ART resistance and DR testing in India

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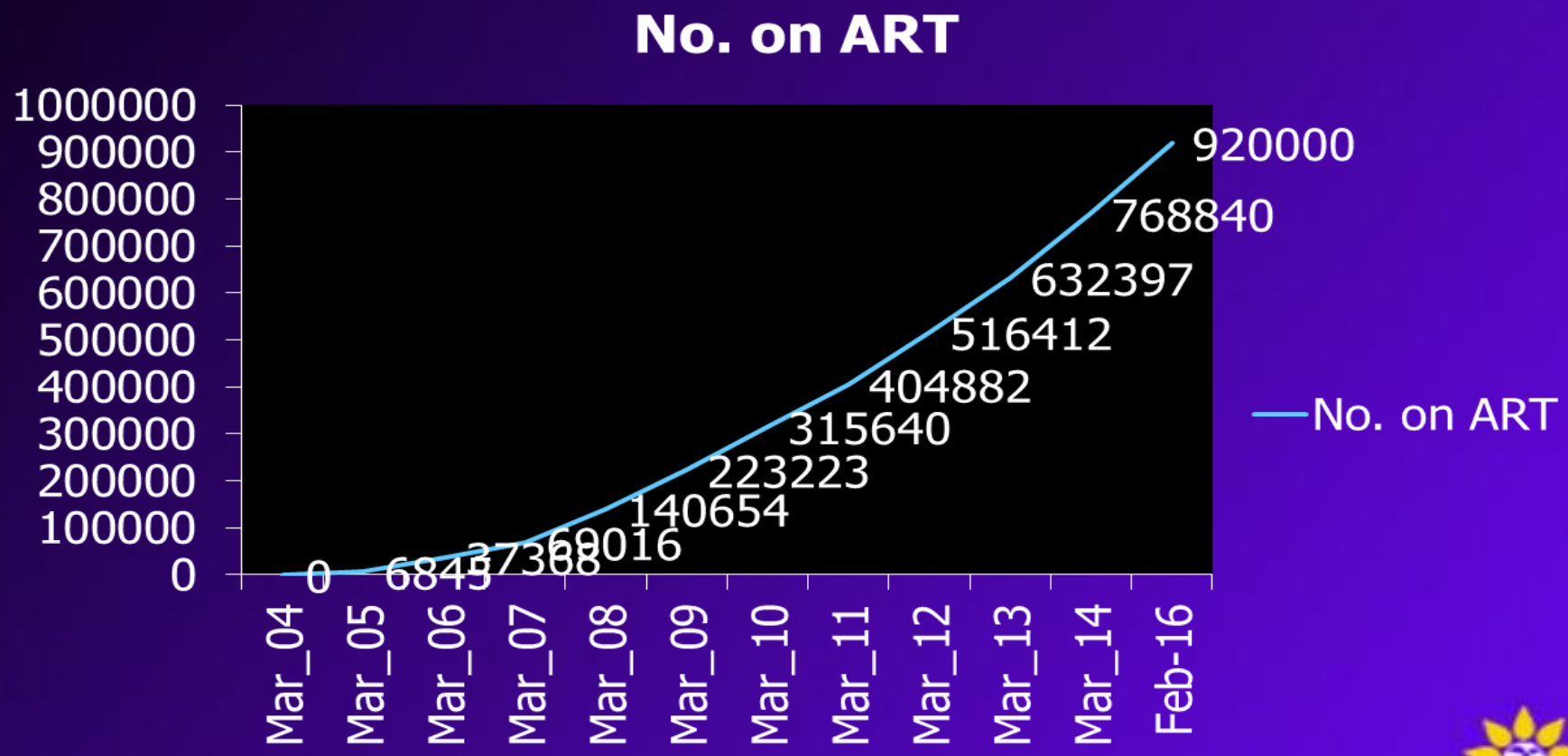
ART

YRG CARE

ART scale up in India

source:NACO



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Antiretroviral Drugs in India

1994……..

