Evidence-based ART adherence

Dr Catherine Orrell

Desmond Tutu HIV Foundation

26 November 2012

Desmond Tutu HIV Foundation

Masibambane Ngezandla

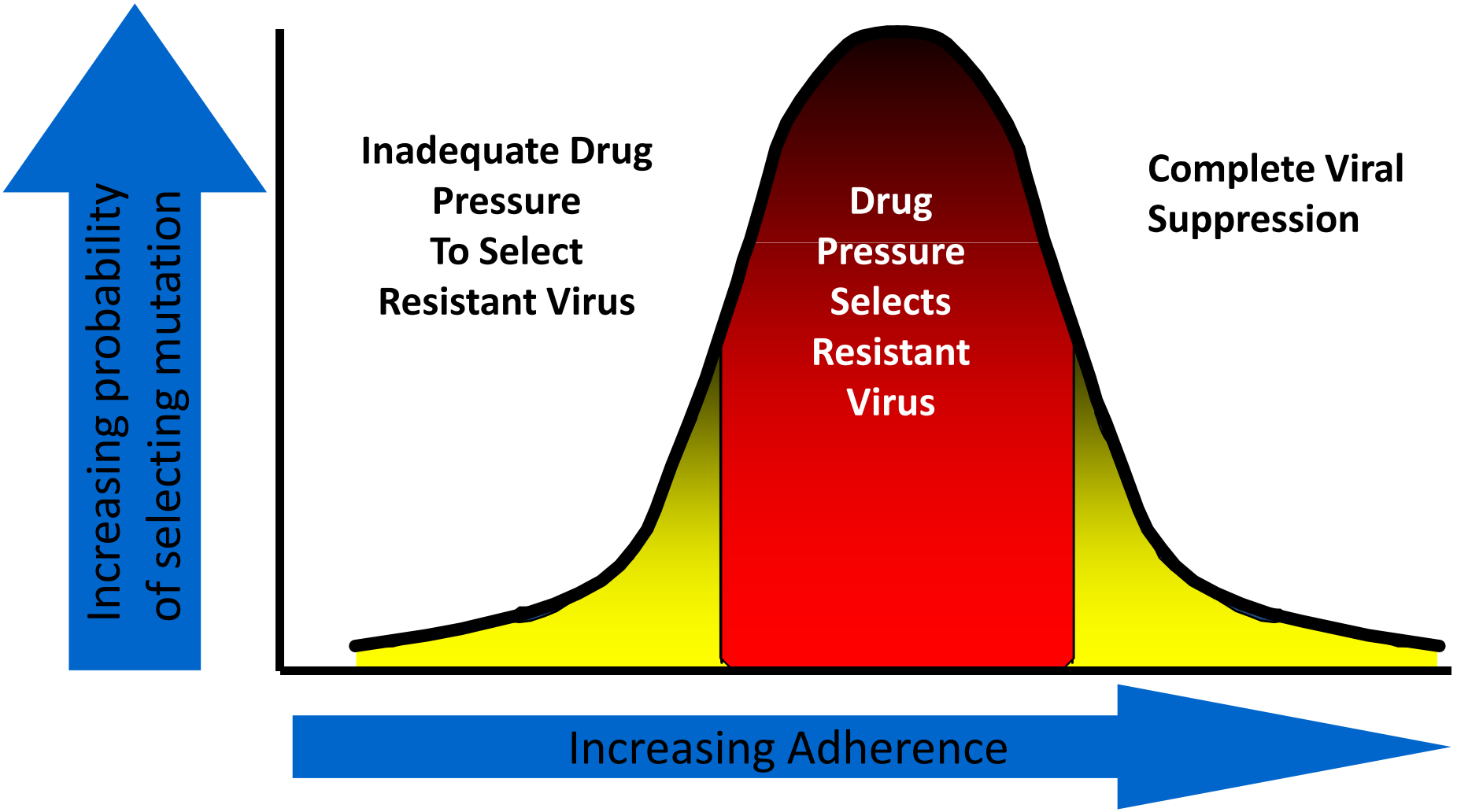
What is adherence?

