HIV/AIDS Clinical Research in Africa

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Objectives

- Identify major clinical research activities conducted in Africa which are important in the control of HIV/AIDS in Africa within the last two years
- Comment on the utilisation of results of research in the strategies for the fight against HIV/AIDS

HIV epidemic in Sub Saharan Africa 2002-07

(UNAIDS)

Year	Adults and Children living with HIV	Adults & children newly infected	Adult prevalence	Adult and child deaths
2002	29.4m	3.5m	7.3%	2.4
2003	24.9 m	2.6m	7.3%	1.9m
2004	25.4 m	2.6m	6%	1.9m
2005	25.8 m	2.7m	7.2%	2.0m
2006	24.7 m	2.8 m	5.9%	2.1m

Comments on general trends of the Epidemic

- In 2006, reported declines in national prevalence in Kenya and Zimbabwe and urban areas in Burkina Faso (UNAIDS, 2006)
- Increase in people on ARV: from 100,000 in 2003 to 810,000 in 2005 (BOT, KEN, RSA, UGA, ZAM)
- UNAIDS carried out adjustments in data in the 2006 report due to corrections arising from country population based studies.

Plan

- Research in prevention
- Research in oral manifestations of HIV/AIDS
- Research in drugs
- Research in mother to child transmission
- Research in paediatric AIDS

Prevention

- Adolescents still at high risk:
  - Knowledge not satisfactory : only 16.2% of youths in Nigeria knew cause of HIV/AIDS
  - This situation is more worrying among the girls who tend to be as ignorant as the boys
  - Educated mothers do not offer sex education to their girls because of residual traditional barriers, religious inhibitions, reliance on books and teachers

(Mbugua, N 2007; Soc Sci & Med 64: 1079–1089)

Male circumcision

- RCT in Orange Farm Trials in RSA followed by NIH studies in KEN and UGA provided evidence of an over 50% protective benefit re HIV infection
  (Sawires *et al.* ***Lancet 2007; 369: 708–13)***
- If uptake were 100%, an estimated 2 million infections and 0.3m deaths in SSA would be averted in 10 years,. and up to 5.7 m new infection in 20y; In Orange Farm a 50% uptake would avert 32-53k new infections over 20 y

Male circumcision: challenges

- Integration and scaling up in existing health system (WHO/UNAIDS)
- Social and cultural barriers (age done)
- Training, availability and sterility of instruments, costs (about USD 25/procedure)
- Effect on HIV control programmes and women uncertain (see Rakai- Gray et al, Lancet 2007; 369: 643-56)

See Abdool Karim, BMJ 2007; 335: 4-5

HIV vaccines: challenges

- CTL responses for multiepitope DNA vaccines not sustained in vaccinees.
- Ab to B-cell epitopes result in rapid evolution of HIV escape mutants, error prone replication and high frequency of recombination during RT resulting in rapid change in the HIV genome (variants during normal infection- escape mutants)
- Peptide vaccines are poorly immunogenic (small size).
- Recombinant subunit gp120 is poorly protective for natural HIV infections.

