients)						
Resistance testing	√	√					√ including if ART initiation is delayed	√

MONITORING RECOMMENDATIONS (2)

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Investigation	Frequency of testing							
	Entry into care	ART initiation/ change	2-12 weeks after ART initiation/ change	Every 3-6 months	Every 6 months	Every 12 months	Clinically Indicated	Treatment failure
Hepatitis A serology (anti HAV total)	√						√ e.g. post-vaccination	
Hepatitis B serology (anti HBs, HBsAg, anti HBc total)	√					√ If non-immune/ vaccinated	√	
Hepatitis C antibody test	√					√ If not infected if risk factors present e.g. MSM, PWID	√	
Hepatitis C RNA	√ if serology positive					√ If previous HCV infection and treated	√	
Varicella serology	√							
Measles IgG	√ if vaccination uncertain							
Syphilis Screening	√				√ If abnormal at last measurement	√ If normal at baseline, annually	√ frequency as per risk behaviour	
Gonorrhea, Chlamydia NAAT	√ from all appropriate sites						√ frequency as per risk behaviour; from all appropriate sites	

MONITORING RECOMMENDATIONS (3)

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Investigation	Frequency of testing							
	Entry into care	ART initiation/ change	2-12 weeks after ART initiation/ change	Every 3-6 months	Every 6 months	Every 12 months	Clinically Indicated	Treatment failure
FBC	√	√	√ If on ZDV	√ If on ZDV	√		√	
ALT	√	√	√	√	√		√	
Total bilirubin			√ if on ATV	√ if on ATV	√ if on ATV		√	
Creatinine	√	√	√	√	√		√	
Fasting lipid panel	√	√				√ if normal at last measurement	√ if treatment required: monitoring as clinically indicated	
Fasting glucose and/or HbA1c	√	√				√ if normal at last measurement	√ if treatment required: monitoring as clinically indicated	
Pregnancy test	√	√					√ Esp if DTG use	
Urine glucose & protein	√	√			√		√	
If on TDF regimens								
Serum phosphate		√				√	√	
Bone mineral density evaluation							√ TDF-based regimens, age >50, and other risk factors	

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Thank you!