There are two main components:

1) Adherence to daily treatment →
   All tablets taken
   At the correct time

2) Adherence to care →
   No treatment interruptions
   Retention in care

Bell-shaped adherence and resistance curve



Overview

- **Local issues and solutions.**
- New technologies – MEMScaps, Wisepill
- New approaches – what can we learn from international literature?
- Cases

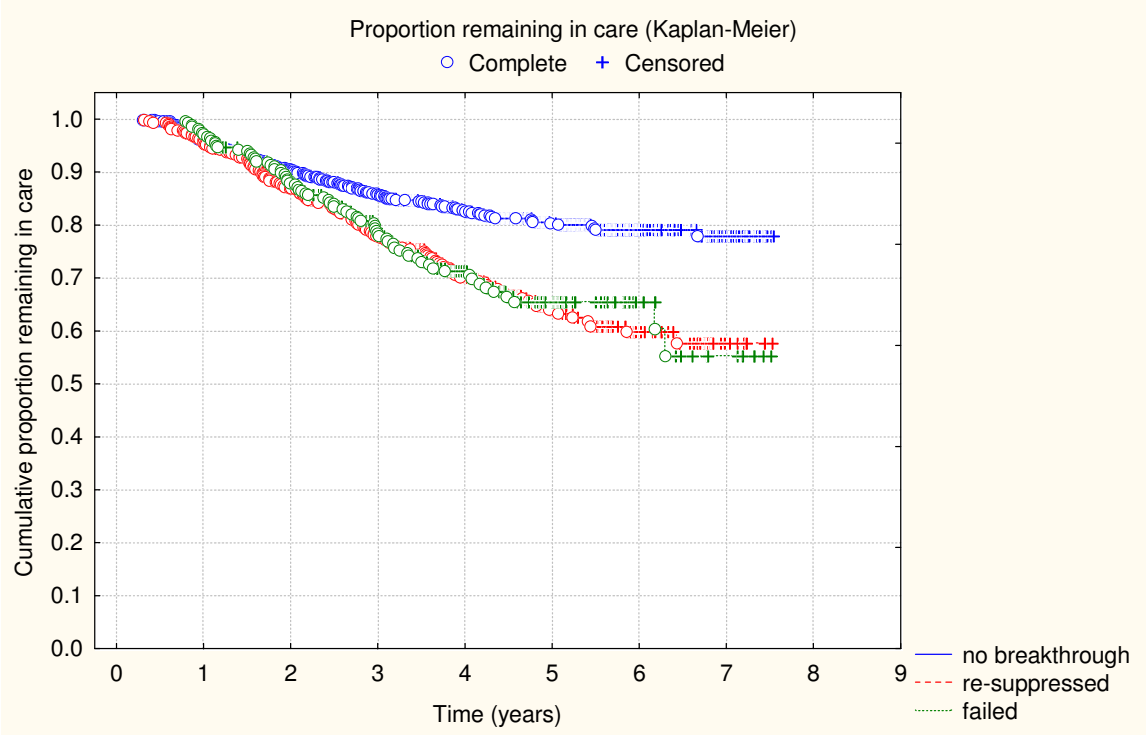
Barriers to Adherence in sub-Saharan Africa

- Routine
  - ETOH/substance use
  - Depression
  - Side effects
  - Pill burden/dosing frequency
  - Memory
  - Adolescence
- Priority
  - Transportation to clinic
  - Food security
  - Stock-outs and substitutions
  - Stigma

Mill PLoS 2006, Oyugyi AIDS 2007, Tuller AIDS Beh 2010, Weiser JAIDS 2003; McCurdy CROI 2010, Nachega AIDS 2008, JAIDS 20090

Retention in care

- Adherence is more than just beginning therapy, it is sticking to it. LTFU rates are high…



