13th Annual Conference of the
National HIV Nurses Association (NHIVNA)

National HIV Nurses Association

Professor Saye Khoo

University of Liverpool

16-17 June 2011, Arena and Convention Centre, Liverpool

UNIVERSITY OF LIVERPOOL

Advances in Antiretroviral Therapy

Saye Khoo

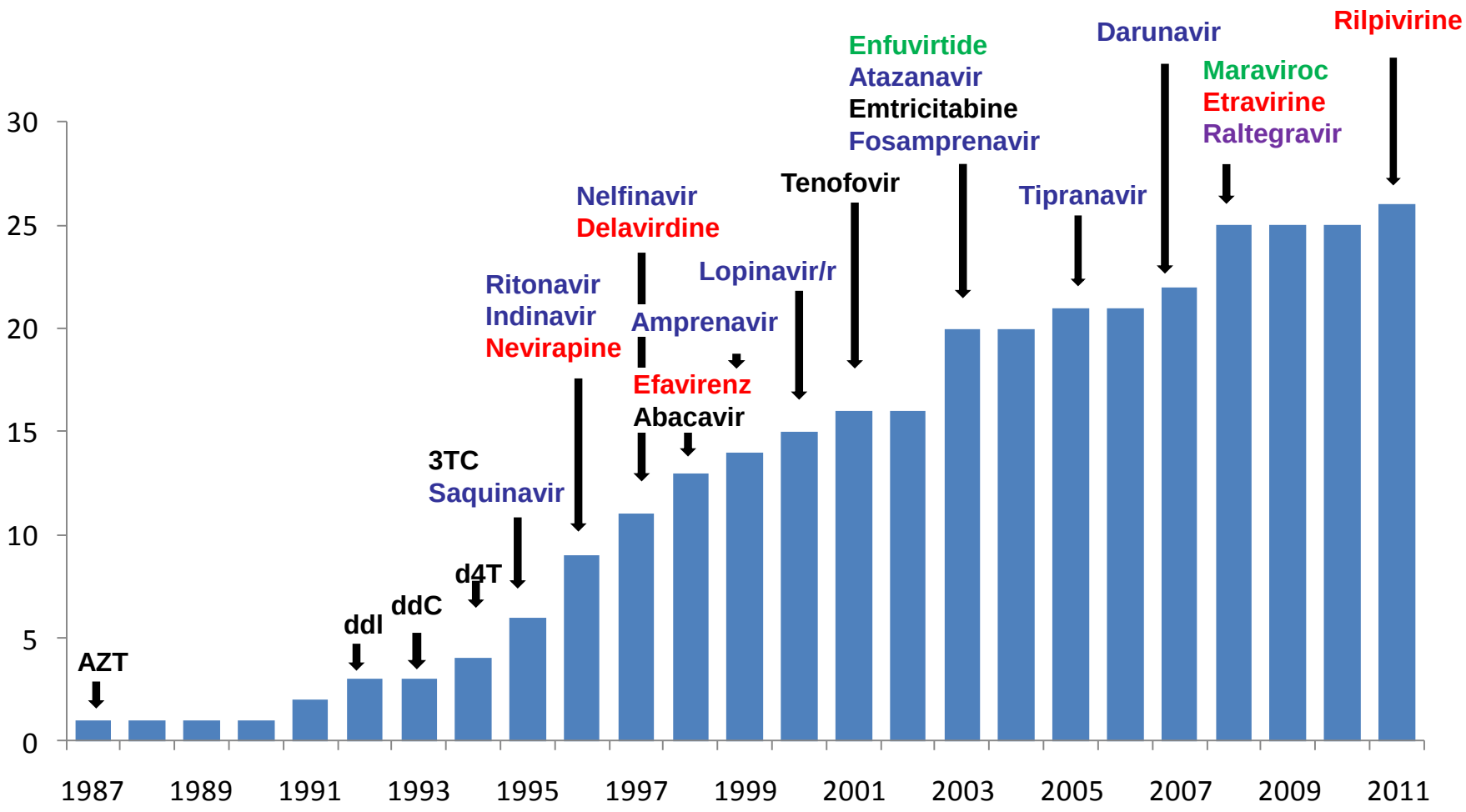
HIV Pharmacology Group

University of Liverpool / Biomedical Research Centre in Microbial Diseases

Antiretroviral Therapy

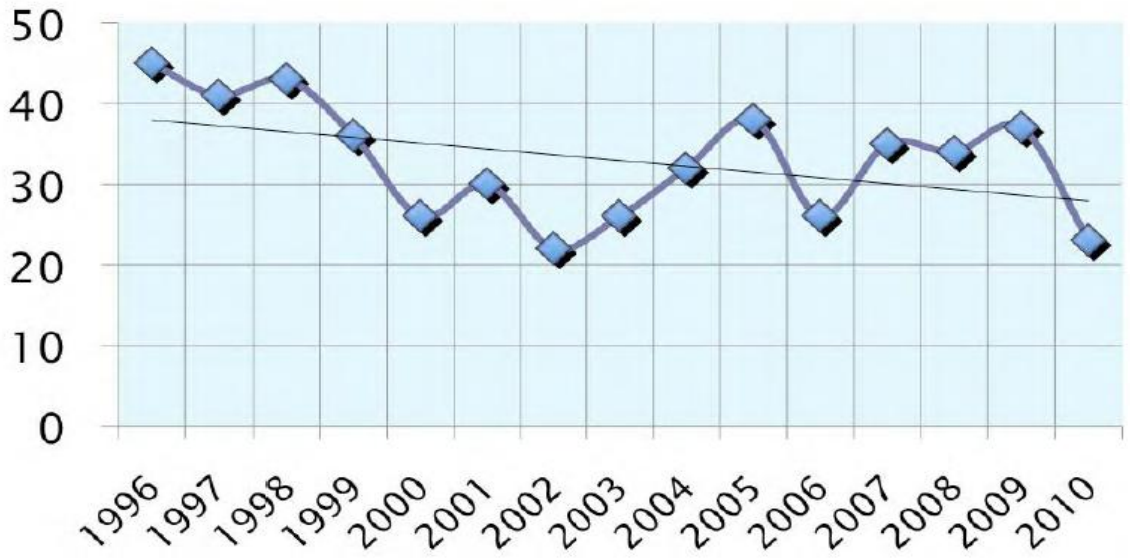
- What does the future hold ?
- Challenges to adherence
- Challenges of an ageing population
- Safer prescribing and drug interactions
- Conclusions

Antiretroviral Therapy: June 2011



Industry

- no of NMEs filed in 2010 lowest for 15 years



FDA CDER 17.2.11

Rilpivirine (Edurant): 25 mg once a day

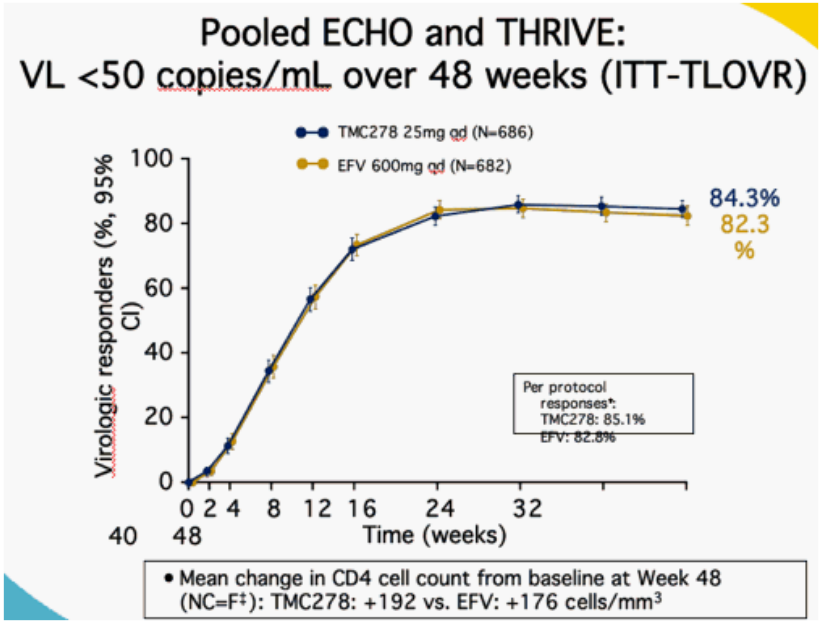
US FDA Approved New HIV Treatment

Posted on 24 May 2011.

