Professor Andrew Lever

University of Cambridge

5 papers to change clinical practice

AMLLever

BHIVA 2013

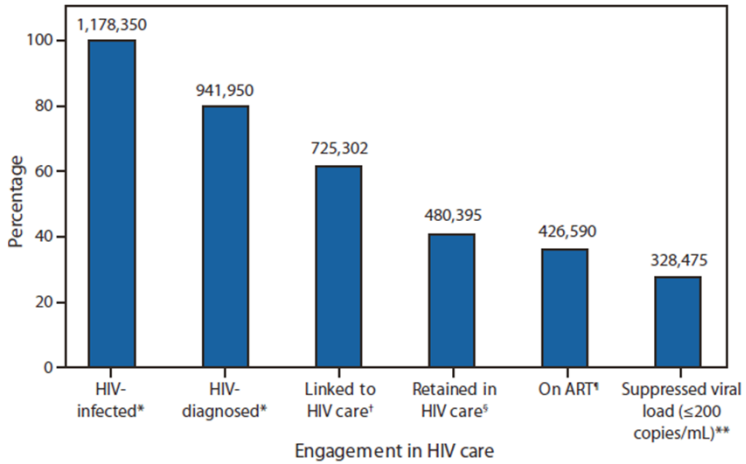
Dolutegravir (DTG; S/GSK1349572) + abacavir/lamivudine once daily statistically superior to Tenofovir/emtricitabine/efavirenz: 48 week results
Walmsley, et al. *ICAAC* 2012; Abstract H-556b

Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy
Archin, et al. *Nature* 2012 Jul 26; 487:482

Short-Course Antiretroviral Therapy in Primary HIV Infection
The SPARTAC Trial Investigators
N Engl J Med 2013; 368:207-217

Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial
Sax et al for the GS-236-0103 Study Team
Lancet. 2012 Jun 30;379(9835):2429-38

U.S. Centers for Disease Control and Prevention (CDC). Vital Signs: HIV prevention through care and treatment – United States.
Morb Mortal Wkly Rep. 2011 Dec 2; 60:1618



Economic Savings Versus Health Losses:
The Cost-Effectiveness of Generic Antiretroviral Therapy
in the United States

Rochelle P. Walensky, MD, MPH; Paul E. Sax, MD; Yoriko M. Nakamura, BA;
Milton C. Weinstein, PhD; Pamela P. Pei, PhD; Kenneth A. Freedberg, MD, MSc;
A. David Paltiel, PhD; and Bruce R. Schackman, PhD

Ann Intern Med. 15 January 2013;158(2):84-92

50% reduction in drug costs and a savings of $960 million in care costs in 1 year

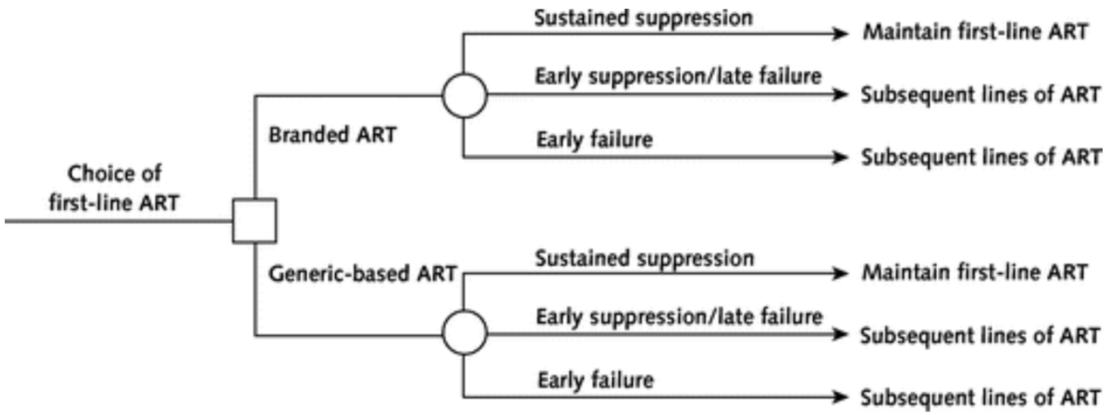
Reduced treatment efficacy, resulting in 4.4 months of life lost per patient lifetime

BBC NEWS Health

Study questions generic HIV drug use

Rises in the use of cheaper, non-branded HIV drugs could potentially see more patients with treatment failure, claim US researchers

Model study paradigm

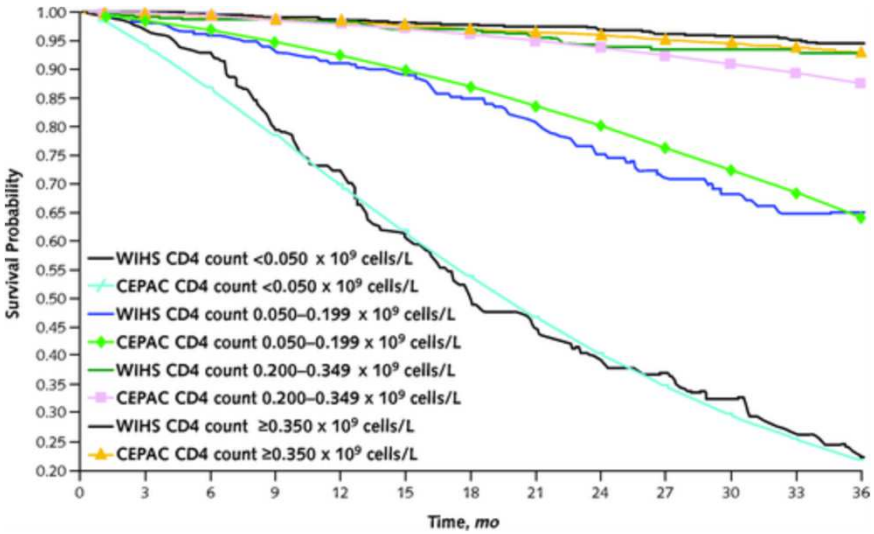


1-pill efavirenz–emtricitabine–tenofovir as first-line antiretroviral therapy (ART).

versus

Once-daily, 3-pill alternative (generic efavirenz, generic lamivudine, branded tenofovir)

