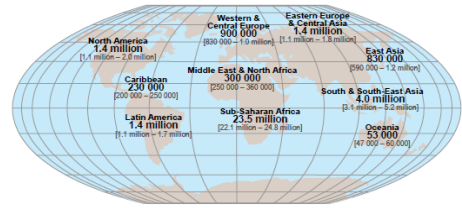


HIV Prevention 2013



Roy M. Gulick, MD, MPH
 Chief, Division of Infectious Diseases
 Professor of Medicine
 Weill Medical College of Cornell University
 New York City January 31, 2013

Adults and children estimated to be living with HIV | 2011



Total: 34.0 million [31.4 million – 35.9 million]

In 2011:

New HIV infections: 2.5 million [2.2, 2.8]

Deaths due to AIDS: 1.7 million [1.5, 1.9]

Adult (aged 15-49) prevalence 0.8%



UNAIDS World AIDS Day Report 2012

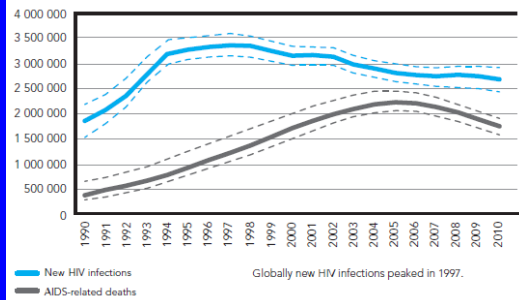
About 7000 new HIV infections a day in 2011

- About 97% are in low- and middle-income countries
- About 900 are in children under 15 years of age
- About 6000 are in adults aged 15 years and older, of whom:
 - almost 47% are among women
 - about 39% are among young people (15-24)

UNAIDS World AIDS Day Report 2012



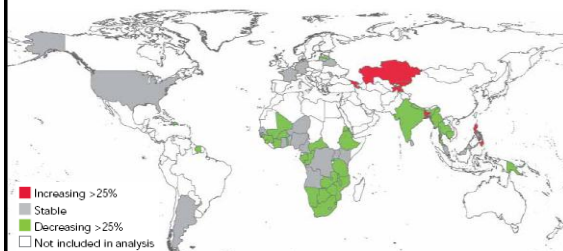
NEW HIV INFECTIONS AND AIDS-RELATED DEATHS



UNAIDS World AIDS Day Report 2011

Changes in the incidence rate of HIV infection, 2001 to 2009, selected countries

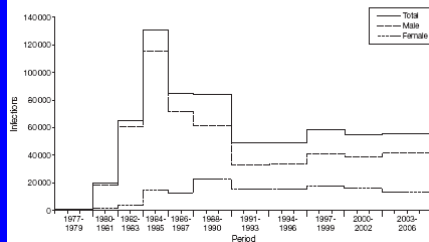
Source: UNAIDS



UNAIDS Report 2010

U.S.: New HIV Infections Per Year

Figure 1. Estimated New Human Immunodeficiency Virus (HIV) Infections, Extended Back-Calculation Model, 50 US States and the District of Columbia, 1977-2006



~50,000 per year

Hall JAMA 2008;300:520

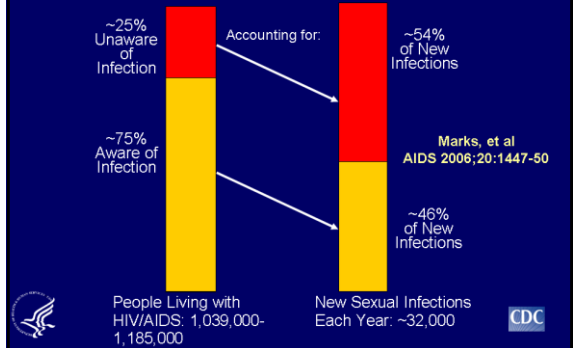
Prejean PLoS One 2011;6:e17502

U.S. Preventive Services Task Force (UPSTF)

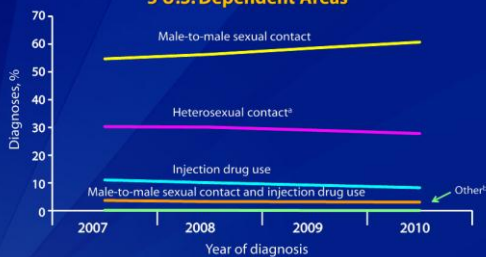
Draft Recommendations (12/12)

- Screen adolescents and adults ages 15 to 65 for HIV infection.
- Younger adolescents and older adults who are at increased risk should also be screened.
- This is a grade A recommendation.