A new treatment for HIV has been approved by the US Food and Drug Administration on Friday. The medication is used with other antiretroviral drugs, which blocks the replication of the virus that causes the disease.

TMC278 or rilpivirine is a pill developed by Johnson & Johnson and will be given mainly for patients who have never started treatment for HIV, the FDA said in a report released on Friday. The American pharmaceutical company will sell it in the market under the brand name Edurant. It will be consumed once a day with meals.

According to Dr. Edward Cox, Office of Antomicrobial Products director in the Center for Drug Evaluation and Research in FDA, patients respond variously on the given HIV treatments; thus, the approval of Edurant provides an alternative option for patients who will start its therapy.

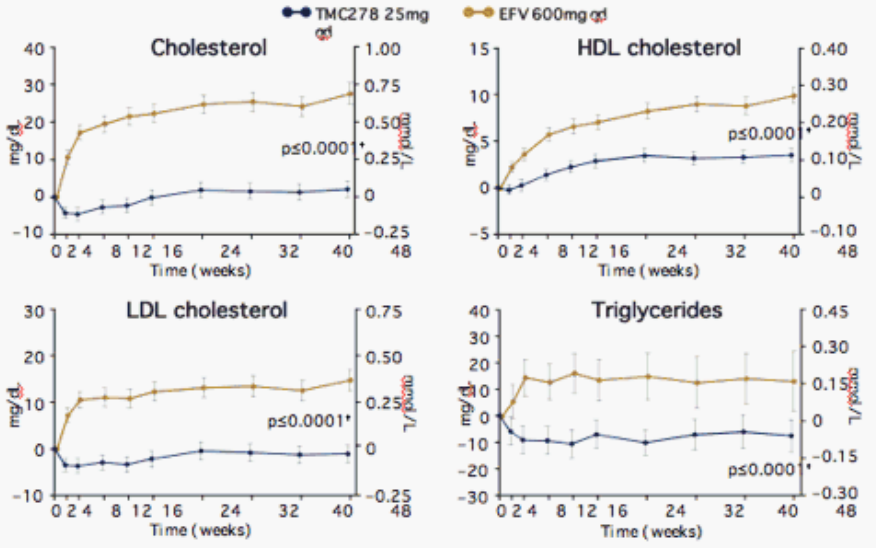


Rilpivirine vs EFV

Pooled ECHO and THRIVE: adverse event summary†

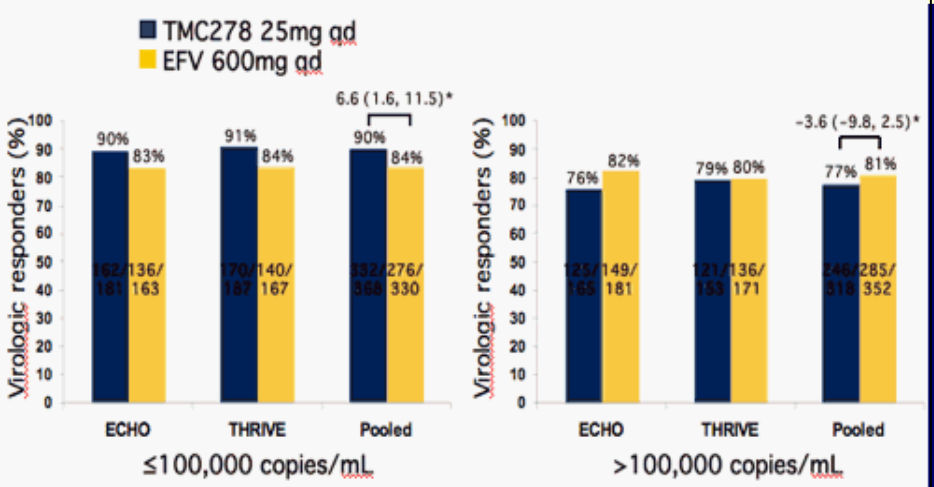
	TMC278 N=686	EFV N=682	p-value TMC278 vs. EFV
Median treatment duration, weeks	56	56	
Any serious AE, %	7	8	NS
Any AE,%	90	92	NS
Grade 2–4 AE at least possibly related to treatment, %	16	31	<0.0001‡
Discontinuations due to AEs, %	3	8	0.0005
Most common AEs of interest,§ %			
Any neurological AE	17	38	<0.0001‡
Dizziness	8	26	<0.0001‡
Any psychiatric AE	15	23	0.0002‡
Abnormal dreams/nightmares	8	13	0.0061‡
Rash (any type)	3	14	<0.0001‡

Pooled ECHO and THRIVE: mean (±95% CI) change from baseline in lipids



Rilpivirine vs EFV

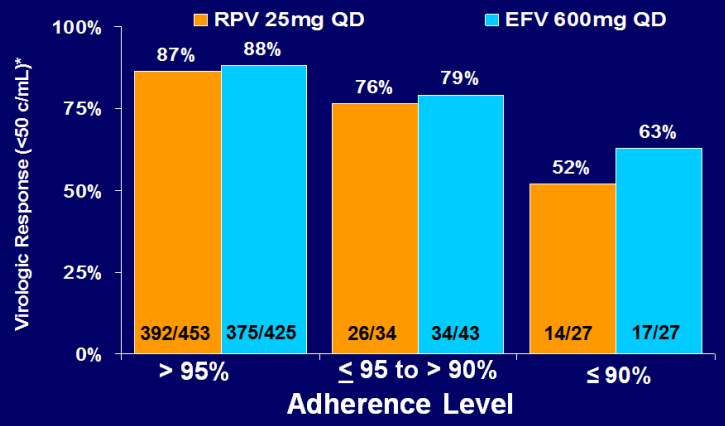
ECHO and THRIVE: VL <50 copies/mL by baseline VL (ITT-TLOVR)



- NRTI background had no effect on virologic response
- No differences between treatment groups in virologic response by gender, region or race

Pooled ECHO and THRIVE: FTC/TDF Dataset

Virologic Response (VL <50 c/mL, ITT TLOVR) by Self-Reported Adherence (M-MASRI)



- Adherence (assessed by M-MASRI) was one of the most important factors associated with virologic response
  - Suboptimal adherence was associated with lower virologic responses in both treatment groups