Validity of model



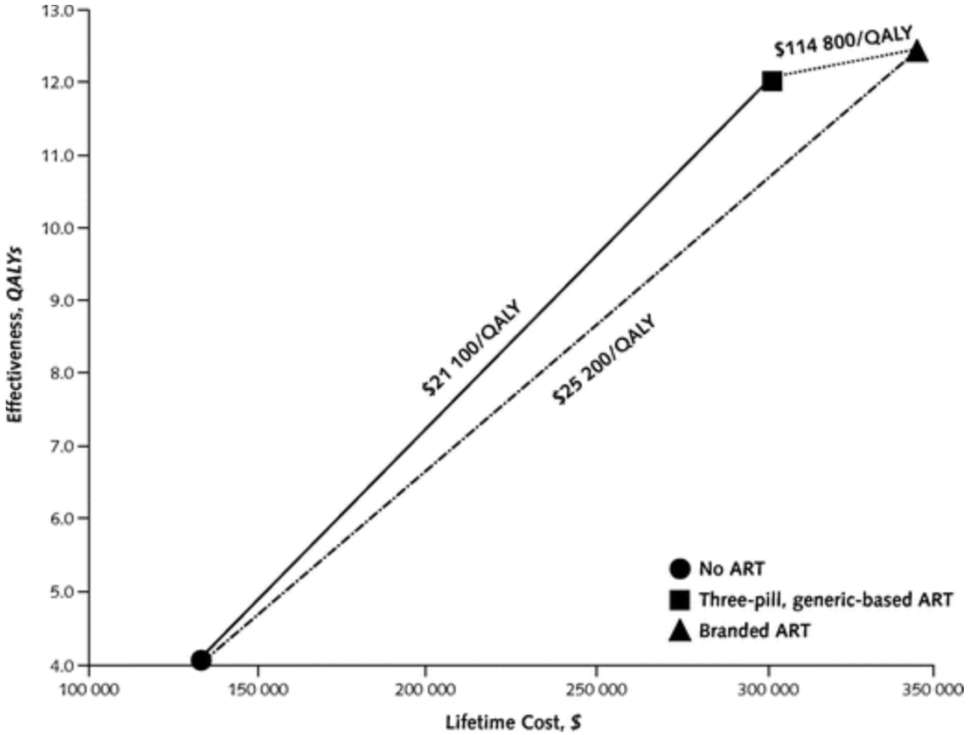
Comparison of CEPAC Model outcomes and data reported from WIHS.

Kaplan–Meier survival curves based on data from WIHS were compared with preliminary, model-estimated survival over 36 mo

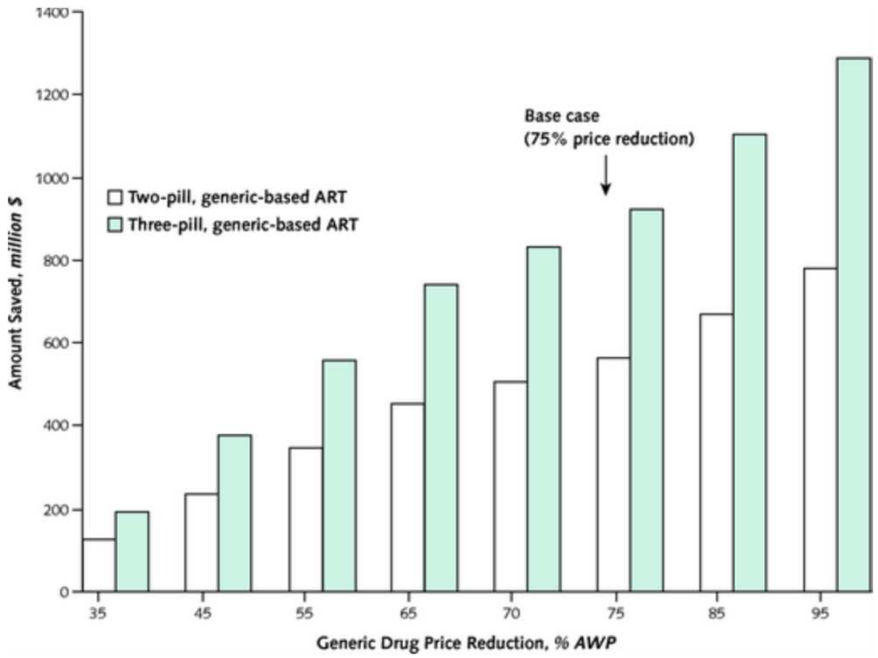
Lines with symbols represent model-based projections, whereas those without symbols represent WIHS data.

CEPAC = Cost-Effectiveness of Preventing AIDS Complications; WIHS = Women's Interagency HIV Study.

Comparative cost/benefit



Potential savings



Potential annual cost savings in the United States with 3-pill or 2-pill, generic-based ART compared with branded ART.

Validity of assumptions

Assumption of inferior efficacy of 3TC versus FTC

WHO report 2013 – no difference in efficacy or safety

Poorer adherence because of separate pills

Fixed dose combinations of generic TDF+FTC+EFV

TDF on patent in US - $9,200/patient/year

Generic TDF =$200/patient/year

- Trade off between cost and efficacy misleading

Patent expiry dates of HAART drugs

Drug	**Type**	**Manufacturer**	**Expiry**
3TC (lamivudine)	NRTI	GlaxoSmithKline	2010
Abacavir	NRTI	GlaxoSmithKline	2012
Efavirenz*	NNRTI	Bristol-Myers Squibb	2013
Delavirdine	NNRTI	Pfizer	2013
Darunavir	PI	Tibotec	2015
FTC (emtricitabine)*	NRTI	Gilead	2015
Tipranavir	PI	Boehringer Ingelheim	2015
Ritonavir	PI	Abbott	2016
Tenofovir*	NRTI	Gilead	2017

(*Atripla**)**

“In ten years this will be a disease treated for $200 per year, or less”

John Bartlett

Generic drugs and HIV

WHO – ‘generic antiretroviral therapy is safe and effective’

Treatment of HCV Infection by Targeting MicroRNA

Harry L.A. Janssen, M.D., Ph.D., Hendrik W. Reesink, M.D., Ph.D., Eric J. Lawitz, M.D.,Stefan Zeuzem, M.D., Maribel Rodriguez-Torres, M.D., Keyur Patel, M.D.,Adriaan J. van der Meer, M.D., Amy K. Patick, Ph.D., Alice Chen, B.A.,Yi Zhou, Ph.D., Robert Persson, Ph.D., Barney D. King, M.D.,Sakari Kauppinen, Ph.D., Arthur A. Levin, Ph.D., and Michael R. Hodges, M.D.

NEJM 27th May 2013

Use of a ‘locked’ nucleic acid (LNA) to target a virus infection

Hepatitis C

170 million chronic carriers

Major cause of cirrhosis, liver failure and HCC

20% HIV infected people are HCV infected

85% HIV+ people with Haemophilia

DAD study 14% deaths liver related 66% had HCV

MicroRNAs (miRNAs)

Small, endogenous, noncoding RNAs

Posttranscriptional regulation of gene expression by binding to partially complementary sites within the 3′ untranslated region of target messenger RNAs (mRNAs),

Cause translational repression or mRNA deadenylation and degradation.