NRTIs	NNRTIs	PIs
zidovudine (AZT)	nevirapine (NVP), efavirenz (EFV)	saquinavir (SQV)
didanosine (ddI)		indinavir (IDV)
	etravirine (ETV)	ritonavir (RTV)
stavudine (d4T)	**Nucleotide RTIs**	nelfinavir (NFV)
lamivudine (3TC)	tenofovir DF (TDF)	lopinavir/ritonavir (LPV/r)
abacavir (ABC)	**Entry Inhibitors**	atazanavir (ATV)
emtricitabine (FTC)	Maraviroc (CCR5)	
	Integrase Inhibitors Raltegravir (RAL) Elvitegravir(ELV), Dolutegravir(DTG)	Darunavir(DRV)

Recommendations in WHO 2015 ART Guidelines-When to Start in Adults

TARGET POPULATION *(ARV-NAIVE)*	2010 ART GUIDELINES	2013 ART GUIDELINES	2015ART GUIDELINES	
HIV+ ASYMPTOMATIC	CD4 ≤350 cells/mm^3	**CD4 ≤500 cells/mm^3 (CD4 ≤ 350 cells/mm^3 as a priority)**	**ALL**	NEW
HIV+ SYMPTOMATIC	WHO clinical stage 3 or 4 regardless of CD4 cell count	No change	ALL	
PREGNANT AND BREASTFEEDING WOMEN WITH HIV	CD4 ≤350 cells/mm^3 or WHO clinical stage 3 or 4	**Regardless of CD4 cell count or WHO clinical stage**	**ALL**	
HIV/TB CO-INFECTION	**Presence of active TB disease, regardless of CD4 cell count**	**No change**	**ALL**	
HIV/HBV CO-INFECTION	Evidence of chronic active HBV disease, regardless of CD4 cell count	**Evidence of severe chronic HBV liver disease, regardless of CD4 cell count**	**ALL**	NEW
HIV+ PARTNERS IN SD COUPLE	No recommendation established	**Regardless of CD4 cell count or WHO clinical stage**	**ALL**	

Genotyping in Naïve population-Indian studies

Primary drug resistance has been reported ranging from 2.5% to 17.5% (Hira *et al.,*2004, Deshpande *et al*.,2005 ; Balakrishnan *et al.,* 2005 ; Arora *et al., 2008 ;* Lal *et al., 2008*).

Few studies reported no major resistance (Eshleman *et al., 2005 ;* Kandathil *et al.,* 2008).

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HIVDR Transmitted Resistance-NACO survey

Threshold survey:

Mumbai –VCT (2006-2007)

Kakinada-MTCT (2007-2008)

-Low prevalence (<5%) of transmitted HIVDR at both the sites.

Monitoring cohort survey:

Sir JJ Hospital-Mumbai (2007)

GHTM-Chennai (2008)

-Baseline ART resistance 10% among cohort of patients initiating ART in large urban centre in Mumbai