Orrell, AIDS Research and Treatment 2011

Retention in care

- People cycle in and out of therapy.
- The odds of failure increased 5 times

  (aOR 5.25, 95% CI 1.58-17.41) in individuals with **treatment interruptions.**
- The odds of failure increased 2.5 times

  (aOR 2.52, 95% CI 1.18-5.38) in individuals with at least one episode of **fluctuating adherence** of >10%

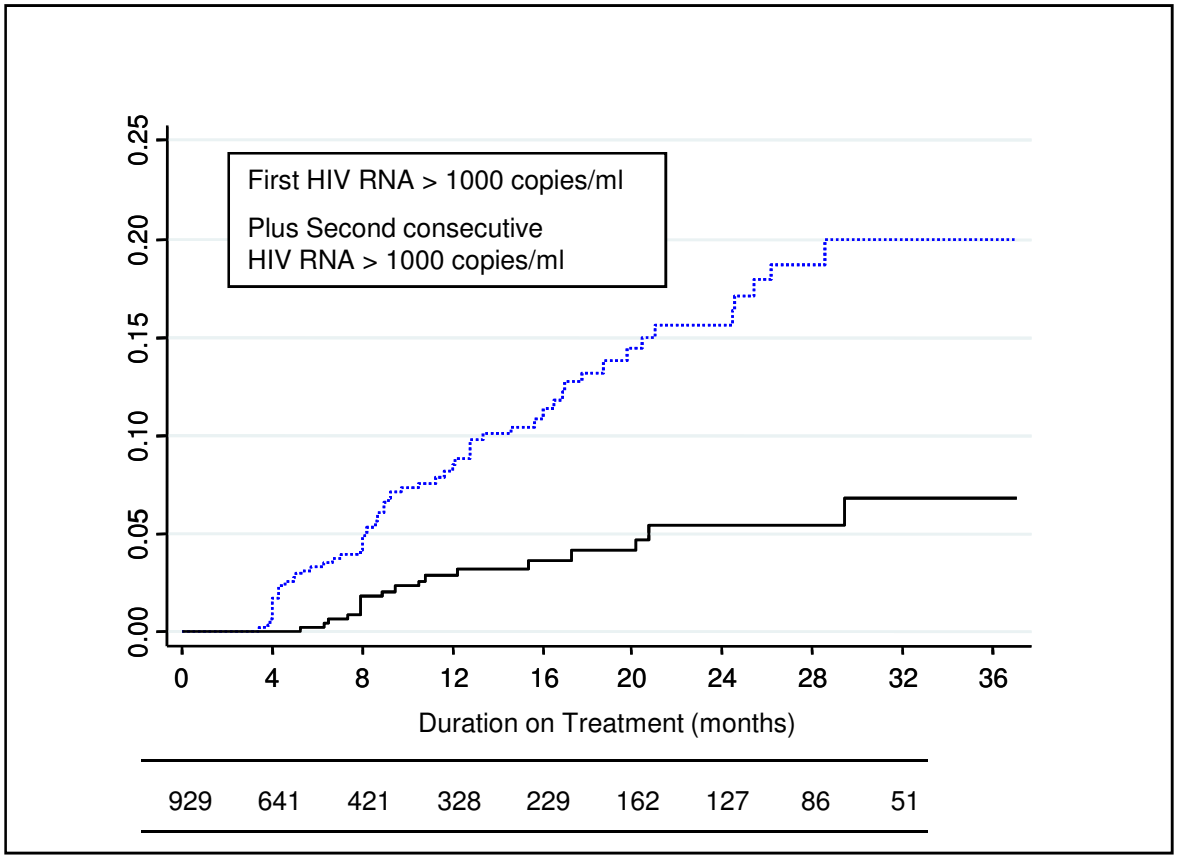
Ncaca, PLoS One 2011

Who is more likely LTFU?

- Youth (van Cutsem)
- Pregnancy (Kaplan 2009)
- Prior virological breakthrough (Orrell 2010).