Awareness of Serostatus Among People with HIV and Estimates of Transmission



Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2007–2010—46 States and 5 U.S. Dependent Areas



Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing risk-factor information, but not for incomplete reporting.

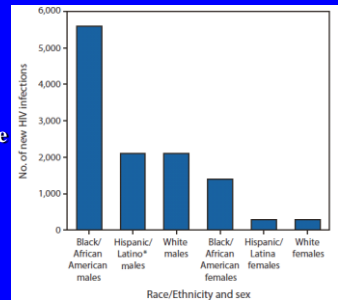
* Heterosexual contact with a partner known to have, or to be at high risk for, HIV infection.

† Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.



New HIV infections among 13–24 year olds — U.S., 2010

- Of all new HIV infections in 2010, 26% occurred in 13–24 year olds
- 60% are not aware they are infected
- 72% were MSM
- 20% were heterosexuals
- 13% were IDU



MMWR 2012;61:971-976

HIV Prevention Strategies

Adapted from Ramjee IAS Meeting 2006, #TUPL02

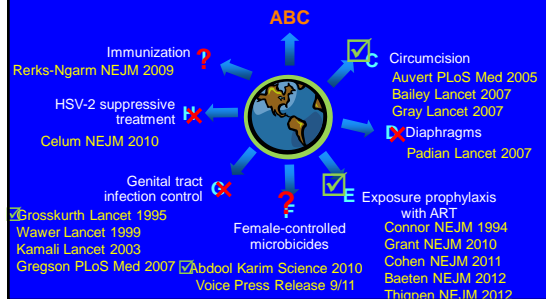
Abstain, Be faithful, Condoms,
Counseling & testing

ABC

HIV Prevention Strategies

Adapted from Ramjee IAS Meeting 2006, #TUPL02

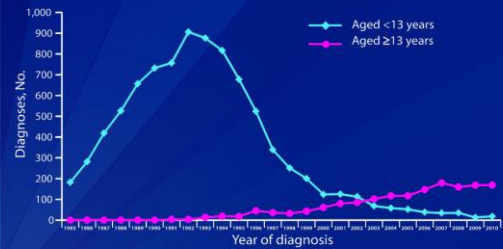
Abstain, Be faithful, Condoms,
Counseling & testing



Antiretroviral Therapy (ART) and Prevention

- Vertical transmission – Prevention of Mother to Child Transmission (PMTCT)
 - AZT alone reduced MTCT from 25% to 8% **Connor NEJM 1994**
 - Current ART reduces MTCT to <0.5%

AIDS Diagnoses among Perinatally Infected Persons, 1985–2010—United States and 6 U.S. Dependent Areas

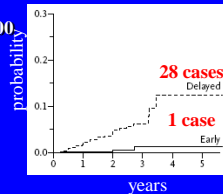


Note. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.



HPTN 052: ART as Prevention

- 1,763 discordant couples (97% heterosexual) in Africa, Asia, Americas with HIV+ with CD4 350-550
- HIV+ partner randomized to start cART immediately or deferred until CD4 <250
- DSMB Interim analysis:
 - 90% on ART had HIV RNA <400
 - 40 incident cases of HIV
 - 29 linked genetically to partner
 - 96% reduction in transmission!