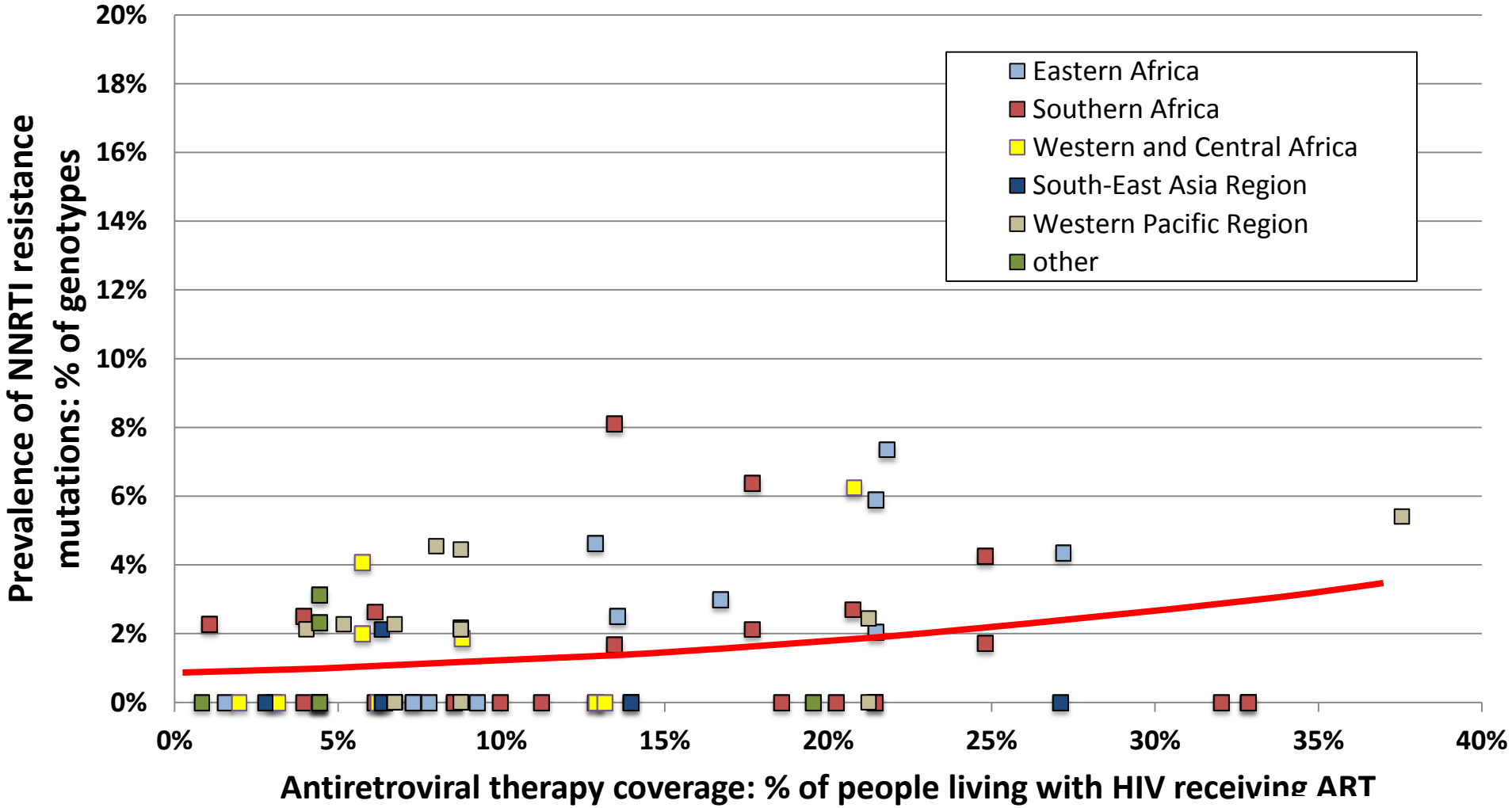
Chaturbhuj DN, et al.AIDS Res Hum Retr 2010 ; Thorat SR, et al.AIDS Res Hum Retr 2011; Hingankar NK, et al. CID 2012

HIVIND/EU - Are Mobile phone reminders effective in influencing treatment success in HIV? BMJ 2014

Characteristic n (%)		Intervention n=315	Control n=316
Social and demographic characteristics			
Sex	Females	136 (43.2%)	137 (43.4%)
Age	18-30 yrs	76 (24.1%)	79 (25.0%)
	31-40 yrs	150 (47.6%)	156 (49.4%)
	>40 yrs	89 (28.3%)	81 (25.6%)
Literacy		252 (79.5%)	250 (79.6%)
Residence	Rural	143 (45.4%)	143 (45.3%)
Ever used a mobile phone		263 (83.5%)	260 (82.3%)
Household income ≤$1000 per year		229 (72.7%)	237 (75.0%)
Recruiting sites	Bangalore	81 (25.7%)	77 (24.4%)
	Chennai	81 (25.7%)	83 (26.3%)
	Mysore	153 (48.6%)	156 (49.4%)
Clinical characteristics			
WHO clinical stage 3 & 4		175 (55.6%)	170 (53.8%)
CD4 count	<250 cells/mm^3	230 (73.0%)	217 (68.8%)
Baseline viral load, $\log_{10}$ copies/ml (IQR)		5.5 (5.1, 6.0)	5.4 (4.9, 5.9)
Regimen			
Zidovudine-based		136 (44.6%)	133 (43.2%)
Stavudine-based		34 (11.2%)	38 (12.3%)
Tenofovir-based		135 (44.1%)	137 (44.5%)
Transmitted drug resistance, n (%)		13/309 (4.2%)	12/308 (3.9%)