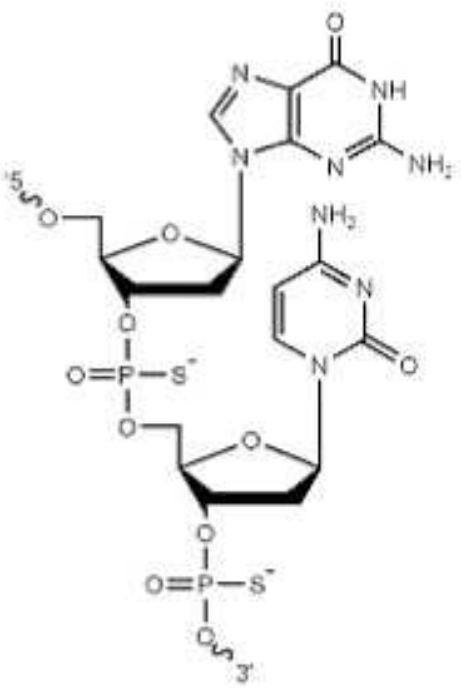
miRNA 122

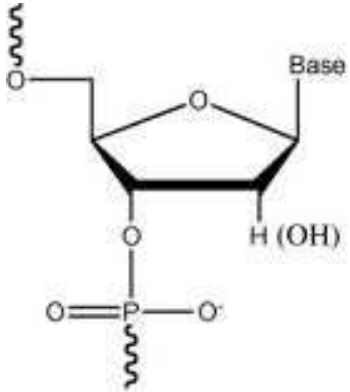
Highly abundant miRNA expressed in the liver

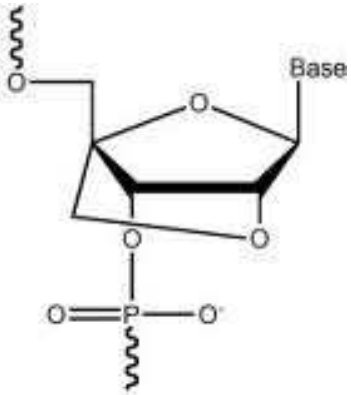
Involved in control of cholesterol metabolism in liver

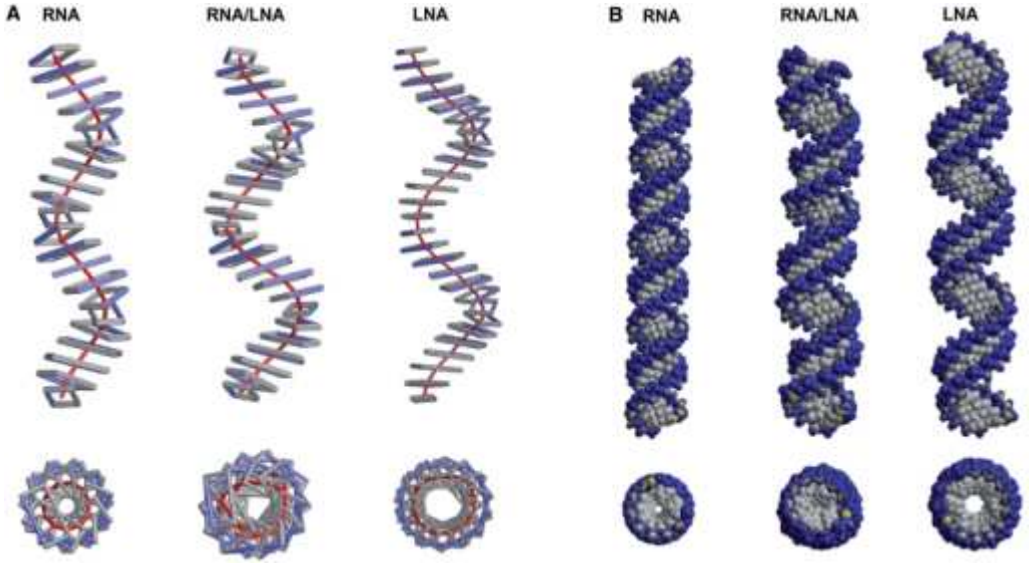
Essential to the stability and propagation of HCV RNA

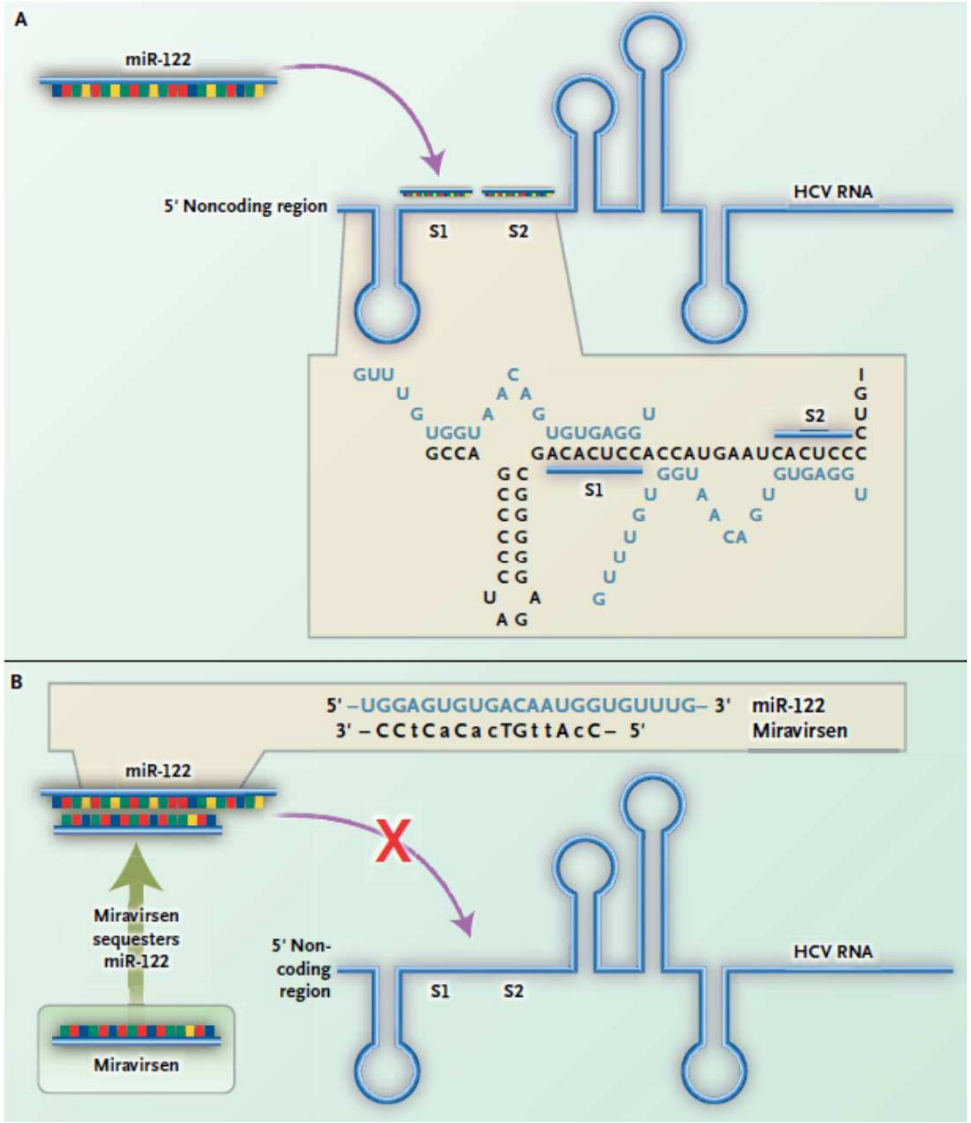
Locked nucleic acid










A
miR-122
5′ Noncoding region
S1
S2
HCV RNA
GUU
C
U
A A
G
A
G
U
UGGU
UGUGAGG
GCCA
GACACUCCACCAUGAAUCACUCCC
G C
C G
C G
C G
C G
C G
U A
A G
S1
GGU
GUGAGG
U
A
U
G
A G
CA
U
U
G
S2
I
G
U
C
B
5′ –UGGAGUGUGACAAUGGUGUUUG– 3′
3′ – C C t C a C a c TG t t A c C – 5′
miR-122
Miravirsen
miR-122
Miravirsen sequesters miR-122
Miravirsen
5′ Non-coding region
S1
S2
HCV RNA