Adherence interventions can be successful

Kaplan-Meier failure estimate for time to first, then second consecutive HIV RNA level > 1000 copies/ml.



Need **two consecutive** viral loads >1000 copies/ml for failure.

Use the first >1000 copies/ml reading to intervene…

Orrell, Antiviral therapy 2007

What works in RLS

- Africa is better than developed world at adherence.
  (Mills, JAMA 2006 – meta-analysis)

- Review of recent literature - studies with comparator arms (case-control or randomised) and an adherence or biological marker as an outcome. 27 studies from resource-limited settings identified by early 2012.

  Bärnighausen, Lancet ID 2011

  Thompson, Annals 2012

What works in RLS

- Electronic adherence reminder devices, including mobile phone text messages, coupled with clinic contact may be effective tools to improve adherence in resource poor settings and are recommended where feasible. (AI)

4 randomised studies from Africa showed 12-13% adherence benefit in ART-naïve adults.

Varying length (8 weeks to one year); most with feedback.

1 RCT: alarm only showed no benefit

What works in RLS

- Shifting the care for people on ART from doctors to nurses and peer counselors does not have a negative impact on adherence or biological outcome.

Are now 3 randomised studies confirming this…

What works in RLS

- Monthly food supplementation packages improve early adherence to first-line antiretroviral therapy and are recommended. (BII)

Two studies showed substantial improvement in adherence by objective adherence measures (pharmacy return, pill counts) in the first 6 or 12 months on ART.

What works in RLS

- Peer-driven group pre-treatment education benefits adherence in the first 12-18 months of ART. (BIII)

No consistent method (by whom, how many sessions, how long) but all improve adherence.

- Peer support may improve adherence in the first 12-18 months of ART. (BIII)

3 studies, also used DOTS – benefit in terms of adherence, but not biological outcomes

Overview

- Local issues and solutions.
- **New technologies – MEMScaps, Wisepill**
- New approaches – what can we learn from international literature?
- Cases

Technologies used in managing adherence

- Pillboxes: simple and effective intervention and should be widely used – improves adherence by ~4.5% (drop VL 0.35 log)

  Best for intermittent non-adherence (80-90%). Not enough of a reinforcement for those with very poor adherence.

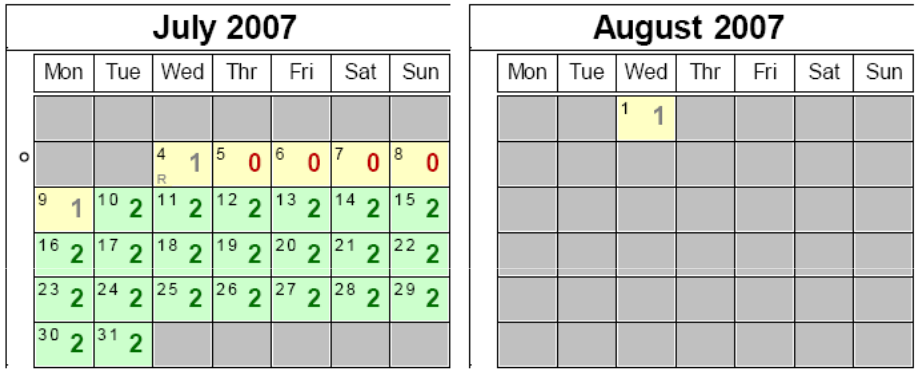
  Pill box of more benefit than changing to once a day therapy. (Petersen, CID 2007)