Higher Level of ART Coverage Associated With Increasing Prevalence of Transmitted NNRTI-Resistance

(82 surveys, 30 countries, 2004-2010, N=3588)



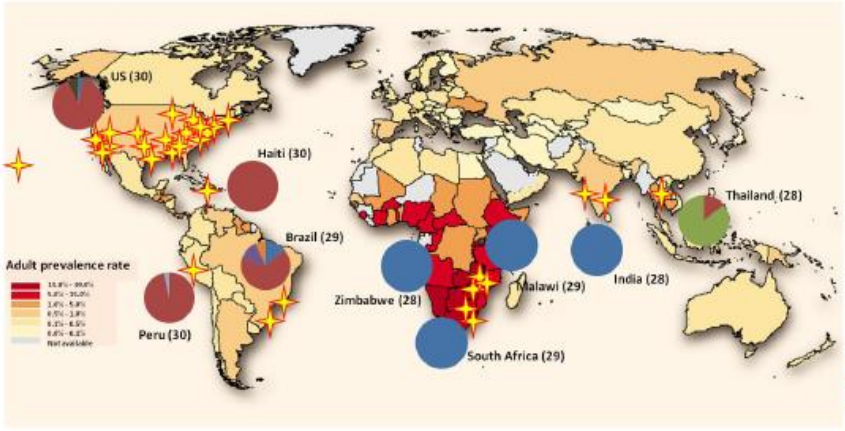
www.who.int/hiv/pub/drugresistance/report2012

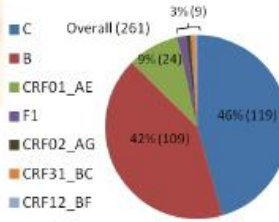
MAJOR ARTICLE

Pretreatment HIV Drug Resistance and HIV-1 Subtype C Are Independently Associated With Virologic Failure: Results From the Multinational PEARLS (ACTG A5175) Clinical Trial

Rami Kantor,[1] Laura Smeaton,[2] Saran Vardhanabhuti,[2] Sarah E. Hud
Mariza G. Morgado,[6] Shanmugham Saravanan,[7] Pachamuthu Balak
John W. Mellors,[9] Elias Halvas,[9] Beatriz Grinsztejn,[10] Mina C. Hosse
Umesh G. Lalloo,[14] Javier R. Lama,[13] Mohammed Rassool,[15] Breno R.
Timothy Flanigan,[1] Nagalingeswaran Kumarasamy,[6] Thomas B. Cam

Impact of Transmitted Drug Resistance





- n = 466/1,571
- 2005 - 2007

→ Pre-treatment drug resistance associated with treatment failure

WHO 2015 Treatment Guidelines : What to Start ?

FIRST-LINE REGIMENS (PREFERRED ARV REGIMENS)				
TARGET POPULATION	**2010 ART GUIDELINES**	**2013 ART GUIDELINES**	2015 ART GUIDELINES	**STRENGTH & QUALITY OF EVIDENCE**
HIV+ ADULTS	AZT or TDF + 3TC (or FTC) + EFV or NVP	**TDF + 3TC (or FTC) + EFV** (as fixed dose combination)	Preferred: **TDF + 3TC (or FTC) + EFV** (as fixed dose combination) Alternate: **TDF + 3TC (or FTC) + DTG*** **TDF + 3TC (or FTC) + EFV400mgs**	***Strong, moderate-quality evidence*** NEW
HIV+ PREGNANT WOMEN	AZT + 3TC + NVP or EFV			
HIV/TB CO-INFECTION	AZT or TDF + 3TC (or FTC) + EFV			
HIV/HBV CO-INFECTION	TDF + 3TC (or FTC) + EFV			