Miravirsen

Phase 2a study

15-nucleotide locked nucleic acid–modified antisense oligonucleotide
Complementary to and with a high affinity and specificity for the 5′ region of mature miR-122

Patients

36 treatment naïve
HCV genotype 1
HBV/HIV negative
Compensated disease
HCV RNA > 75,000 IU/ml

4 groups of 9
Placebo, 3mg/kg, 5mg/kg, 7mg/kg
5 weekly doses over 29 days

PEG/IFN ribavirin at week 7 (3mg, n= 5) or 10 (5mg, n=3, 7mg, n=2)

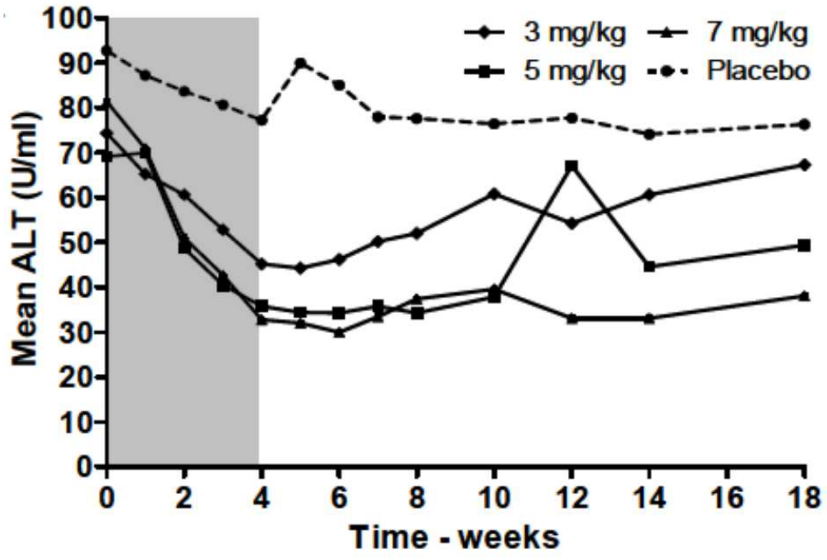
Results

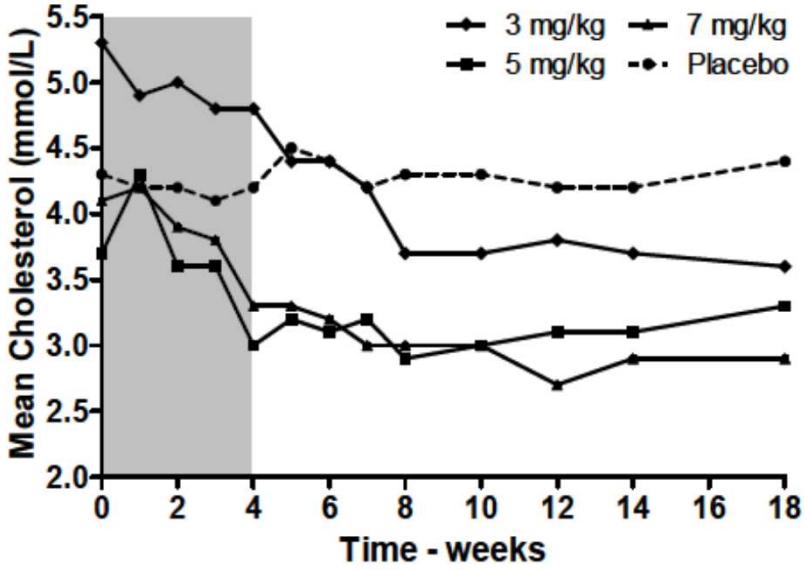
Sustained decrease in transaminases

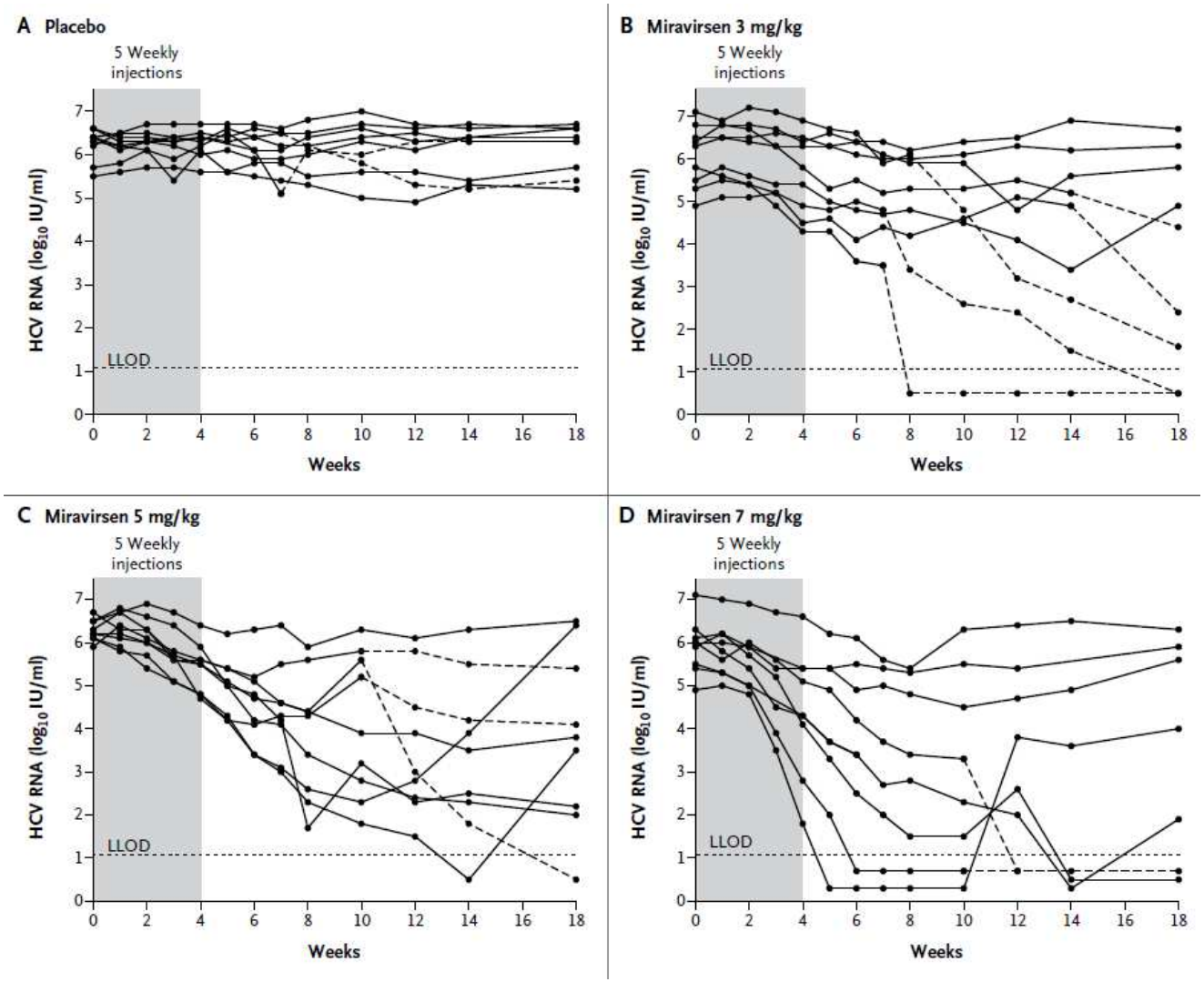
No biochemical toxicity of note

Decrease in serum cholesterol

No evidence of viral resistance






A Placebo
5 Weekly injections
HCV RNA (log10 IU/ml)
LLOD
Weeks
B Miravirsen 3 mg/kg
5 Weekly injections
HCV RNA (log10 IU/ml)
LLOD
Weeks
C Miravirsen 5 mg/kg
5 Weekly injections
HCV RNA (log10 IU/ml)
LLOD
Weeks
D Miravirsen 7 mg/kg
5 Weekly injections
HCV RNA (log10 IU/ml)
LLOD
Weeks

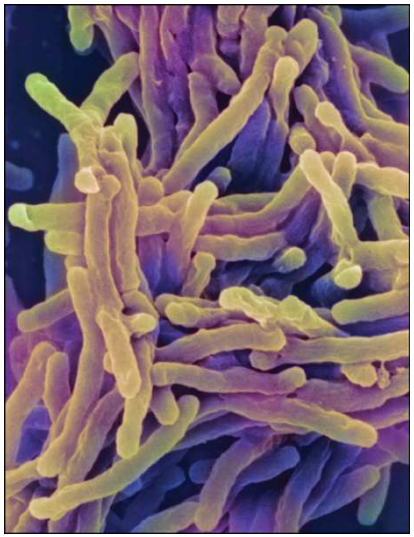
LNA against HCV effective

Pharmacokinetics

Safety

Other applications