Cohen #MOAX0102 and NEJM 2011;365:493

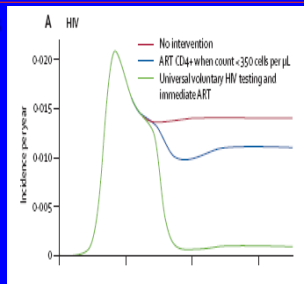
Guidelines for Initiation of ART

	AIDS/ sympts.	CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS '12 www.aidsinfo.nih.gov 3/27/12	YES	YES	YES	YES	YES
IAS-USA '12 Thompson JAMA 2012;308:387	YES	YES	YES	YES	YES
BHIVA '12 Writing Group, Williams HIV Med 2012 Sep;13 Suppl 2:1-6 www.bhiva.org	YES	YES	YES	certain patients	certain patients

Mathematical Modeling Universal Test and Treat

Utopian Assumptions

- South Africa
- High uptake of annual testing by all individuals >15 year old
- Treat all HIV+
- 99% decrease in infectiousness
- High adherence and low failure with 1st line ART



Granich P et al Lancet 2009; 373:48-57

Prevention and Antiretroviral Therapy (ART)

Post-exposure prophylaxis (PEP)

- AZT reduced risk of seroconversion in HCW by 81% in a case-control study **Cardo NEJM 1997**
- Current CDC Guidelines recommend 2- or 3-drug antiretroviral treatment for 4 weeks following exposure

PHS Guidelines 1/21/05 and 9/30/05
<www.aidsinfo.nih.gov>

Definitions

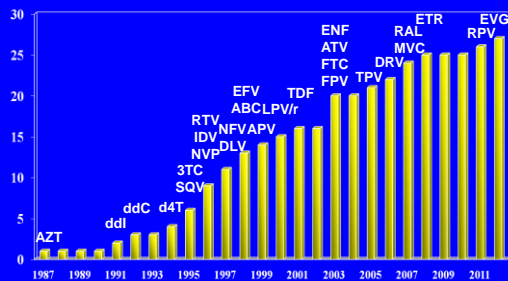
- **Microbicides**
 - compounds that can be applied inside the vagina or rectum to protect against sexually transmitted infections (STIs), including HIV
 - formulated as gels, creams, films, or suppositories
<http://who.int/hiv/topics/microbicides/microbicides/en/>
- **PREP**
 - Pre-exposure prophylaxis
 - Strategy of administering ART to uninfected, at-risk individuals

Criteria: DAIDS Working Group

- Safe
- Penetrates target tissues
- Protects against HIV infection in tissues
- Long-lasting activity for convenient dosing
- Unique resistance profile or high barrier to resistance
- No significant drug-drug interactions
- Possibly, not a part of current rx regimens
- Affordable, easy to use and implement

DAIDS Working Group Report 4/09

Antiretroviral Drug Approval: 1987 - 2013



Antiretroviral Drugs: 2013

nucleoside/tide RTIs (NRTIs)

- zidovudine (ZDV, AZT)
- didanosine (ddI)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TDF)

NNRTIs

- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)

protease inhibitors (PIs)

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- fosamprenavir (FPV)
- tipranavir (TPV)
- darunavir (DRV)

entry inhibitors (EIs)

- enfuvirtide (T-20, fusion inh)
- maraviroc (MVC, CCR5 inh)

integrase inhibitors (IIs)

- raltegravir (RAL)
- elvitegravir (EVG)

Antiretroviral Drugs: 2013

nucleoside/tide RTIs (NRTIs)

- lamivudine (3TC)
- emtricitabine (FTC)
- tenofovir (TDF)

entry inhibitors (EIs)

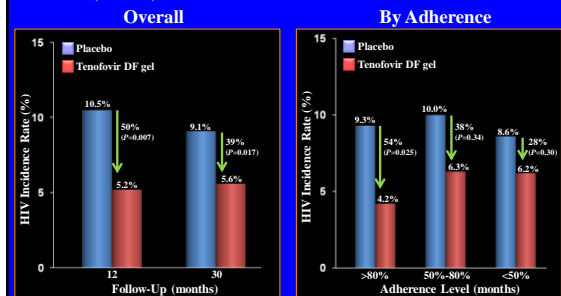
- maraviroc (MVC, CCR5 inh)

integrase inhibitors (IIs)

- raltegravir (RAL)

CAPRISA 004: 1% vaginal TFV gel

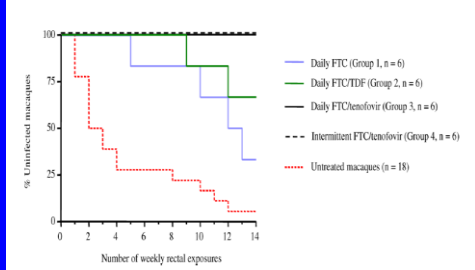
Study population: 18-44 year old South African HIV-uninfected women (N=889)



Abdool Karim Q, et al. *Science*. 2010;329:1168-1174.