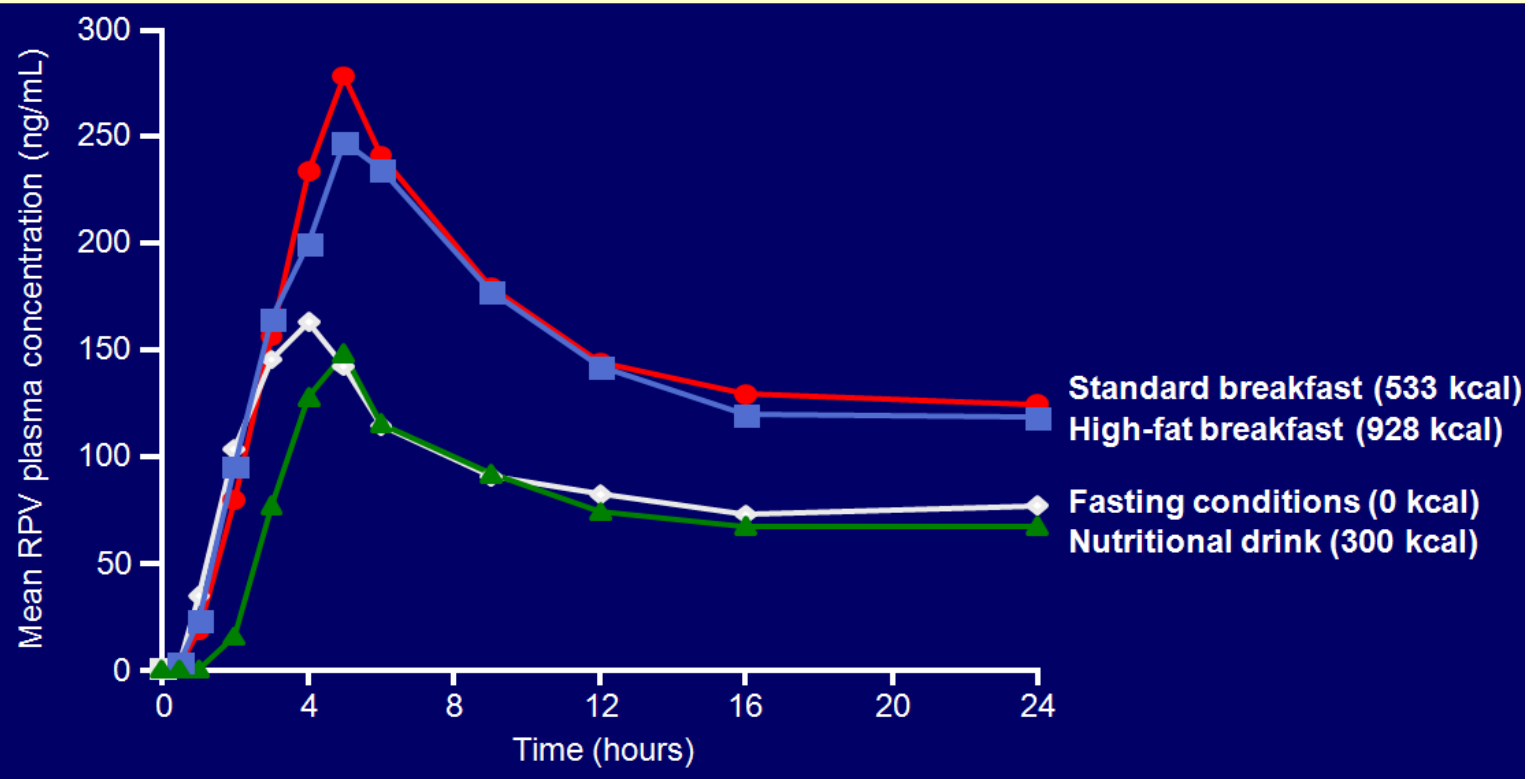
*ITT-TLOVR

Clion R, et al. IAPAC 2011; Miami, FL. LB Oral #70365

Rilpivirine vs EFV

Importance of Adherence to Taking RPV with a Meal

Mean RPV PK Profile

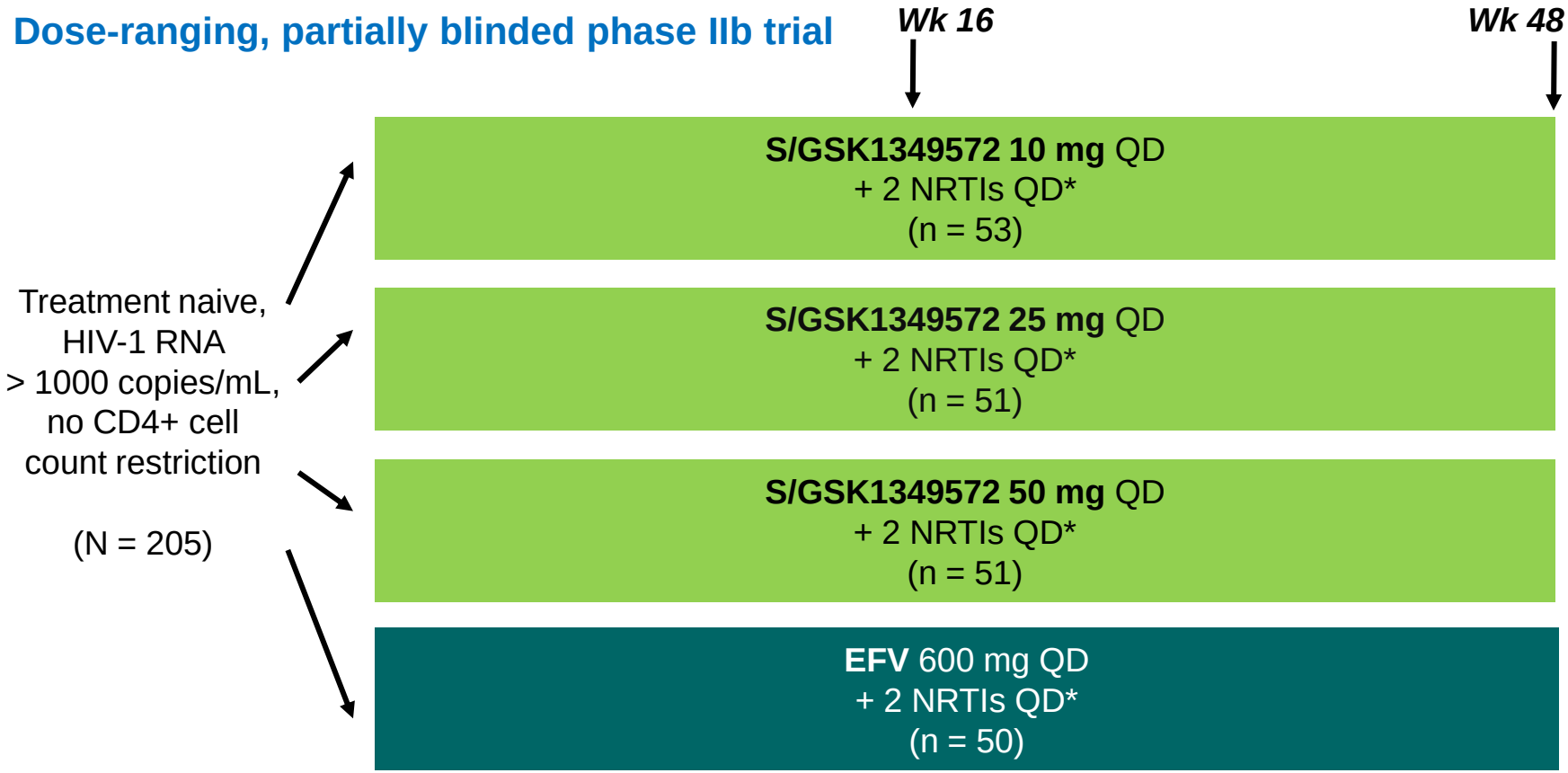


Taking RPV with food increases RPV exposure by 57% compared to fasting. RPV AUC was similar when administered after a high-fat or standard breakfast.