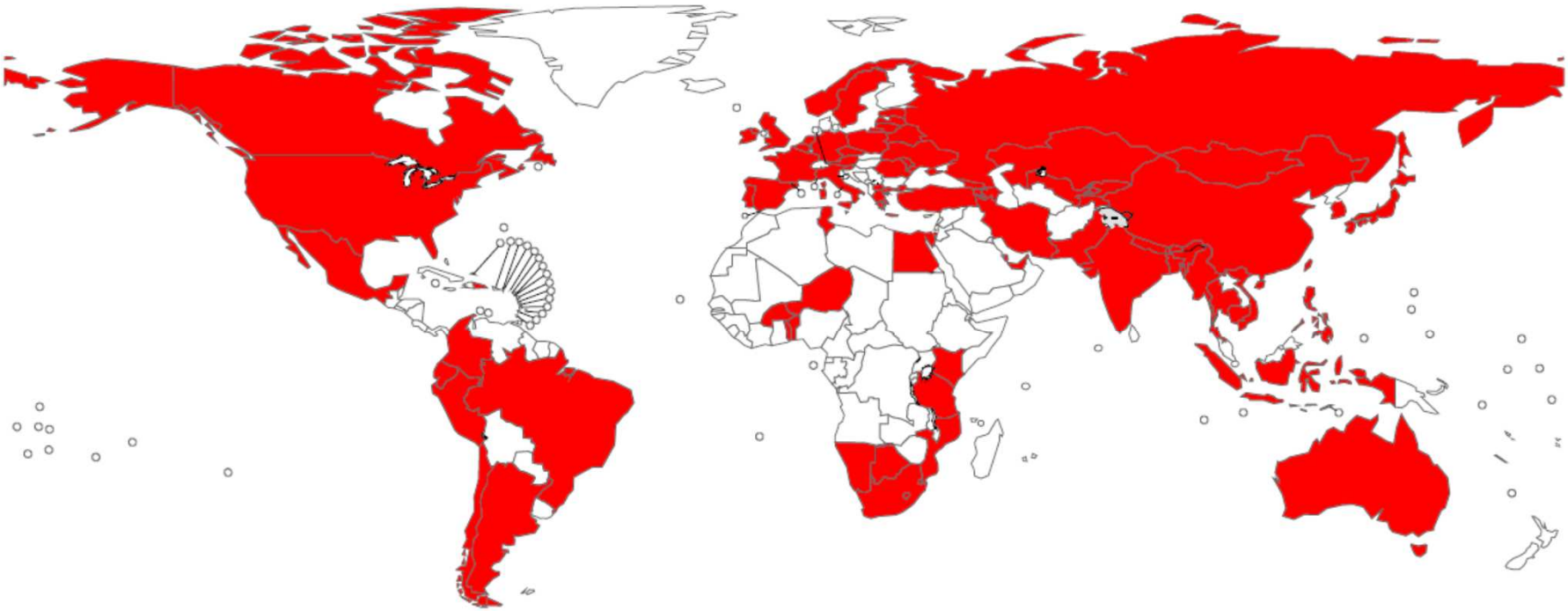
Emergence and Spread of Extensively and Totally Drug-Resistant Tuberculosis, South Africa
Klopper et al *EID* Volume 19, Number 3—March 2013



Countries that had reported at least one XDR-TB case by Oct 2011

World Health Organization

THE STOP TB DEPARTMENT



Argentina	Burkina Faso	Estonia	Japan	Namibia	Republic of Korea	The Former Yugoslav Republic of Macedonia
Armenia	Bhutan	France	Kazakhstan	Nepal	Republic of Moldova	Togo
Australia	Cambodia	Georgia	Kenya	Netherlands	Romania	Tunisia
Austria	Canada	Germany	Kyrgyzstan	Niger	Russian Federation	Turkey
Azerbaijan	Chile	Greece	Latvia	Norway	Slovenia	Ukraine
Bangladesh	China	India	Lesotho	Pakistan	South Africa	United Arab Emirates
Belarus	Colombia	Indonesia	Lithuania	Peru	Spain	United Kingdom
Belgium	Czech Republic	Iran (Islamic Rep. of)	Mexico	Philippines	Swaziland	United Republic of Tanzania
Benin	Dominican Republic	Ireland	Mongolia	Poland	Sweden	United States of America
Botswana	Ecuador	Israel	Mozambique	Portugal	Tajikistan	Uzbekistan
Brazil	Egypt	Italy	Myanmar	Qatar	Thailand	Viet Nam