INNOVATIVE's Vaccine programme

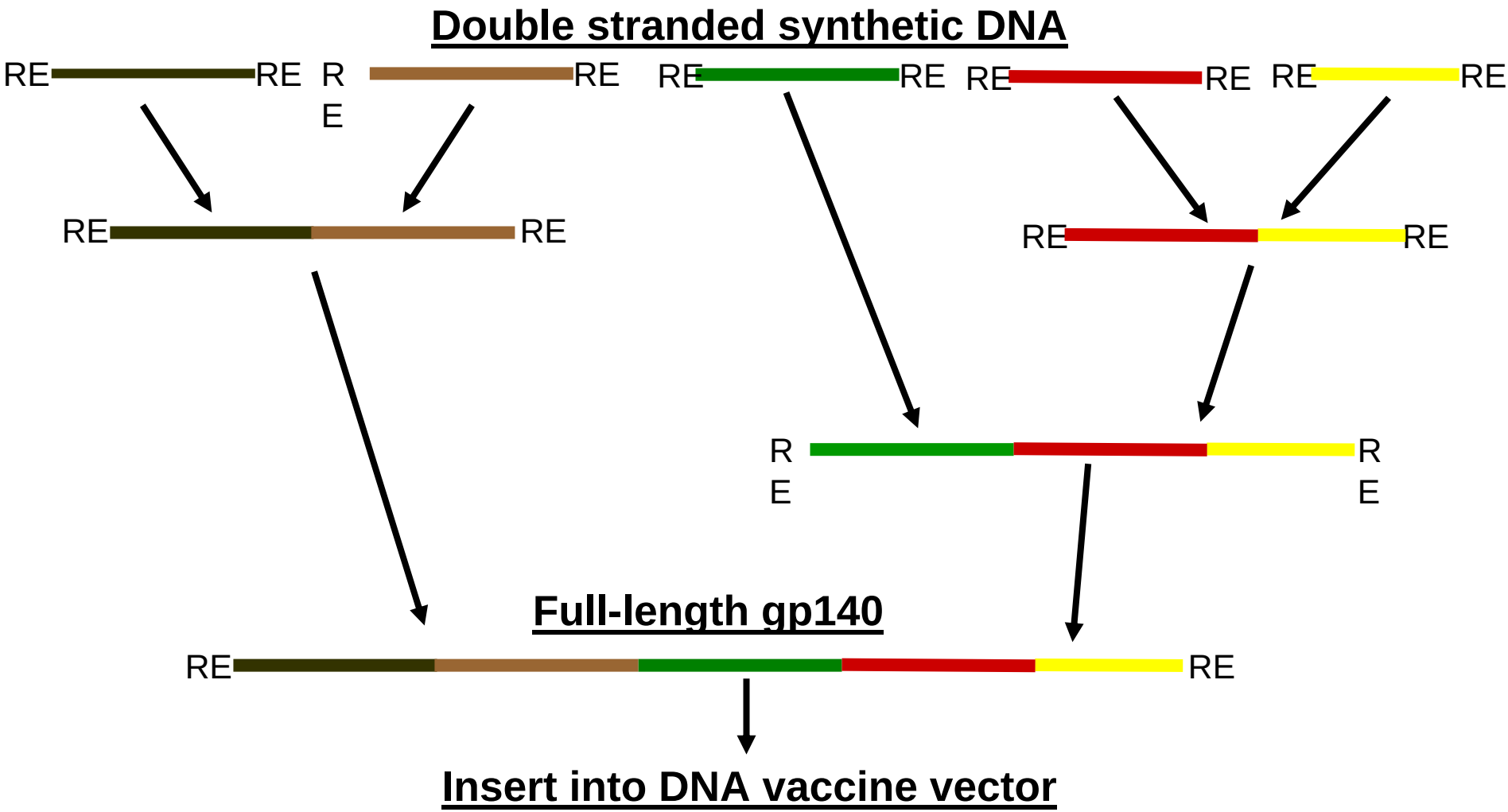
- Agwale et al in Nigeria have embraced the challenge to produce locally relevant vaccines
- Their goal is "to develop an HIV vaccine capable of inducing broadly neutralizing antibodies and CTL to prevent and treat HIV infection"

Ab neutralization titer against heterologous viruses

	Plasmas/Sera (IC50 1/diln)																						
	FU	MD	NB	NIPRD/CBN /015802	NIPRD/CBN /017302	NIPRD/GSH /0169/02	NIPRD/GSH /0408/02	NIPRD/SHC /030402	NIPRD/SSC /0175/02	NIPRD/VRC/ 001	NIPRD/VRC/ 033	NIPRD/VRC/ 034	NIPRD/VRC/ 039	NIPRD/VRC/ 043	NIPRD/VRC/ 044	NIPRD/VRC/ 045	NIPRD/VRC/ 055	NIPRD/VRC/ 059	NIPRD/VRC/ 061	NIPRD/VRC/ 064	NIPRD/VRC/ 067	NIPRD/VRC/ J/O	NIPRD/VRC/ Jacob/Onah
MD	33	146	70			166	193	52	89	339	139	224	67	100	59	61	107	34	61	247	347		205/190*
NIPRD/GSH/0169/02	43	305	44			96	189	122	28	324	97	219	47	152	42	42	55	37	51	176	336		213/136
NIPRD/SSC/0175/02	37	305	58			159	323	56	79	398	172	295	47	86	39	57	107	46	90	351	591		234/237
NIPRD/VRC/033	45	183	117	360	23	90	194	59	206	288	97	349	57	88	46	70	57	44	33	237	350	172	210/135
NIPRD/VRC/033	<20	151	192			55	177	24	177	331	24	143	23	41	22	35	22	<20	22	232	462	155	
NIPRD/VRC/039	31	316	115			120	290	79	49	406	424	290	50	513	45	100	65	48	56	250	438		263/258
NIPRD/VRC/045	52	122	97			143	211	101	321	335	356	227	61	221	79	84	86	64	61	214	368		290/182
NIPRD/VRC/055	46	343	152			126	234	79	479	337	269	345	70	153	44	95	168	33	55	188	495		311/256
NIPRD/VRC/059	20	198	189	241	35	78	329	190	255	617	226	257	21	253	34	33	91	37	44	471	398	232/257	
NIPRD/VRC/061	45	516	63			195	242	181	181	445	529	220	79	210	64	63	141	55	133	292	411		202/169
NIPRD/VRC/J/O-1	39	63	68	168	60	58	324	27	176	414	44	205	21	28	30	23	41	<20	26	224	496	164/184	
NIPRD/VRC/J/O-2	23	106	46	283	30	72	241	46	220	368	40	140	21	56	27	24	25	<20	27	203	443	196/239	
NIPRD/VRC/Jacob/Onah	49	111	99			178	177	112	201	371	182	271	81	88	39	36	74	37	47	212	394		270/186
NL43 - CONTROL - Replicate #1	64	2165	1399	2564	1457	1375	2808	1048	1219	1372	708	1295	178	384	247	654	1116	516	218	594	1141	521	518
NL43 - CONTROL - Replicate #2	74	2730	1078			1480	3800	1320	1302	1552	715	1448	210	328	272	713	982	476	214	709	1476	591	449
JRCSF - CONTROL - Replicate #1	42	377	<20	243	<20	115	167	192	257	319	187	246	75	258	65	71	96	63	80	189	312	155	219
JRCSF - CONTROL - Replicate #2	<20	200	49			27	174	74	163	249	33	131	<20	95	<20	21	<20	<20	<20	149	315	171	151
aMLV - control - Replicate #1	61	90	<20	243	<20	79	135	60	23	399	192	323	100	150	112	96	138	102	73	248	378	145	284
aMLV - control - Replicate #2	53	61	31			<20	171	42	22	228	20	164	<20	43	35	42	30	22	25	186	295	214	203