rauwels HM, et al. IWCPHIV 2008. #P32

SPRING-1: S/GSK1349572 vs Efavirenz in Treatment-Naive Patients

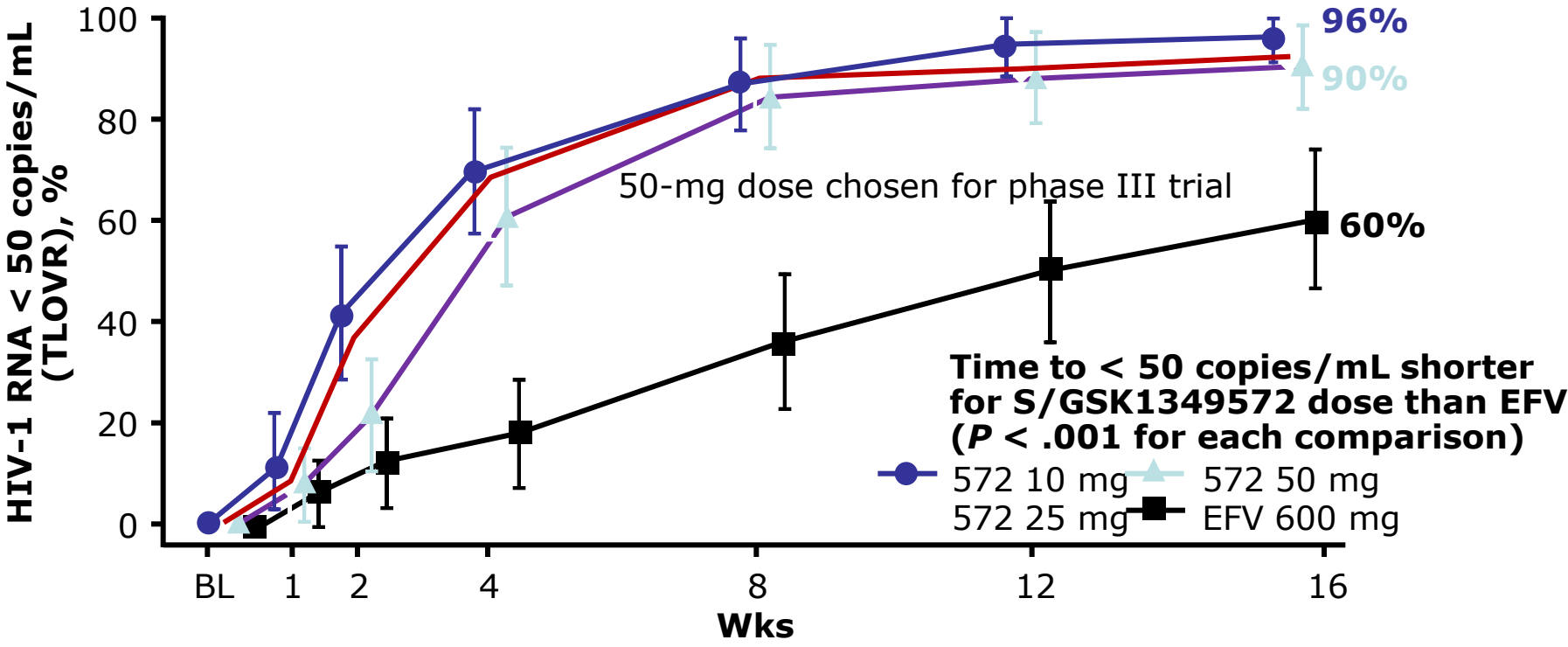
- **Dose-ranging, partially blinded phase IIb trial**



*NRTIs individually selected by trial investigators (TDF/FTC, 67%; ABC/3TC, 33%).
†After Wk 48, all patients continue at dose selected for phase III trial.

Arribas J, et al. AIDS 2010. Abstract THLBB205.

SPRING-1: Virologic Response to S/GSK1349572 vs Efavirenz at Week 16



- CD4+ cell count increases 153-176 cells/mm³ on S/GSK1249572 vs 116 cells/mm³ on EFV
- No serious adverse events related to S/GSK1349572

Arribas J, et al. AIDS 2010. Abstract THLBB205.

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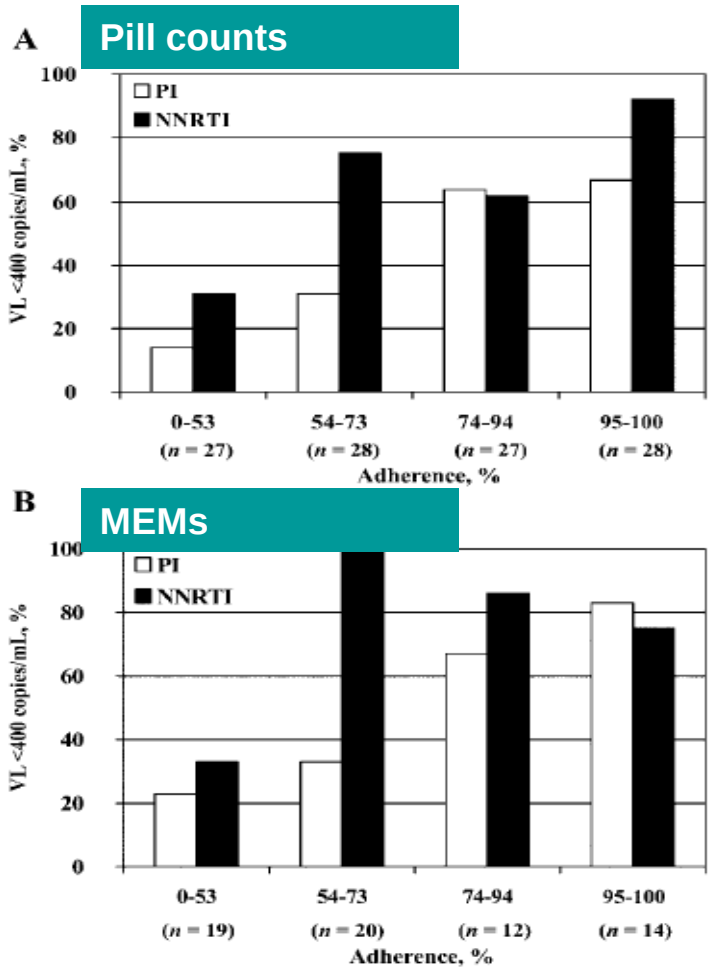
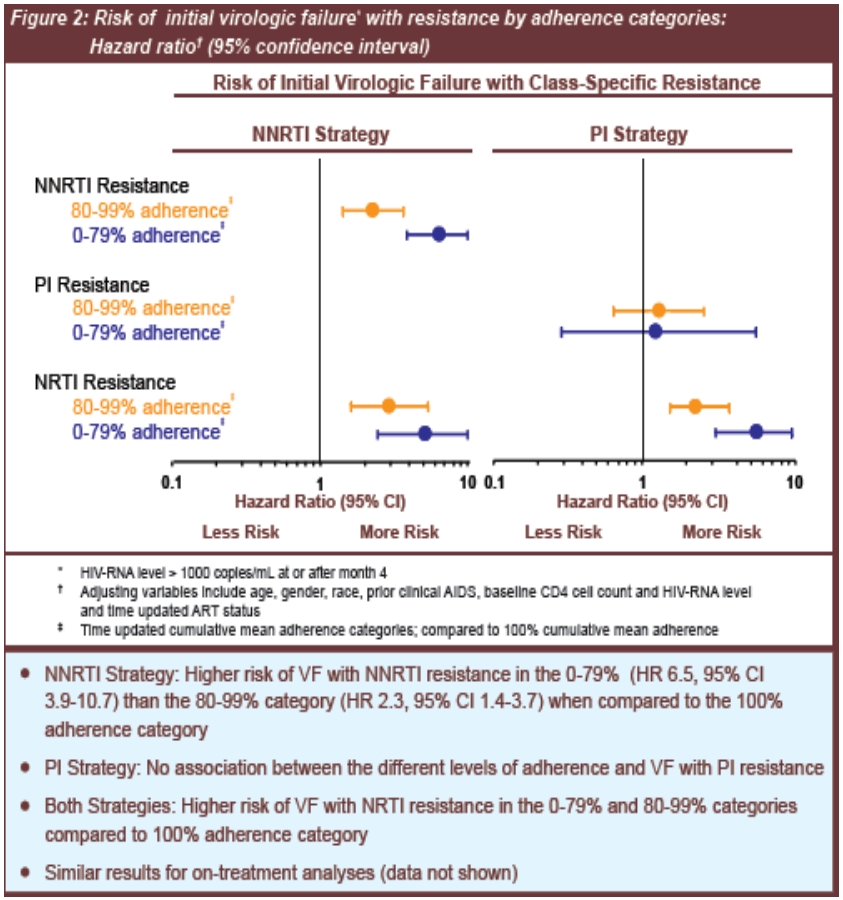
Adherence-viraemia-resistance relationships