TDR-TB

Migliori (Italy) *Euro Surveill. 2007*	2 patients with TDR-TB
Velayati (Iran) *Chest 2009*	146 MDR-TB assessed 8 XDR 15 TDR resistant to all first-line (INH, RF, SM, ETB, and PZA) and second-line drugs tested (OFX, CYC, PTH, AMK, KAN, ETH, PAS, and CAP)
Udwadia (India) *CID 2011*	4 patients with TDR-TB
2012 WHO consultation	TDRTB not clearly defined
2013 WHO	Annual need of at least US$ 1.6 billion in international funding for treatment and prevention of drug resistant TB (and malaria)

TB South Africa

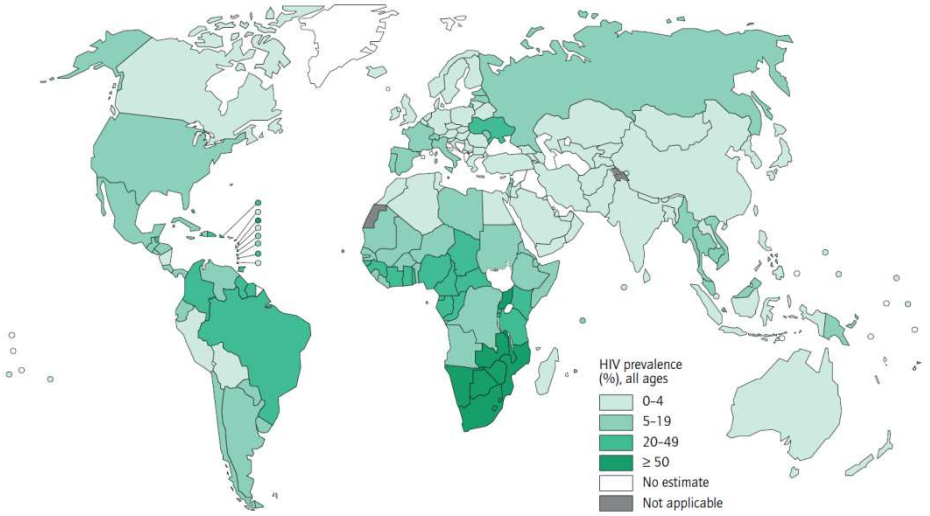
9.6% MDR-TB

One of highest burden MDR-TB countries in the world

One of highest HIV burden countries in the world

Epidemic driven by transmission

Culture conversion rates for XDR-TB <20%



Streicher et al
Infection, Genetics and Evolution
Volume 12, Issue 4, June 2012, Pages 686–694

Study

Molecular analysis of 309 drug-susceptible and 342 multidrug-resistant TB (MDR-TB) isolates collected from 2008 to 2009 from Eastern Cape Province,

Results

69% of MDR-TB were Beijing subtype

92% of these 236 MDR-TB strains belonged to an atypical Beijing genotype resistant to 10 (4 first-line and 6 second-line) anti-TB drugs

INH, RF, SM, ETB, PZA, OFX, AMK, KAN, ETH, and CAP (some PAS resistant)

Cause of high levels of resistance

Absence of routine second line drug testing

2004 guidelines 6/12 KAN ETH PZA OFX CYC/ETB then 18/12 ETH PZA OFX CYC/ETB

May have led to undertreatment of ‘pre-XDR’ TB

2007 Second line DST introduced, CAP and PAS available

2010 Guidelines

MDR TB		**XDR TB**	
Intensive phase	**Continuation phase**	**Intensive phase**	**Continuation phase**
Kanamycin (IM)		Capreomycin (IM)	
Ethionamide	Ethionamide	Ethionamide	Ethionamide
Pyrazinamide	Pyrazinamide	*p*-aminosalicylic acid	*p*-aminosalicylic acid
Ofloxacin	Ofloxacin	Moxifloxacin	Moxifloxacin
Terizidone/cycloserine	Terizidone/cycloserine	Terizidone/cycloserine	Terizidone/cycloserine


SOUTH AFRICA
0 km 75 150 225 km
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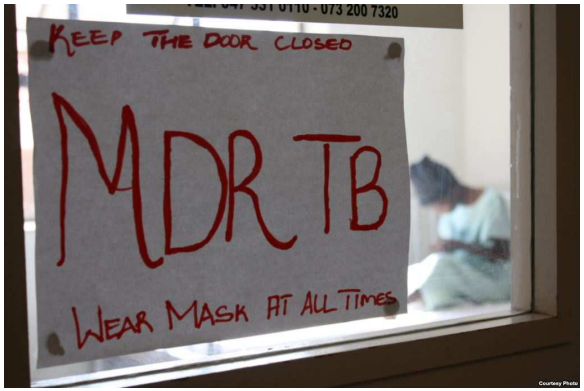
National Capital (692,000 in 98)
over 1,500,000
over 500,000
over 100,000
other main city
other city
Capital of province
BOTSWANA
NAMIBIA
MOZ
SWAZILAND
LESOTHO
SOUTH ATLANTIC OCEAN
Kalahari Desert
Namib Desert
Windhoek
Rehoboth
Keetmanshoop
Gaborone
Serowe
Maputo
Mbabane
Maseru
NORTHERN PROVINCE
NORTH WEST
GAUTENG
MPUMALANGA
FREE STATE
KWAZULU NATAL
NORTHERN CAPE
EASTERN CAPE
WESTERN CAPE
PRETORIA
Johannesburg
Soweto
Soshanguve
Evaton
Sasolburg
Benoni
Brakpan
Springs
Kathlehong
Vereeniging
Messina
Louis Trichardt
Pietersburg
Potgietersrus
Phalaborwa
Nylstroom
Steelpoort
Rustenburg
Mmabatho
Nelspruit
Witbank
Vryburg
Kuruman
Hotazel
Sishen
Warrenton
Kimberley
Postmasburg
Upington
Kakamas
Kenhardt
Prieska
Copperton
Brandvlei
Sakrivier
Carnarvon
De Aar
Victoria West
Calvinia
Springbok
Okiep
Port Nolloth
Alexander Bay
Welkom
Kroonstad
Bloemfontein
Bethlehem
Botshabelo
Harrismith
Newcastle
Vryheid
Ladysmith
Estcourt
Pietermaritzburg
Ulundi
Empangeni
Richards bay
KwaMashu
Durban
Umlazi
Amanzimtoti
Port Shepstone
Margate
Kokstad
Aliwal North
Colesberg
Middelburg
Cradock
Queenstown
Umtata
Port St. Johns
The Haven
Wild Coast
Graaff-Reinet
Beaufort West
Great Karoo
Little Karoo
East London
Mdantsane
King William's Town
Bisho
Grahamstown
Port Alfred
Port Elizabeth
Uitenhage
Humansdorp
George
Knysna
Mossel Bay
Oudtshoorn
Worcester
Paarl
Stellenbosch
Strand
Cape Town
Khayelitsha
Bellville
Gansbaai
Bredasdorp
Cape of Good Hope
Cape Agulhas
Saldanha
Velddrif
Lamberts Bay
Bitterfontein
Drakensberg
ezilon.com