Sequencing Therapy in 2016

2 NRTIs(TDF+3TC/FTC) + 1 NNRTI (EFV)

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Failure of first line regimen

Sequencing Therapy in 2016

2 NRTIs(TDF+3TC/FTC) + 1 NNRTI (EFV)

2 NRTIs(AZT+3TC) + 1 PI/RTV(ATVr or LPVr or DRVr)

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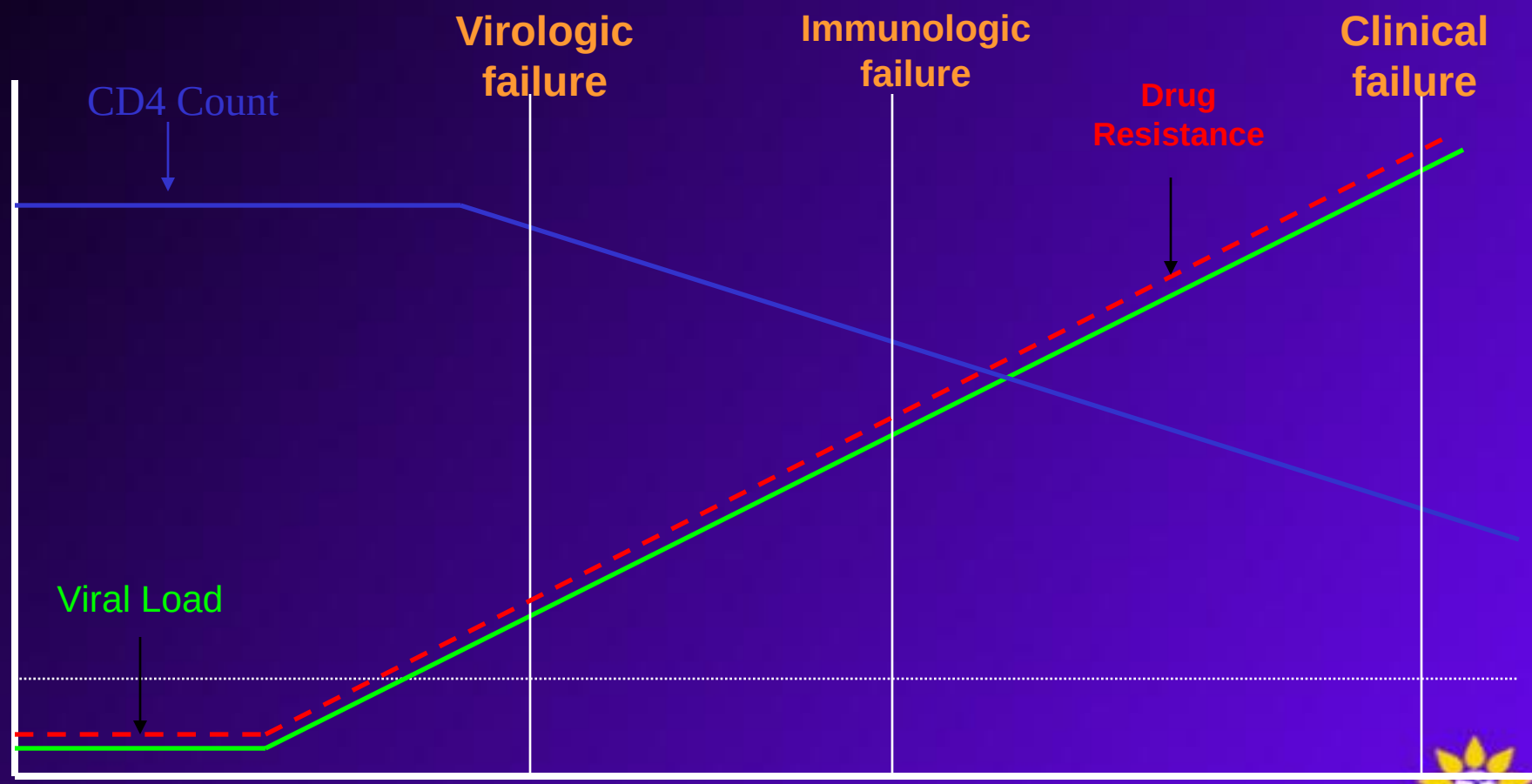
Treatment Failure and Drug Resistance: Virologic, Immunologic, and Clinical Definitions