*IC50s from replicate runs

Synthetic gp140 Nigerian gene construction strategy(Subtypes CRFO2_AG and G-Bivalent)



Innovative Findings

- **All vaccine constructs induced Ag specific antibodies after the 3rd immunization as demonstrated by WB using lysates of cells transiently transfected with the corresponding pORT1-antigen expressing constructs.**

- ***Gag* construct induced a very strong antigen specific CD8-positive T cell-mediated response as detected by FACS and ELISPOT**

- ***Gp140* constructs did not induced cellular immune responses probably because the peptides used represented only a small fragment of *env V3* region and also the experiment was restricted to Balb/c mice.**

Oral manifestations

- Oral diseases in HIV may worsen the evolution of HIV, affect drug compliance and the nutritional status of subject.
- Most care givers do not know how to manage oral manifestations of HIV
- Programmes for teaching care givers should be extended to traditional healers

Rudolph et al 2007; Curations, 30: 56-61 (Wits)

Research in drugs

- *The CYP2B6 polymorphism 983T>**C*** (either alone as *CYP2B6*18 or linked with 785A>G as* the *CYP2B6*16 allele) was found in Africans and* African-Americans but not in Caucasians and Asians.
- This is *associated with significantly higher mean* plasma efavirenz levels in the African HIV patients.
- Outcome of treatment with efavirenz may prove different in subjects ([*CYP2B6*6 +] [983T>C –])*

Mehlotra,RK et al (2007) Br J Clin Pharmacol, *DOI:10.1111/j.1365-2125.2007.02884.x*

Importance of CYP2B6

- ARVs efavirenz (EFV) and nevirapine (NVP) are commonly used in national programmes
- Principally metabolized by the human hepatic cytochrome P450 2B6 (CYP2B6) which *CYP2B6* gene (chromosome 19) is highly polymorphic- 28 alleles (*CYP2B6*1A* [wild type] to *CYP2B6*28*
- The variant allele *CYP2B6*6* has shown a 50% decrease in the mean enzyme activity
- Studies show *CYP2B6*6* allele associated with 2- to 3-fold higher plasma EFV concentrations, 50–60% lower EFV clearance, and increased neuropsychiatric side-effects

Research in drugs

- ART adherence factors
- Methods of expansion of ART
- Cotrimoxazole in opportunistic infections not always effective
- Role of microbicides in prophylaxis
- Cryptococcus resistance to fluconazole

Cryptococcus resistance to Fluconazole

- Christine Bii (KEMRI) worked with 80 clinical isolates of *C neoformans (Bii et al 2006,* Mycoses 50: 25–30)
- Broth microdilution susceptibility testing to amphotericin B (AMP), flucytosin, fluconazole (FLC), itraconazole (ITC) and miconazole (MCZ)
- Only 23.8% of the strains were susceptible to FLC with 65% susceptible dose-dependent (SDD) and 11.2% resistant
- Antifungal drug resistance surveillance as HIV case management requires prophylactic use of FLC.

Mother to Child Transmission

- Maternal knowledge of MTCT of HIV tends to influence choice of feeding
- MTCT may be reduced in situations of exclusive breast feeding as opposed to mixed feeding or exclusive bottle feeds
- Urgent need for review of UNICEF-WHO-UNAIDS guidelines on HIV and breastfeeding

Coutsoudis et al.1999 Lancet 354: 471-6;
Doherty et al. 2007 AIDS 21: 1791-7

Paediatric AIDS

- HIV infected children need thoughtful and sensitive management on HAART
- Outcomes of paediatric HAART cohorts show promise (Sinikithemba Clinic, KZN)
- Challenges: GI infections and oral drugs, TB co-infection, HIV in caregivers
- Standard of care: CD4 and Viral Loads

(Reddi, A et al *BMC Pediatrics 2007,* ***7:13 doi:10.1186/1471-2431-7-13)***

Conclusion

- Important studies on HIV/AIDS in Africa on prevention, drugs, MTCT and AIDS in children have been done with true participation of African scientists;
- Still a wide gap between knowledge and implementation overall;
- Integration of activities into the health system, training and retention of personnel, rolling out of strategies remain key challenges

Messages

- Relevance of research to solving problems encountered on the ground
- Rolling out of interventions need to be accompanied by relevant studies to make them meaningful
- HIV vaccines: what lessons may we learn?
- EDCTP may indeed help **building** bridges for better health

Thank you