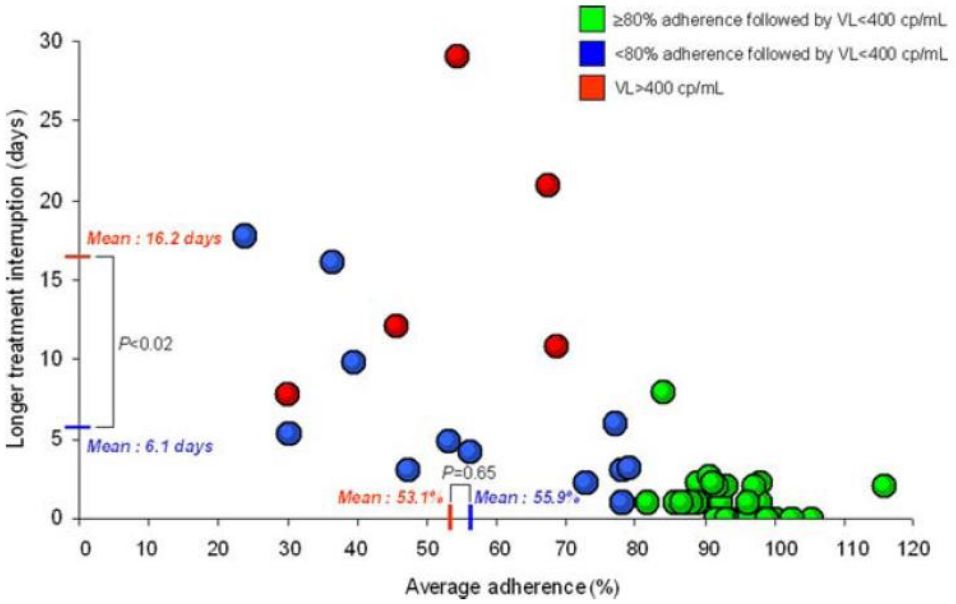
Bangsberg et al CID 2006;43:939



FIRST Trial: Relationship between Adherence and resistance by drug class:

Gardner et al CROI 2008 Abs 777
& AIDS 2010;24:395

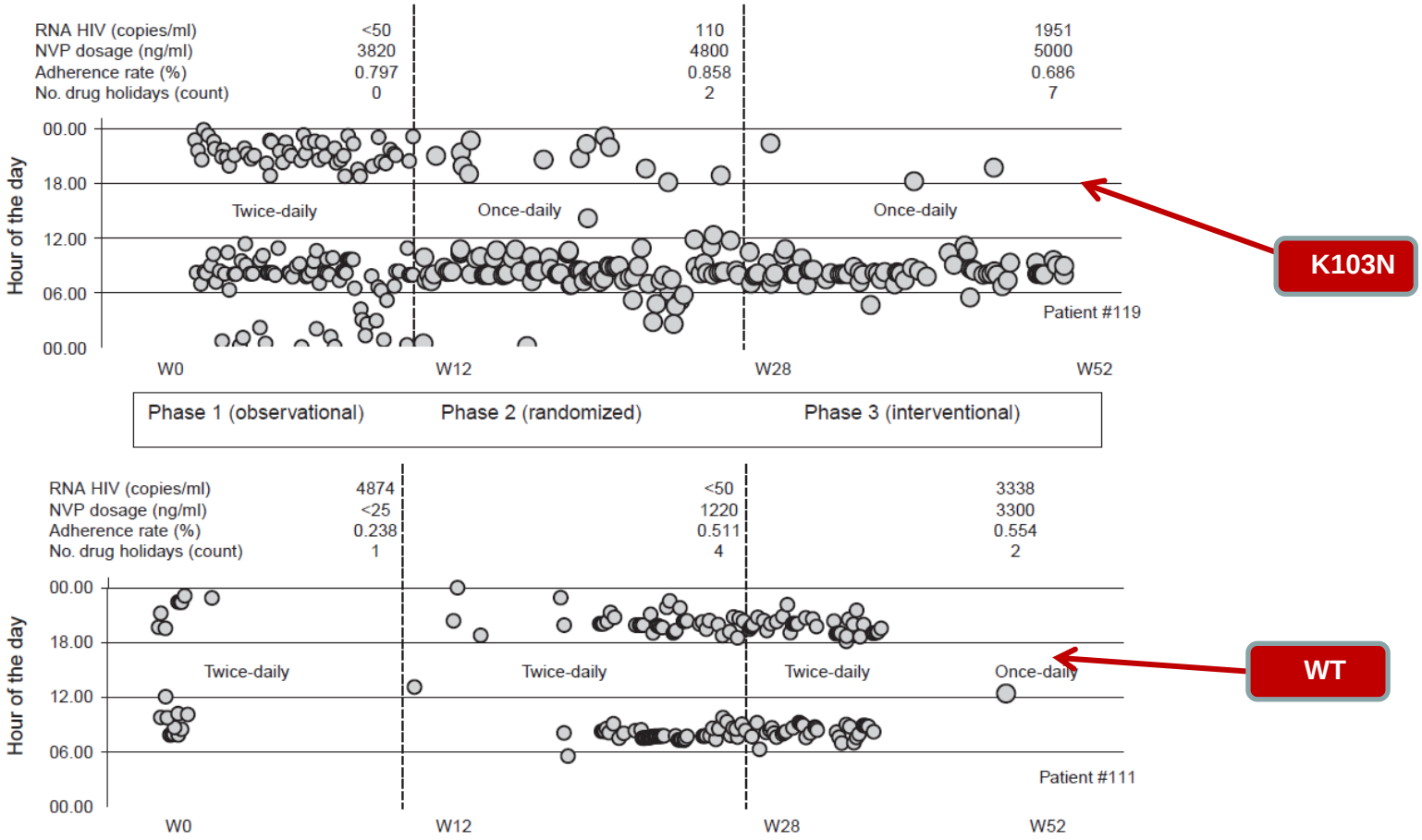
Not all missed doses have the same effect



Patients on NNRTIs in France & USA (N = 72)
Electronic monitoring
Sustained treatment interruption gives greater risk of rebound in patients with low – moderate adherence

Parienti et al PLoS One 2008;3:

Not all missed doses have the same effect



Parienti et al. AIDS 2007

POSAVIR Study – NVP bd changing over to od.
Electronic monitoring of adherence
OD dosing associated with 2 consecutive days without dose
(OR 4.4; 95% CI 1.9, 10.3; P<0.001

A Simple Adherence Checklist

1 Assess readiness to start treatment (may take several visits)	• Understand why treatment is offered? • Understand what they stand to gain ? • Understand how long it is for ?
2 Assess barriers to treatment	• Language • Cultural • Social • Psychological • Physical • Financial
3 Select a regimen with input from patient	• Compact and convenient • Low pill burden • od or bd • minimise food restrictions
4 Ensure understanding of side effects	• Patient information & contact details • Don't forget drug interactions
5 Need for adherence tools ?	• Peg to a routine • Pill box / bleepers/ timers • Peer support
6 Continued monitoring at subsequent visits	• Assess adherence • Allow patients to answer honestly • Feedback – CD4, viral load.

HIV Pharmacist Screening

Move from *passive* to *active* identification of DDIs

- **Pharmacist input**
  Effective as an alternative, but probably not in addition to computer aided systems
  Liverpool N=104 patients [Seden, P115]

	Told physician something they did not know	Changed management of the patient
Medication History	12 (18%)	2 (4%)
DDI Check	21 (32%)	6 (11%)
Adherence Check	24 (37%)	2 (4%)
Total for 1 or more intervention	40 (62%)	10 (15%)

	Benefit in patients taking ≤2 co-meds	Benefit in patients taking >2 co-meds	P-Value
Medication History	4 /41 (9.8%)	8 /24 (33.3%)	0.0224*
DDI Check	8 /41 (19.5%)	13 /24 (54.2%)	0.0028*
Adherence Check	14 /41 (34.1%)	10 /24 (41.7%)	0.5911

De Maat et al. J Clin Pharm Ther 2004;29:121
Seden et al. HIV10 P115

Clinical implications of fixed-dose coformulations of antiretrovirals on the outcome of HIV-1 therapy

Josep M. Llibre[a], José R. Arribas[b], Pere Domingo[c], Josep M. Gatell[d], Fernando Lozano[e], José R. Santos[a], Antonio Rivero[f], Santiago Moreno[g], and Bonaventura Clotet[a] the Spanish Group for FDAC Evaluation

The substitution by generic equivalents of some of the drugs included in fixed-dose antiretroviral coformulations (FDACs) poses the potential risk of disrupting these combinations and administering the components separately in order to incorporate the new generic drug, which offers a more competitive sales price. This may represent a step backwards in the advances achieved in simplicity and adherence to therapy, posing an increased risk of selective non-compliance of some of the separately administered drug substances. Available antiretroviral drugs must be administered for life in the affected individuals – both children and adults.