Clinical Infectious Diseases 2009; 49:000–000

1058-4838/2009/4902-00XX$15.00
DOI: 10.1086/600044

BRIEF REPORT HIV/AIDS

High Frequency of Clinically Significant Mutations after First-Line Generic Highly Active Antiretroviral Therapy Failure: Implications for Second-Line Options in Resource-Limited Settings

N. Kumarasamy,[1] Vidya Madhavan,[1] Kartik K. Venkatesh,[2] S. Saravanan,[1] Rami Kantor,[2] P. Balakrishnan,[1] Bella Devaleenal,[1] S. Poongulali,[1] Tokugha Yepthomi,[1] Suniti Solomon,[1] Kenneth H Mayer,[2] Constance Benson,[3] and Robert Schooley[3]

[1]YRG Centre for AIDS Research and Education, VHS, Chennai, India; [2]Miriam Hospital–Brown University Medical School, Providence, Rhode Island, and [3]University of California, San Diego, California

Continuation of failed highly active antiretroviral therapy regimens can lead to the accumulation of mutations that may limit options for second-line treatment. We studied the pattern of drug resistance mutations among 138 Indian patients

line treatment [3, 4]. Understanding patterns of mutations among patients who are experiencing failure of first-line HAART with use of immunologic monitoring can assist clinicians in selecting second-line regimens in resource-limited settings with already constrained second-line treatment options. Therefore, the present study was undertaken to examine the pattern and severity of genotypic mutations among HIV subtype C–infected South Indian patients experiencing failure of first-line HAART.

Patients and methods. YRG Centre for AIDS Research and Education (CARE) is a nonprofit medical and research institution in Chennai, India, that provides medical care to >11,000 HIV-infected individuals. All patients were treated according to WHO treatment guidelines [1]. Patients were seen every 3 months or as clinically indicated. CD4 cell count monitoring was performed every 3–6 months. Plasma viral load monitoring was not standard of care. Data were collected under the approval of YRG CARE's free-standing institutional review board.

Patients naive to antiretroviral therapy before initiation of HAART who later underwent genotyping after immunologic

79% of them had M184V,
71 % had NNRTI mutations, (K103N,Y181C,G190A)
60% had TAMS, (M41L,T215Y/F,K70R,L210W,K219E/Q)
11% had Q151M
5% had K65R and
5% had L74V.

26% had 3 or more NNRTI mutations

This data clearly warns that patients with immunological failure with standard WHO criteria have severe mutations and which can jeopardize future 2nd line NRTI options and newer drugs. Urgent need for VIRAL LOAD monitoring

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2nd line Trials

Secondline International Trial- Univ New South Wales(96/550)

Multicenter Study of Options for SEcond-Line Effective Combination Therapy (SELECT)- ACTG 5273 (111/500)

EARNEST

Phase IIIb/IV, international, randomised, open label study comparing two regimens for 96-weeks