Technologies used in managing adherence

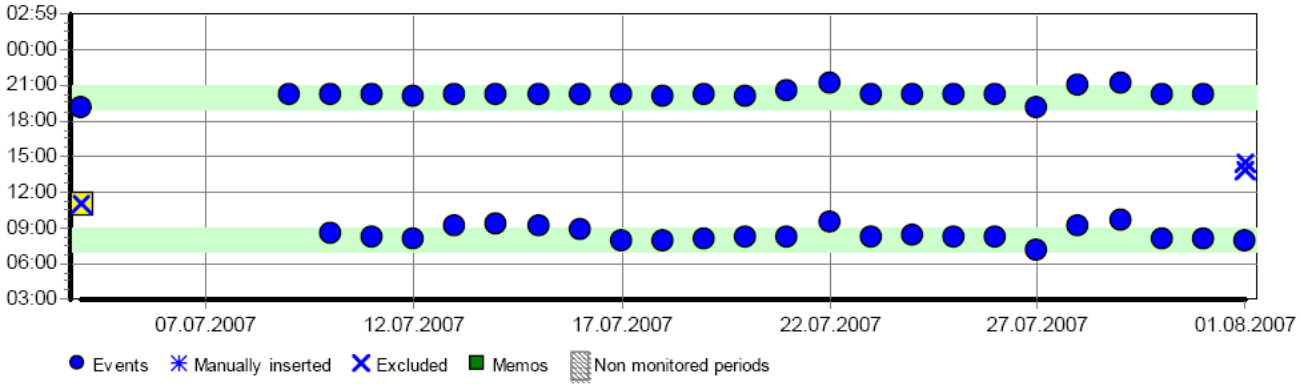
- MEMS caps: considered gold standard for adherence monitoring. Expensive – R800 each + software.

Technologies used in managing adherence

Example of MEMscaps output



Chronology



Missing doses

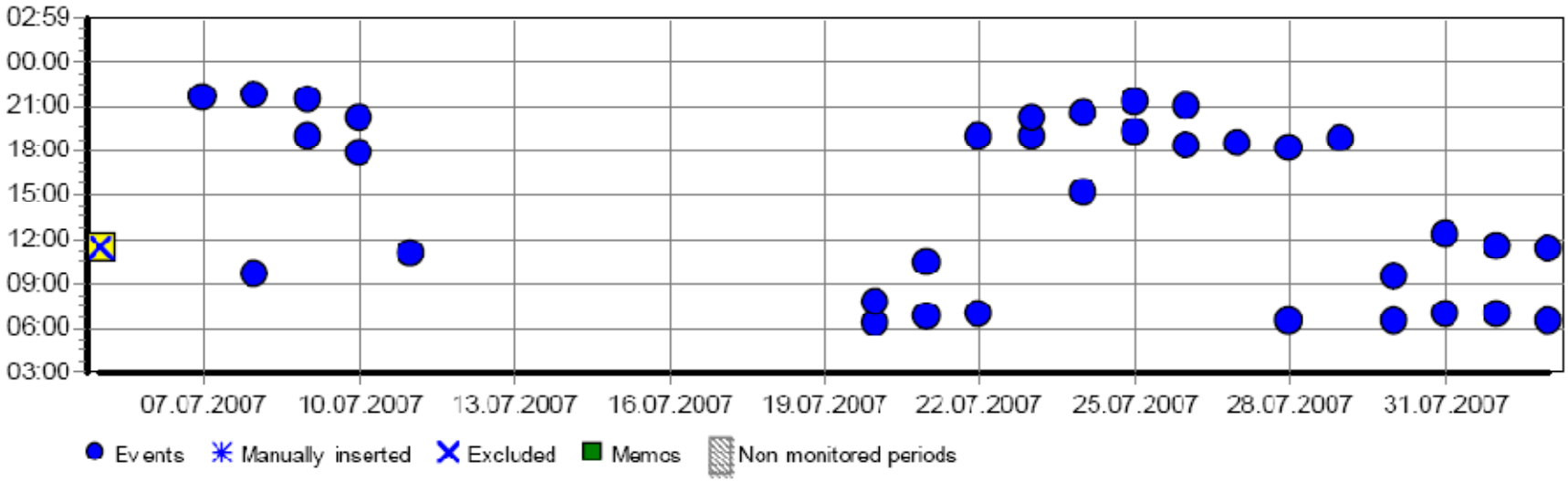
July 2007

Mon	Tue	Wed	Thr	Fri	Sat	Sun
			5 R 0	6 0	7 1	8 2
9 2	10 2	11 1	12 0	13 0	14 0	15 0
16 0	17 0	18 0	19 0	20 2	21 2	22 2
23 2	24 2	25 2	26 2	27 1	28 2	29 1
30 2	31 2					