PREP: Animal Model

Effect of daily and intermittent PREP in monkeys: SHIV rectal challenge



Garcia-Lerma PLoS Med 2008

TDF and FTC/TDF for PrEP

Optimal PrEP candidates:
potency, safety, tolerability, and convenience



= TDF (tenofovir)

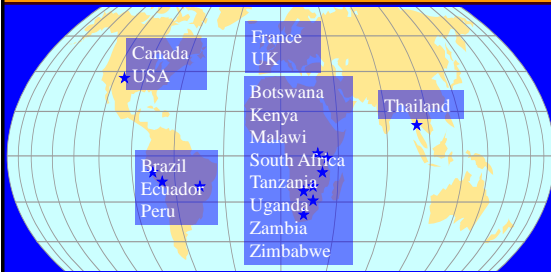


= FTC/TDF (co-formulated emtricitabine + tenofovir)

Potential concerns:

- Used widely; preferred first-line treatment
- Drug resistance
- Toxicities: renal, bone
- Cost >\$10,000/year

Completed and Current Studies of Oral PrEP

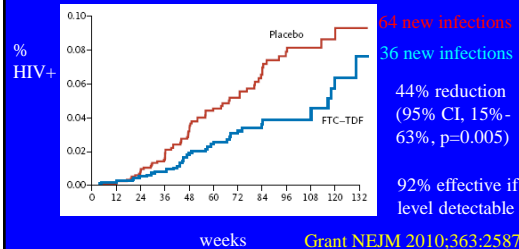


14 studies and projects, up to 16 countries
32,000+ participants

IPREX: PrEP in MSM

Phase III study of PREP with TDF/FTC or placebo

Study population: HIV uninfected MSM or transgendered women from South America, South Africa, Thailand and U.S. (N=2499)
Ten were HIV-infected at enrollment

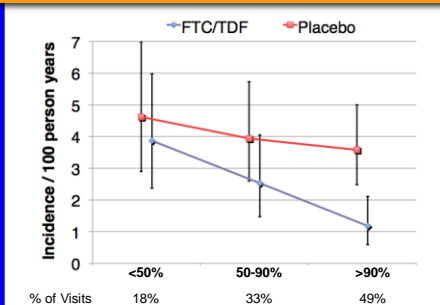


92% effective if drug level detectable

Grant NEJM 2010;363:2587

IPREX: Recorded Adherence and Efficacy

Slide #29



Efficacy 16% 34% 68%

95% CI -54 - 54 -20 - 64 36 - 84

Grant et al. CROI 2010

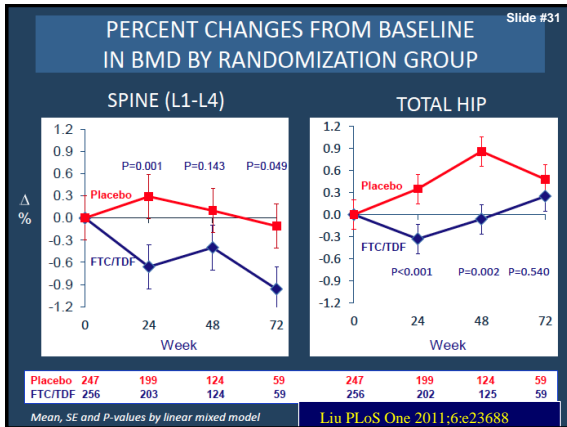
Adverse events

Slide #30

Adverse Event	TDF/FTC		Placebo		P value
	n (%)	Events	n (%)	Events	
Creatinine Elevated	25 (2%)	28	14 (1%)	15	p=0.08
Headache	56 (4%)	66	41 (3%)	55	p=0.10
Nausea	20 (2%)	22	9 (<1%)	10	p=0.04
Weight Decreased	27 (2%)	34	14 (1%)	19	p=0.04