ritonavir boosted lopinavir (LPV/r) + 2N(t)RTIs

vs

II. ritonavir boosted lopinavir (LPV/r) + raltegravir

Sequencing Therapy in 2016

2 NRTIs(TDF+3TC/FTC) + 1 NNRTI (EFV)

2 NRTIs(AZT+3TC)/Integrase + 1 PI/(ATVr or LPVr or DRVr)

WHO 2015 ART Guidelines

YRGCARE CART Cohort-Pattern of mutations on 2nd line

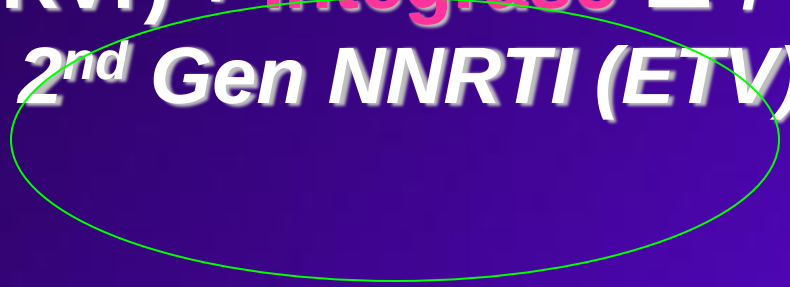
Number of patients initiated on 2nd line; n = 2209 (ATV/r = 1869, LPV/r = 340)

Genotyping (PI) Mutations (n=111)

		30	32	33	46	47	48	50	54	76	82	84	88	90
Cons	No PI mutations %	D	V	L	M	I	G	I	I	L	V	I	N	L
ATV/r (N=94)	**63**		I (4.2)	F (1.1)	IL (0)	V (0)	VM (0)	L (8.5)	VTALM (0)		ATFS (0)	V (7.4)	S (6.4)	M (5.3)
LPV/r (N=17)	**75**		I (5.8)	F (5.8)	IL (0)	VA (0)	VM (0)	V (0)	VTALM(0)	V (0)	AFTS (0)	V (0)		M (11.7)
DRV/r			I	F		VA		V	LM	V	F	V		

Sequencing Therapy in 2016

- 2 NRTIs(TDF+3TC/FTC) + 1 NNRTI (EFV)
- 2 NRTIs(AZT+3TC) + 1 PI/RTV(ATVr or LPVr or DRVr)
- 1 PI/RTV(DRVr) + Integrase ± / CCR5 inhibitor/ *2nd Gen NNRTI (ETV)*



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26% had 3 or more NNRTI mutations

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WHO 2015 Guidelines

POPULATION	1ST LINE REGIMEN	2ND LINE REGIMENS	3RD LINE REGIMENS
Adults	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r	DRV/r[1] + DTG (or RAL) ± 1–2 NRTIs
		2 NRTIs + DRV/r LPV/r+RAL	
	2 NRTIs + DTG	2 NRTIs + ATV/r or LPV/r	DRV/r + 2 NRTIs ± NNRTI
		2 NRTIs + DRV/r	Optimize regimen using genotype profile
Pregnant/breastfeeding women	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r	DRV/r + DTG (or RAL) ± 1–2 NRTIs
		2 NRTIs + DRV/r	
Children	2 NRTIs + LPV/r	If less than 3 years: 2 NRTIs + RAL[2]	DTG[4] + 2 NRTIs DRV/r[3] + 2 NRTIs DRV/r[3] + DTG[4] ± 1–2 NRTIs
		If older than 3 years: 2 NRTIs + EFV or RAL	
	2 NRTIs + EFV	2 NRTIs + ATV/r[5] or LPV/r	

DR Testing in India

- YRGCARE-ACTG/HPTN
  Home brewed Cost: RT-60$; PI-30$; InI-40$
- NARI- Surveillance/Research purpose
- NIRT- Surveillance/Research purpose
- 2 Private laboratories- Viroseq

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Suggested indications for resistance testing in India

- ?Baseline testing- Partner on failing regimen
- Sub-optimal exposure
  - Mono, dual therapy
  - NVP for MTCT
- Immunologic failure
- After first line- to know how many TAMs, K65R,NNRTI mutations
- After second line: how many PI mutations

POC resistance testing

Point mutation assays may be developed and tailored to widely used first-line,2nd line regimens.

- **No mutations**
  -Contine the same ART, Improve adherence

- **Mutations- A**
  -Continue same ART, improve adherence

- **Mutations-B**
  -Switch ART

- **Mutations-C**
  -Refer to specialist/tertiary center

Collaborators

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Bharat Ramratnam
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UCSD & ACTG CTU
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Rush University
Alan Landay

Emory Univ
Amara Rao
Carlos Del Rio

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