UMTATA
Libode
Misty Mount
Ntshilini
Gemvale
Port St. Johns
Tombo
Ngqeleni
Old Bunting
Bunting
Viedgesville
Notintsila
Mqanduli
Ngqungqu
Hluleka Nature Reserve
Tshani
Coffee Bay
Old Morley
Elliotdale
Zithulele Hospital
Mncwasa Point
Alderley
Rothmere
Hobeni



doconsafari.wordpress.com

Zithulele hospital, Eastern Cape, South Africa

		2010	2011	2012	2013	Total
MDR-TB						
	Active	2(c)	5	24	(13)	44
	Died		5	23	(1)	29
	Defaulted					5
XDR-TB				1 (died)	(4)	5

Eastern Cape 2004-2009 6211 MDRTB 488 XDRTB

HIV Prevention in Action on the Football Field: The Whizzkids United Program in South Africa

Louise Balfour, Thomas Farrar, Marcus McGilvray, Douglas Wilson, Giorgio A. Tasca, Johanna N. Spaans, Catherine Mathews, Lungile Maziya, Siphosihle Khanyile, Tracy L. Dalgleish, William D. Cameron

AIDS Behav 2013

South African national surveys indicate that 12.6 % of youth have initiated sex before age 14

Sex education should be offered as early as age 10
Aims to impart knowledge and life skills critical to HIV prevention

The Africaid Trust, has been operating a 12-week educational soccer program in elementary schools in Pietermaritzburg, South Africa
‘‘On The Ball’’ WhizzKids United

Using the game of soccer as an analogy for life (e.g., not using a condom during sex is like playing soccer without a goalkeeper)

Aims

WKU compared HIV knowledge,stigma and health care seeking behaviours of elementary youth (grades 5–8) who had received the WKU OTB program in addition to traditional classroom-based HIV education to students who had only received traditional HIV education

Establish the baseline level of HIV knowledge, sexual behaviors and health seeking behaviors of older youth in grades 9–12

Method

Survey was administered in schools using a novel, cell phone based technology that allowed for the secure reporting and uploading of sensitive information

Participants

972 participants (99 % South African black, 498 boys and 472 girls grades 5-12)

267 WKU programme (142 boys, 119 girls)

Edendale Township HIV prevalence of 42.3 % among pregnant women presenting at antenatal clinics

Differences between WKU and non-WKU participants in grades 5–8 (n = 629)

Outcomes	Received WKU program		Did not receive WKU program		p value
Grades 5–8	Mean (%)	SD (%)	Mean (%)	SD (%)	
HIV stigma	27	21	33	23	>0.001*
HIV general knowledge	49	28	37	28	>0.001*
Grade 8 participants only		(n = 41)	(n = 46)		
HIV general knowledge	70	24	66	29	0.074
HIV sex-related knowledge	59	27	49	26	0.014*

Means for HIV knowledge are presented as mean percent correct
* Statistical significance

Descriptive Statistics: Grades 9–12

55.6 % respondents in grades 9–12 reported being sexually active

29 % self-reported use of a condom during the most recent sexual encounter

31 % HIV counselling within the last 6 months

Less than one-third of survey respondents tested for HIV in previous 6 months

90% would use a youth friendly health clinic affiliated with the WKU clubhouse if available

Systematic identification of synergistic drug pairs targeting HIV

Xu Tan, Long Hu, Lovelace J Luquette III Geng Gao, Yifang Liu, Hongjing Qu, Ruibin Xi
Zhi John Lu, Peter J Park & Stephen J Elledge

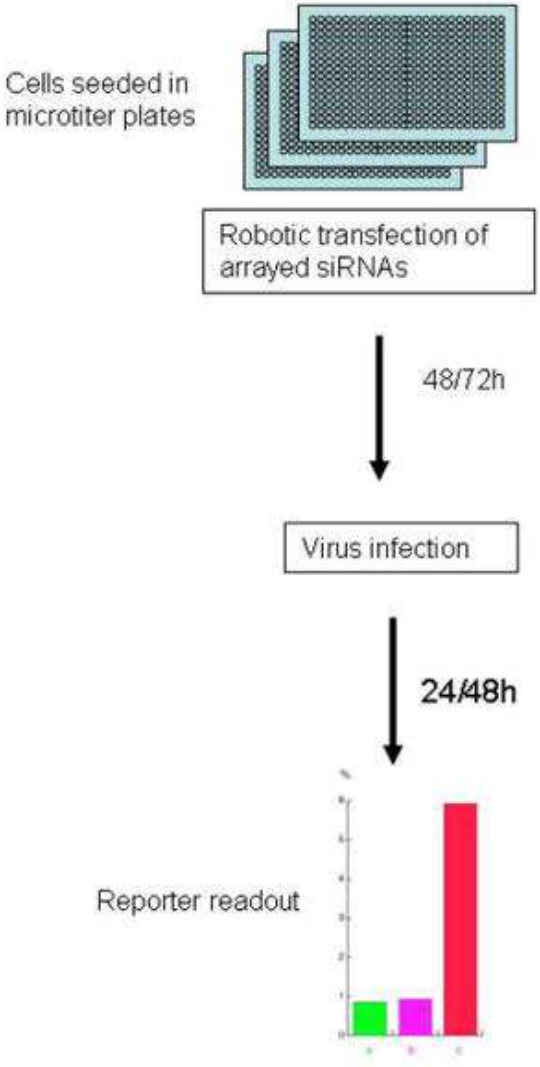
Nature Biotechnology Vol 30 No11 Nov 2012 p1125

Identification of Host Proteins Required for HIV Infection Through a Functional Genomic Screen

Abraham L. Brass,[1,2] Derek M. Dykxhoorn,[3*] Yair Benita,[4*] Nan Yan,[3] Alan Engelman,[5] Ramnik J. Xavier,[2,4] Judy Lieberman,[3] Stephen J. Elledge[1†]

Science. 2008 Feb 15;319(5865):921-6.

siRNA based screening approaches for cellular factors that assist viral replication