August 2007

Mon	Tue	Wed	Thr	Fri	Sat	Sun
		1 2	2 2			

Chronology



Missing doses

Technologies used in managing adherence

- Wisepill: South African invention. Allows real-time adherence monitoring by GPRS. Useful in TB and HIV.

  ?for second-line

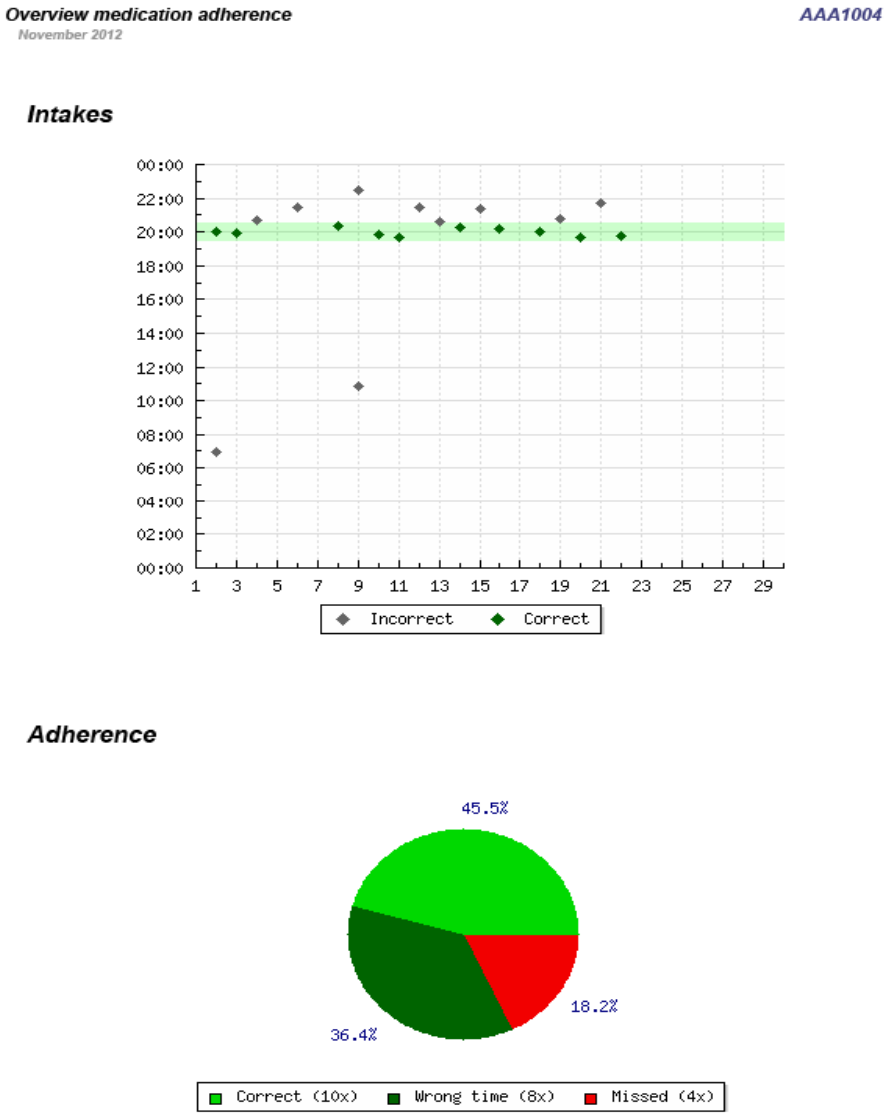
  ?replace viral load monitoring

  Could be developed for

  R120-200 per annum.