The FDACs represent a significant advance in the simplification of antiretroviral therapy, facilitating adherence to complex and chronic treatments, and contributing to a quantifiable improvement in patient quality of life. These drug coformulations reduce the risk of treatment error, are associated with a lower risk of hospitalization, and

Metanalysis : FDCs afforded a 26% reduction in the risk of treatment non-compliance with respect to administration of the same drugs separately (RR: 0.74; 95%CI: 0.69–0.80, p<0.0001)

AIDS 2011, **25**:000–000

Bangalore et al Am J Med 2007

Antiretroviral Therapy

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Considerations in Management of the Older HIV Patient

- **Co-morbid conditions**
  - ***eg., cardiovascular, hepatic, metabolic***
  - ***may be exacerbated by effects of HIV or its treatment***
- **Greater medication use**
  - ***overlapping side effects or potential interactions with ARVs and concomitant medications***
- **Age-related changes in drug handling (PK) and response (PD)**
  - ***toxicity***

Ageing and drug handling

- **Lower Renal Clearance**

- **Lower hepatic elimination**

  Decrease in liver volume
  Impaired hepatic blood flow
  Decrease in some drug metabolising enzymes.
  Increased amount of fat, which impairs metabolism
  Decline in regenerative response following injury

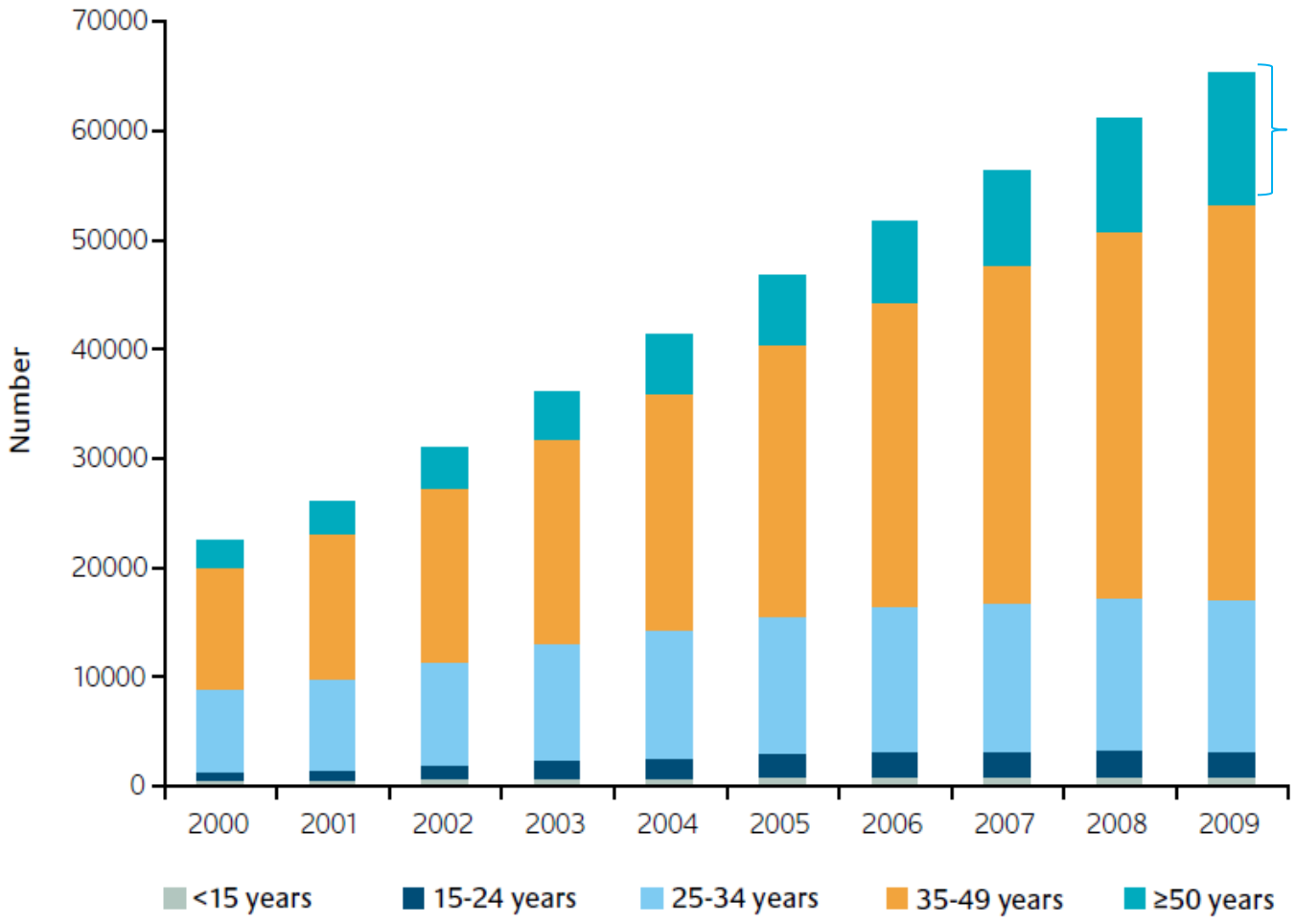
- **Poorer absorption of drugs**

  Increased gastric pH - Implications for ATV (decreased) & RAL (increased)
  Delayed gastric emptying
  Decreased gi motility
  Decreased absorption surface

- **Changes in body fat and water**

- **Increased susceptibility to drug toxicity**

Figure 3: Number of people living with diagnosed HIV infection and accessing HIV-related care, by age group, UK: 2000-2009