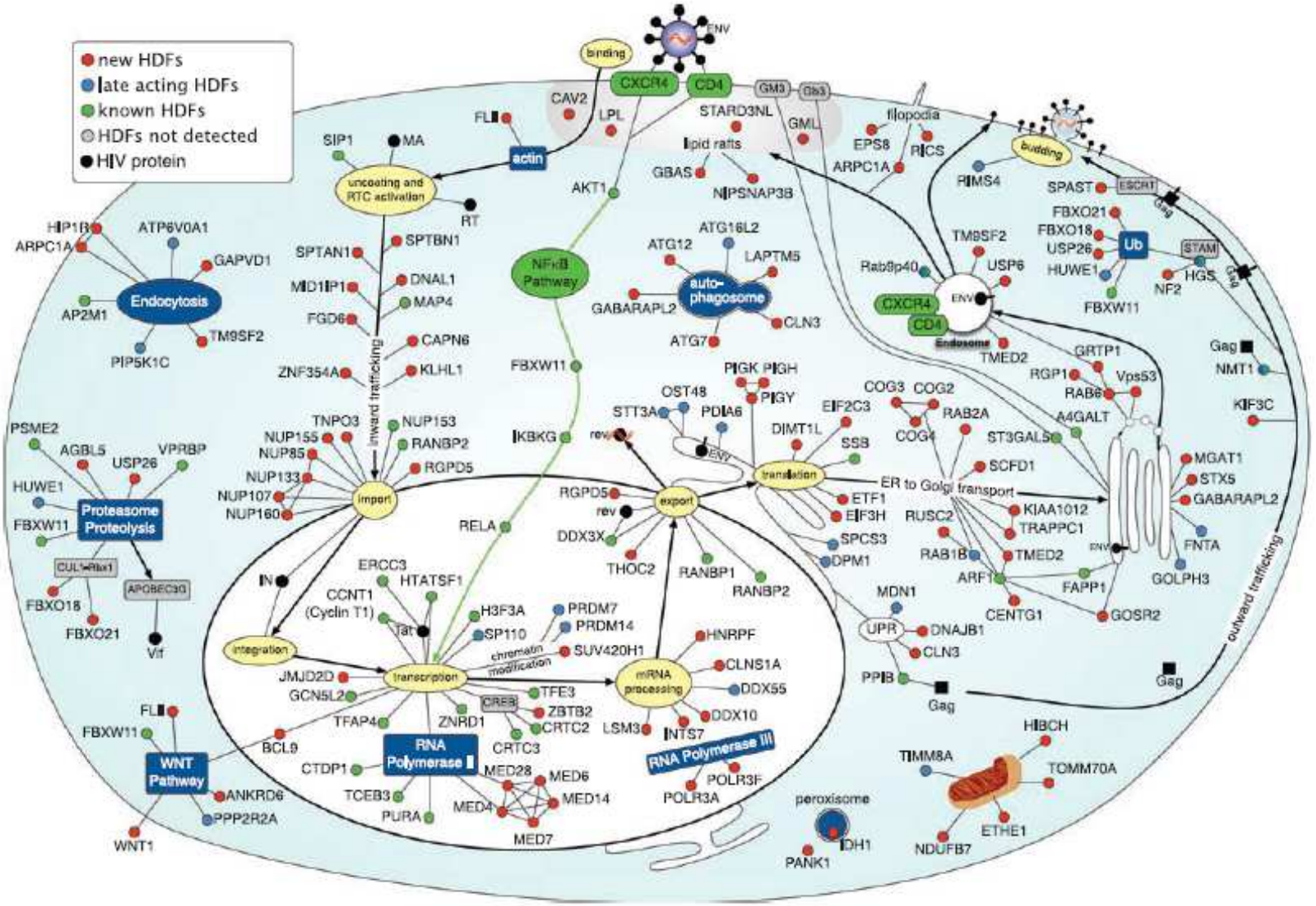


Fig. 5. Model of HDF roles in the HIV life cycle. With the stages of the HIV life cycle as a framework, each HDF was placed at the position most likely to elicit HIV dependency. The function and subcellular location of HDFs were determined with the use of multiple databases (rationale, table S4). Some proteins are in multiple locations to represent more than one possible role in the HIV life cycle. Newly identified HDFs (red or blue, the latter if they inhibited HIV in part two only); previously implicated HDFs detected in the screen (green), or not detected but with a relevant interaction (gray); HIV protein (black): matrix (MA), reverse transcriptase (RT), integrase (IN), envelope (gp41, gp120) (ENV). Unfolded protein response, UPR.

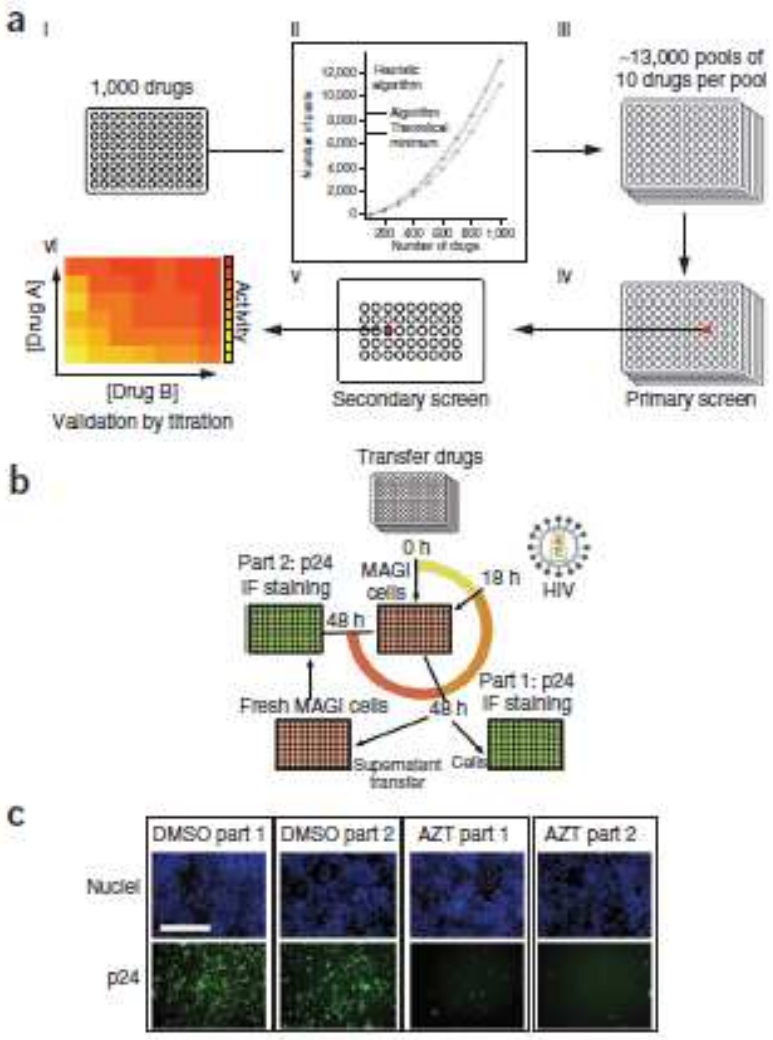
Method

1,000 FDA approved dugs

500,000 pairwise combinations

Eliminated:

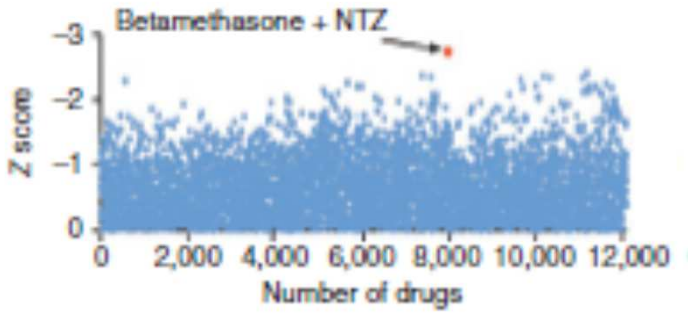
- Cytotoxic
- Topical
- HAART
- Antivirals
- Structural duplicates



Results

Enrichment of anti-inflammatory drugs in combinations that synergise against HIV

Glucocorticoids and Nitazoxanide synergise by targeting different steps in lifecycle



Low dose combinations of known approved drugs may have powerful anti-HIV effects with minimal side effects

This strategy is applicable to other infections