Grant NEJM 2010;363:2587



Slide #32

Drug Resistance

Genotypic Resistance	HIV Status at Enrollment			
	Infected (N=10)		Uninfected (N=100)	
	Placebo N=8	FTC/TDF N=2	Placebo N=83	FTC/TDF N=48
65R	0 (0%)	0 (0%)	0 (0%)	0 (0%)
70E	0 (0%)	0 (0%)	0 (0%)	0 (0%)
184I	0 (0%)	1 (50%)	0 (0%)	0 (0%)
184V	1 (13%)	1 (50%)	0 (0%)	0 (0%)
TDF Resistance	0 (0%)	0 (0%)	0 (0%)	0 (0%)
FTC Resistance	1 (13%)	2 (100%)	0 (0%)	0 (0%)

Grant NEJM 2010;363:2587

- ### CDC Guidance for PrEP for MSM: (Interim; 1/27/11)
- **Before starting:**
 - document HIV Ab- and r/o acute infection
 - CrCl ≥ 60 , screen for STIs and HBV
 - **Rx TDF/FTC 1 po daily X 90 days**
 - provide risk reduction, adherence counseling, condoms
 - **On treatment:**
 - check HIV Ab every 2-3 months
 - check BUN/creat at 3 months and yearly
 - risk reduction, condoms, STI assessments/rx
- <http://www.cdc.gov/hiv/prep/index.htm>

PrEP Studies

Study (reference)	Study population	Design	Results: Reduction in HIV Infection
CDC – TDF-2 Thigpen NEJM 2012;367:423	1200 Botswana adults (45% women)	TDF/FTC vs. placebo	TDF/FTC: 63%
Partners PREP Baeten NEJM 2012;367:399	4758 discordant Kenya and Uganda couples	TDF vs. TDF/FTC vs. placebo	TDF: 67% TDF/FTC: 75% (86-90% if TFV detected)

- ### U.S. Food and Drug Administration (FDA) Approval of PrEP (7/16/12)
- U.S. FDA approves Truvada for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-infection in adults at high risk.

PrEP Studies

Study (reference)	Study population	Design	Results: Reduction in HIV Infection
FEM-PREP Van Damme NEJM 2012;367:411	2120 women in Kenya, South Africa, Tanzania	TDF/FTC vs. placebo	TDF/FTC: 6% (overall adherence was <40%)
VOICE Press release 9/29/11	>5000 women in South Africa, Uganda, Zimbabwe	1% TDF gel vs. placebo gel; oral TDF vs. TDF/FTC vs. placebo	DSMB: TDF oral arm stopped early due to fertility; TDF gel not effective

CDC Guidance for PrEP for heterosexuals (8/9/12)

- Targeted to high-risk individuals, such as those with an HIV+ sex partner.
- It is critical to take PrEP consistently.
- Discuss risks/benefits with pregnant women or those trying to conceive; data are incomplete and mostly from HIV+ women.
- PrEP is not a stand-alone solution.
- Individuals must be confirmed HIV- prior to PrEP; monitor HIV status, side effects, adherence, and risk behaviors.

WHO Guidance for PrEP (7/20/12)

- ensure that people seeking PrEP are HIV-
- encourage continued condom use
- check for pre-existing medical conditions (e.g. kidney or bone disease)
- monitor for adverse events
- help people adhere to daily medication
- ensure uninterrupted supply
- test regularly for HIV infection and check for drug resistance if infection is found
- gather cost-benefit information

Ongoing PrEP Efficacy Studies

Study/Location	Sponsor	Population	N	PrEP Agent	Status
Bangkok TDF Study Thailand	CDC	IDU	2413	TDF	Fully enrolled: Results End of 2012
VOICE / MTN 003 South Africa, Uganda, Zimbabwe	MTN / NIH	women	5029	TDF/FTC	Fully enrolled: Results 2013
FACTS 001 South Africa		women	2200	TFV gel	Enrolling: Results 2014