Technologies used in managing adherence

- Wisepill report:



Overview

- Local issues and solutions.
- New technologies – MEMScaps, Wisepill
- **New approaches – what can we learn from international literature?**
- Cases

Approaches to managing adherence

Clinical Guidelines

Guidelines for Improving Entry Into and Retention in Care and Antiretroviral Adherence for Persons With HIV: Evidence-Based Recommendations From an International Association of Physicians in AIDS Care Panel

Melanie A. Thompson, MD; Michael J. Mugavero, MD, MHSc; K. Rivet Amico, PhD; Victoria A. Cargill, MD, MSCE; Larry W. Chang, MD, MPH; Robert Gross, MD, MSCE; Catherine Orrell, MBChB, MSc, MMed; Frederick L. Altice, MD; David R. Bangsberg, MD, MPH; John G. Bartlett, MD; Curt G. Beckwith, MD; Nadia Dowshen, MD; Christopher M. Gordon, PhD; Tim Horn, MS; Princy Kumar, MD; James D. Scott, PharmD, MEd; Michael J. Stirratt, PhD; Robert H. Remien, PhD; Jane M. Simoni, PhD; and Jean B. Nachega, MD, PhD, MPH

Annals of Internal Medicine, 2012

Quality of the body of evidence

Quality of Body of Evidence	Interpretation
Excellent (I)	**RCT** evidence without important limitations **Overwhelming** evidence from observational studies
High (II)	RCT evidence with important limitations **Strong evidence** from observational studies
Medium (III)	RCT evidence with critical limitations **Observational** study evidence without important limitations
Low (IV)	Observational study evidence with important or critical limitations

Strength of Recommendations

Strength of Recommendation	
Strong (A)	**Almost all** patients should receive the recommended course of action.
Moderate (B)	**Most** patients should receive the recommended course of action. However, other choices may be appropriate for some patients.
Optional (C)	There may be **consider**ation for this recommendation on the basis of individual patient circumstances. Not recommended routinely.

Monitoring ART Adherence

- Self-reported adherence should be obtained routinely in all patients (II A)
- Pharmacy refill data are recommended for adherence monitoring when medication refills are not automatically sent to patients (II B)
- The following are not routinely recommended:
  - Drug concentrations in biological samples (III C)
  - Pill counts performed by staff or patients (III C)
  - Electronic Drug Monitors for clinical use (I C)

ART Strategies

- Among regimens of similar efficacy and tolerability, once-daily regimens are recommended for treatment-naive patients beginning ART (II B).
- Switching treatment-experienced patients receiving complex or poorly tolerated regimens to once-daily regimens is recommended, given regimens with equivalent efficacy (III B).
- Among regimens of equal efficacy and safety, fixed-dose combinations are recommended to decrease pill burden (III B).

Adherence Tools for Patients

- Reminder devices and use of communication technologies with an interactive component are recommended (I B).
- Education and counseling using specific adherence-related tools is recommended (I A).

Education and Counseling Interventions

- Individual one-on-one ART education is recommended (II A).
- Providing one-on-one adherence support to patients through 1 or more adherence counseling approaches is recommended (II A).
- Group education and group counseling are recommended; however, the type of group format, content, and implementation cannot be specified on the basis of the currently available evidence (II C).
- Multidisciplinary education and counseling intervention approaches are recommended (III B).
- Offering peer support may be considered (III C).

Health Service and Service Delivery Interventions

- Nurse- or community counselor–based care is recommended in under-resourced settings (II B)
- Case management interventions providing resources to address food insecurity, housing, and transportation needs are recommended (III B)
- DAART is not recommended for routine clinical care settings (I A).

Pregnant Women

- Targeted pMTCT treatment (including HIV testing and sero-status awareness) improves adherence to ART for pMTCT and is recommended, compared with an untargeted approach (treatment without HIV testing) in high-HIV-prevalence settings (III B).
- Labour ward–based pMTCT adherence services are recommended for women who are not receiving ART before labour (II B).