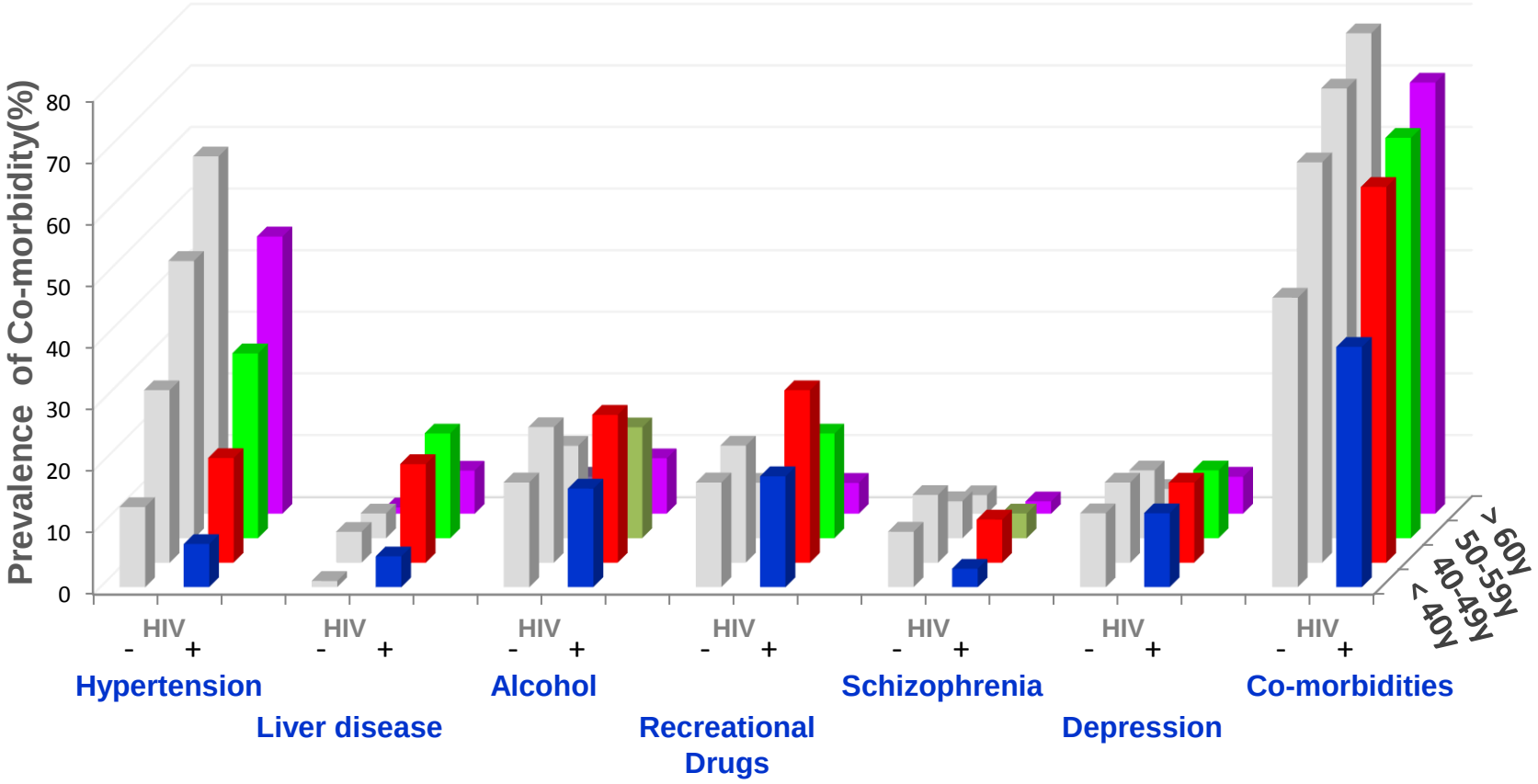


HIV+ Adults >50 years increased between 2000-2009 from 2,042 to 12,063.

HPA 2010

Co-morbidities increase with age

Medical comorbidities amongst 66,840 HIV- and 33,420 HIV+ veterans



Adapted from Goulet CID 2007;45:1593

Risk for clinically significant interactions

Study	Year	Setting	N	CSDI	lower	Screening Tool	Adverse	Notes
de Maat et al	2004	Netherlands (hospital)	115 105	26% 23%	N/A	Liverpool website	N/A	Pharmacy screening effective, further pharmacy input not
Shah et al	2007	USA (Medicaid)	571 (689)	30% (15%)	8% (4%)	Liverpool website Micromedex	no VL impact	Audit, and re-audit.
Miller et al	2007	USA (hospital)	153	41%	N/A	DHHS SPC / PI Micromedex	N/A	Age >42y (OR 2.9) >3 conditions (OR 3.0) >3 ARVs (OR 2.4) PI use (OR 11.5)
Kigen et al	2009	Kenya (hospital)	996	34%*	12%	Liverpool website	N/A	
Marzolini et al	2009	Switzerland (hospital)	1497	40%	4%	Liverpool website	no CD4 or VL impact	
Evans-Jones et al	2009	UK (hospital)	159	27%		Liverpool website	N/A	Only 36% CSDIs correctly identified

* excludes ARV-ARV interactions

Miller et al Pharmacother 2007;27:1379
De Maat et al. *Clin Pharmacokinet* 2003;42:223
Shah et al. CROI 2007, Abstr 573. 2007
Marzolini et al. AVT 2010;15:413
Evans-Jones et al. CID 2010;50:1419
Kigen et al. Plos One 2010

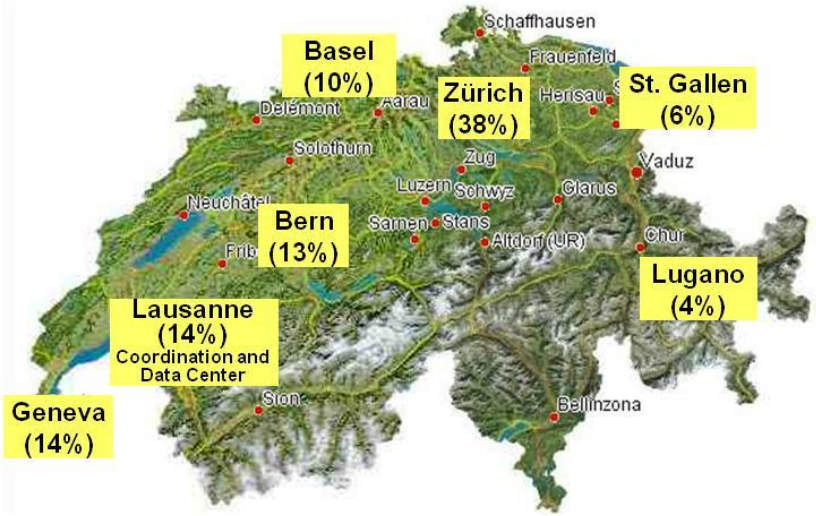
‘High Risk’ comedications – developed countries

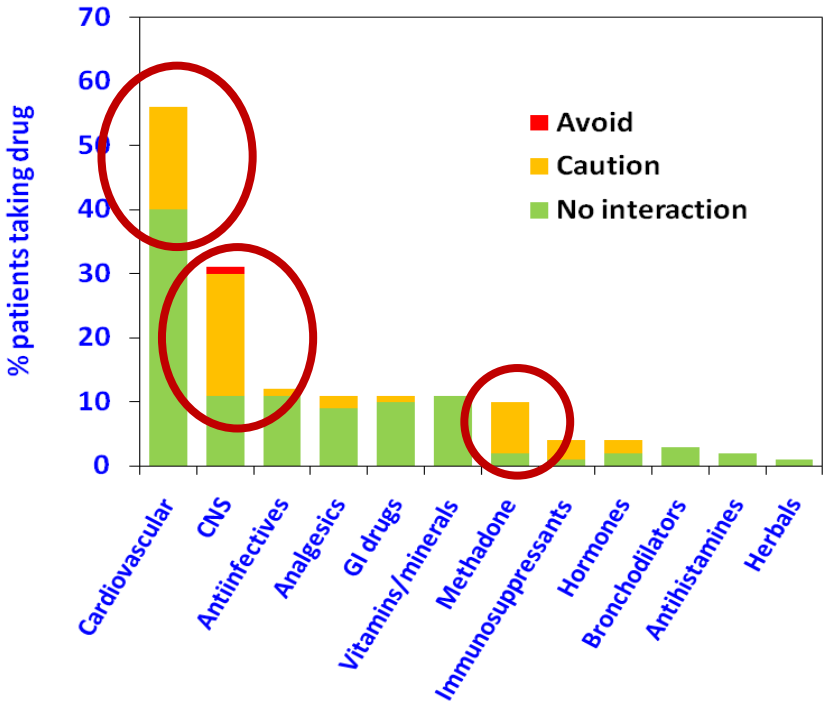
- **Swiss HIV Cohort**

  68% of 1497 HIV patients were taking co-medications.