IPREX F/U: Modeling PK

- Using data from a separate PK study (STRAND):
 - 2 doses/week: 76% risk reduction
 - 4 doses/week: 97% risk reduction
 - 7 doses/week: 99% risk reduction

Anderson Sci Transl Med 2012;4:151ra125

Antiretroviral Drugs: 2012

nucleoside/tide RTIs (NRTIs)

- lamivudine (3TC)
- emtricitabine (FTC)
- tenofovir (TDF)

entry inhibitors (EIs)

- maraviroc (MVC, CCR5 inh)

integrase inhibitors (IIs)

- raltegravir (RAL)

HPTN 069: NEXT-PrEP

Slide #42

- Design: Phase II, 4-arm, multisite, study
- Study population (N=400)
 - At-risk HIV-negative gay men
- Study Treatment:
 - MVC monotherapy
 - MVC + FTC
 - MVC + TDF
 - TDF + FTC (control)
- Duration: 48 weeks
- Primary endpoint: Grade ≥ 3 toxicities; time to study treatment discontinuation

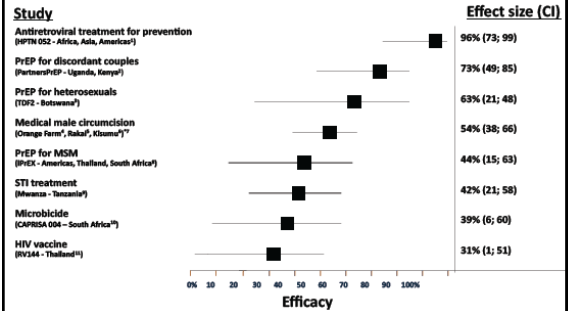
Amendment:
Cohort of 200 women

Newer PrEP Agents

Slide #43

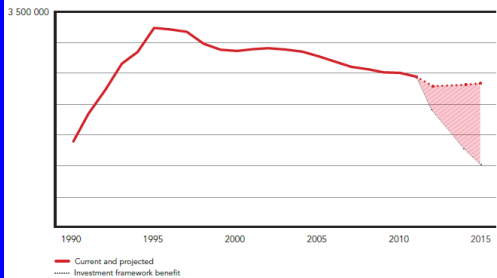
	mechanism	dosing route	dosing frequency	PrEP stage
rilpivirine-LA	NNRTI	injectable, SC	once monthly	Phase 1 pilot
S/GSK 1265744 (*744)	integrase inhibitor	injectable, SC	once monthly (or less)	Phase 1 pilot
ibalizumab	CD4 attachment inhibitor	injectable, SC	once every 1-4 weeks	Phase 1 pilot

HIV Prevention Strategies



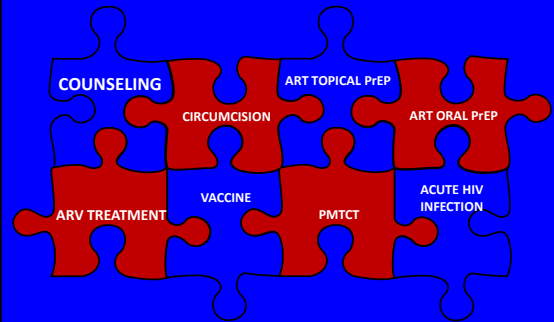
Abdool Karim IAS 2011

GLOBAL NEW HIV INFECTIONS



UNAIDS World AIDS Day Report 2011

HIV Prevention 2012



Clinton Speech November 8, 2011



Conclusions

- Newer prevention strategies are needed, particularly in MSM.
- PrEP was effective in reducing HIV infections in MSM and heterosexual men.
- Conflicting data in heterosexual women (CDC TDF-2 and Partners PrEP vs. Fem-PrEP and Voice).
- Updated CDC guidelines anticipated.
- Logistical and implementation issues.
- **Additional research in progress.**

Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Medical College of Cornell University
- AIDS Clinical Trials Group (ACTG)
- Division of AIDS, NIAID, NIH
- The patient volunteers!



Cornell HIV Clinical Trials Unit