Children and Adolescents

- Intensive youth-focussed case management is recommended for adolescents and young adults to improve entry into and retention in care (IV B).
- Pediatric- and adolescent-focused therapeutic support interventions using problem-solving approaches and addressing psychosocial context are recommended (III B).
- Pill swallowing training is recommended and may be particularly helpful for younger patients (IV B).

Mental Health

- Screening, management, and treatment for depression and other mental illnesses in combination with adherence counseling are recommended (II A).

General Recommendations for Future Research

- Comparative research designs, where possible
- Long-term studies of intervention and post-intervention with adherence and HIV biomarker outcomes

Overview

- Local issues and solutions.
- New technologies – MEMScaps, Wisepill
- New approaches – what can we learn from international literature?
- **Cases**

Case 1 – for the clinicians

- MK is a 26 year old woman, 6 months pregnant with her 2nd child. She has been on TDF, 3TC and EFV for a year.
- Her viral load at 4 months was 1250 copies/ml and at a year is 17534 copies per ml. Her tablet counts have varied from 85 – 95%. She had one treatment interruption in her early pregnancy for 6 weeks while in the Eastern Cape over December.

Case 1 – for the clinicians

- List the issues needing to be addressed here.
- Think of all the resources **you** have available and try to address the problems.
- No wishful thinking!

Case 2 – for the clinic managers

After a folder review the CNP in charge of the ART programme notices that 87 of 972 people thought to be in care have not been seen in the clinic for more than 3 months.

A 10% drop in numbers is going to be noticed at district level!

How can this be rectified and prevented from happening again?

Case 3 – for the researchers

People who interrupt treatment and return to care are often given a hard time and frequently default again.

How could you intervene to improve this and how could you assess your intervention?

Case 1 – for the clinicians

- MK is a 26 year old woman, 6 months pregnant with her 2nd child. She has been on TDF, 3TC and EFV for a year.
- Her viral load at 4 months was 1250 copies/ml and at a year is 17534 copies per ml. Her tablet counts have varied from 85 – 95%. She had one treatment interruption in her early pregnancy for 6 weeks while in the Eastern Cape over December.

Case 1 – for the clinicians

Issues:

- Poor and varying pill counts
- Treatment interruption
- Pregnancy – high risk LTFU
- Failing treatment: risk to baby

Case 1 – for the clinicians

Tools:

- pillbox,
- counselors (intensive adherence counselling),
- monthly prescribing,
- peer support at home.

Case 2 – for the clinic managers

After a folder review the CNP in charge of the ART programme notices that 87 of 972 people thought to be in care have not been seen in the clinic for more than 3 months.

A 10% drop in numbers is going to be noticed at district level!

How can this be rectified and prevented from happening again?

Case 2 – for the clinic managers

Issues:

Need to notice when people are missing.

Should we trace those not attending their appointments?

Need to address why this happens – employed people, harangued people, disclosure issues, clinic and staff attitudes etc.

Case 2 – for the clinic managers

Tools:

- Pharmacy dispensing system (iDART / CDU)
- CCWs
- Team building activities

Case 3 – for the researchers

People who interrupt treatment and return to care are often given a hard time and frequently default again.

How could you intervene to improve this and how could you assess your intervention?

Case 3 – for the researchers

Idea:

“Return to care” non-judgemental, exploratory counseling. Specifically trained clinic-based counsellor.

A number of options for study design:

- pre-and post (numbers LTFU and RTC a month);
- stepwise implementation by clinic
- RCT

Summary

- Treatment preparedness and ongoing adherence monitoring and support is key
- Particular groups are at risk of poor adherence and LFTU.
- Retention in care defines the success of our programmes.
- Room for more answers… RCT, biological outcomes, longer duration

Acknowledgements

- Melanie Thompson and IAPAC guideline team
- Dr Jean Nachega for some slides
- Desmond Tutu HIV Centre team

University of Cape Town