  31% - CNS drugs (anxiolytics – 13%, antidepressants – 12%, anti-psychotics – 3% anticonvulsants – 3%)

  4% of interactions could have lowered ARV levels





Marzolini et al. AVT 2010;15:413

‘High Risk’ comedications – developing countries

OPEN ACCESS Freely available online

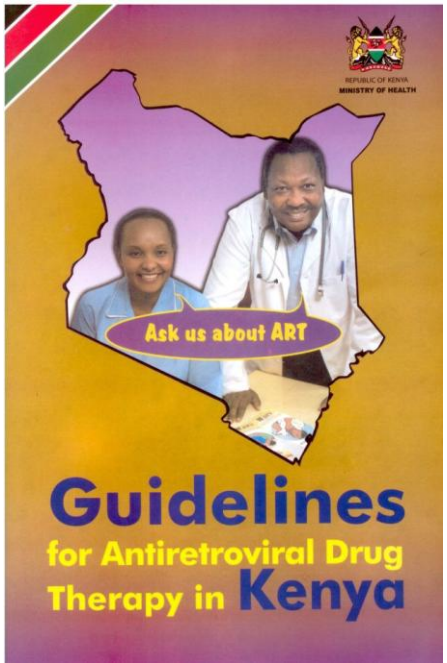
PLoS one

Prevalence of Potential Drug-Drug Interactions Involving Antiretroviral Drugs in a Large Kenyan Cohort

Gabriel Kigen[1,2], Sylvester Kimaiyo[3], Winstone Nyandiko[3], Brian Faragher[4], Edwin Sang[3], Beatrice Jakait[1], Andrew Owen[2], David Back[2], Sara Gibbons[2], Kay Seden[5], Saye H. Khoo[2,5]*, on behalf of the USAID-Academic Model for Prevention Treatment of HIV/AIDS

1 Department of Pharmacology and Toxicology, Moi University School of Medicine, Eldoret, Kenya, 2 Department of Pharmacology, Institute of Translational Medicine, The University of Liverpool, Liverpool, United Kingdom, 3 USAID-Academic Model Providing Access to Healthcare (AMPATH), Moi University School of Medicine, Eldoret, Kenya, 4 Liverpool School of Tropical Medicine, Liverpool, United Kingdom, 5 NIHR Biomedical Research Centre for Microbial Diseases, Royal Liverpool University Hospital, Liverpool, United Kingdom

- 996 consecutive patients receiving ARVs
- Moderate / Major drug interactions identified in 34%
- 12% (1:3 CSDIs) could have lowered ARV concentrations
- Rifampicin > Azoles > Steroids > Antimalarials > PPIs



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27 February 2011 Last updated at 22:13 ET

'Whoonga' threat to South African HIV pa

By Pumza Fihlani
BBC News, Durban

Whoonga smoking is gaining in popularity in South Africa's townships

HIV patients in the South African township of Umlazi live in fear of being robbed of their live-saving anti-retroviral drugs.

HIV patients in the South African township of Umlazi live in fear of being robbed of their live-saving anti-retroviral drugs.

They have become attractive targets for gangs who steal their pills, which are then combined with detergent powder and rat poison to make "whoonga" - a highly toxic and addictive street drug.

Smokers use it to lace joints, believing the anti-retroviral Stocrin increases the hallucinogenic effects of marijuana - though there is no scientific proof of this.

Drug Interactions - HIV vs HCV

- **multiple co-morbidities necessitating polypharmacy**
- **Chronic therapy**
  Lifelong (HIV) vs fixed term (HCV)
- **Drugs have high propensity for interactions**
  mainly CYP P450-mediated
  often complex- mixed picture of enzyme inhibition and induction
- **HCV – drug interactions may be superimposed on a background of liver impairment**
- **Unlike HIV, HCV treatment may provided by a variety of specialists**
  not all of whom have HCV as their 'core' or main service.
  Physician awareness and education often lacking for both diseases

Liverpool HIV Drug Interactions website

www.hiv-druginteractions.org

Interaction Charts | News & Archive | About Us | Pharmacology Resources | Links | Meetings | TDM | Feedback | Home

LATEST ARTICLES

Meeting Report - 11th PK Workshop, Sorrento, April 2010.

Case Reports - IV docetaxel and ritonavir.

Review - Warfarin and antiretrovirals.

Review - Management of HIV/TB co-infection.

Drug Interactions - Ritonavir and quinine.

Drug Interactions - Tenofovir and boosted or unboosted fosamprenavir.

Click here for previous news items

SITE UPDATES

WEBSITE MAINTENANCE
Added: Friday 30th April 2010
The website is having to undergo essential maintenance on its infrastructure which will be completed by August. ...
>>more

DRUG INTERACTIONS CHARTS

Access our comprehensive, user-friendly, free, drug interactions charts

CLICK HERE

Providing clinically useful, reliable, up-to-date evidence-based information

NEWS ALERT

The recently initiated Editorial Board provides oversight, strategic vision and direction for the site. It also advises on developmental opportunities and the interface with end users.

Editorial Board members are:
David Back (Liverpool – Chair)
Saye Khoo (Liverpool – Website Team)

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British HIV Association BHIVA

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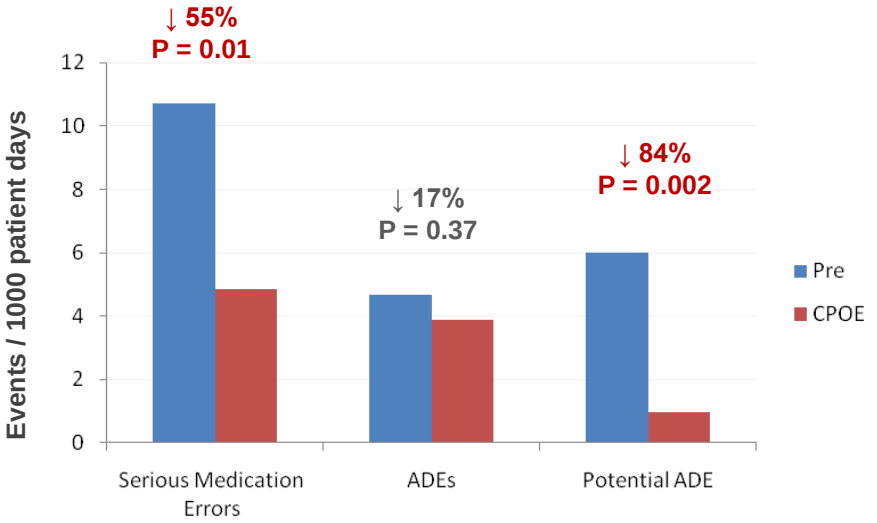
Drug Therapy in HIV Infection 7-11 NOVEMBER 2010 GLASGOW, UK

ASSOCIATED SITES

Computer-aided Decision Support

Wizorder:

- Allergy checking
- Dose checking
- Drug interactions
- FDA alerts

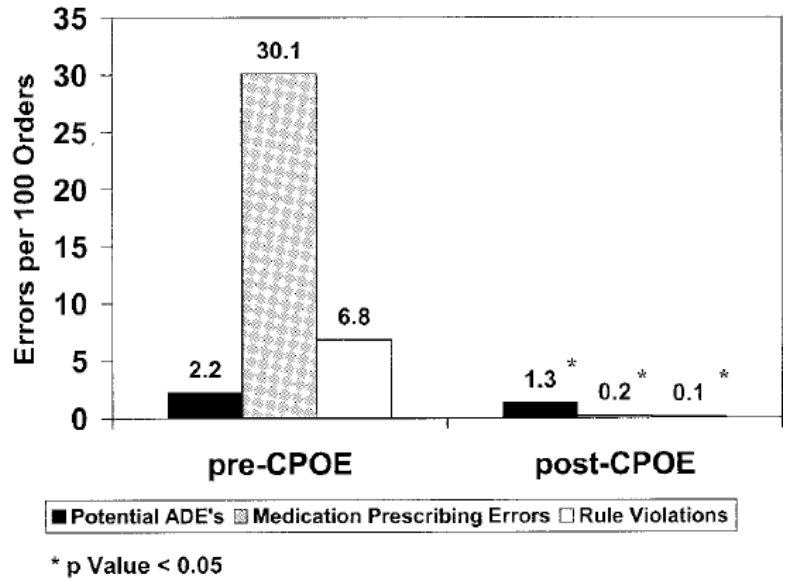


ADULTS

Boston Hospitals
Admissions Pre (N = 2491) & Post (N = 4220)
across 8 specialty units
Potential and *actual* adverse drug events
No additional benefit of team (pharmacist, etc)

CHILDREN

Pediatric CCU Vanderbilt Children's Hospital
514 patients; 13,8282 medication orders
Pre- and post Computerised Physician Order Entry



Bates et al. JAMA 1998;280:1311
Potts et al. Pediatr 2004;113:59

Conclusion

- **DDIs are frequent, largely unavoidable, frequently unrecognised**
  Most can be managed, if recognised

- **Older patients = different challenges**
  - *long term adherence*
  - *long term toxicities*

- **Drug pipeline hopeful, but will it always be so ?**

- **Newer models of healthcare**
  Electronic health records & prescribing
  Nurse-led clinics, deployment into primary health settings