

1 **A CRITICAL ANALYSIS OF THE EVIDENCE
CONSIDERED PROOF THAT NEVIRAPINE PREVENTS
MOTHER-TO-CHILD TRANSMISSION OF HIV**

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www.virusmyth.net/aids/perthgroup
www.theperthgroup.com/aids

PLEASE REFER TO LAST SLIDE BEFORE PROCEEDING

This presentation has been prepared by Eleni Papadopulos and the Perth Group and several other colleagues. The subject is an analysis of the data claimed to prove nevirapine an effective agent for the prevention of mother to child transmission of HIV. The presenter is Dr. Val Turner from the Department of Emergency Medicine, Royal Perth Hospital.

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MOTHER TO CHILD TRANSMISSION OF HIV AND ITS PREVENTION WITH AZT AND NEVIRAPINE

A CRITICAL ANALYSIS OF THE EVIDENCE



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Consistsingof 204 A4 paqes, 137,000 words,
several graphs, 491 references and eleven
appendices. Appendix XI is a comprehensive
review of the evidence for the existence of HIV
-including 213 references.

<http://aidsmyth.addr.com/report/news/newperthpaper.htm>

Members of the audience may wish to note that this presentation is an amplification of one part of our recently published monograph. Unfortunately time does not permit an analysis of every possible factor and most unfortunately of all, the data said to prove heterosexual transmission. Such proof is obviously a prerequisite for any scientific evaluation of this topic. Members of the audience who wish to study this and other relevant aspects are cordially invited to visit the link displayed at the bottom right hand side of the slide.

This presentation will focus on the HIVNET 012 study published on the 4th of September 1999 in the *Lancet*. However, before we do that, there are several matters we need to address.

Slide number 3 please

EVIDENCE REQUIRED

- Proof of HIV infection of mothers and babies
- Proof of drug efficacy
- High benefit/risk profile

Any doctor, institution or indeed any government contemplating the use of particular drug for a specified disease is placed under an ethical obligation to be satisfied, beyond all reasonable doubt, that patients are definitively diagnosed with the disease in question, that the drug under consideration is capable of producing the intended result, and that the anticipated benefit is far outweighed by any undesirable effects and toxicities the drug may possess.

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DIAGNOSIS OF HIV INFECTION

MOTHERS

ANTIBODY TESTS

- Blood sample
- HIV proteins
- Technique (ELISA and Western blot)

The diagnosis of HIV infection is performed differently in mothers and infants.

Mothers are said to be HIV infected if a blood sample contains antibodies which react with particular proteins deemed unique to a retrovirus HIV. These antibody reactions may be demonstrated using either an ELISA or Western blot technique. We will not be discussing the ELISA as most experts do not regard reactive ELISAs as proof positive of HIV infection. That is, the ELISA lacks specificity. Rather we will focus on the Western blot which is said to be virtually 100% specific and if positive, proof of HIV infection.

Slide number 5 please

HIV PROTEINS

Montagnier 1983 & Gallo 1984

On the basis of isolation/purification of a unique, novel retrovirus from supernatant obtained from cell co-cultures of tissues of AIDS patients and banded in a sucrose density gradient

1.16 gm/ml band = “Purified virus”

Barré-Sinoussi, F *et al.* (1983). “Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS).” *Science* **220**: 868-71.

Gallo, RC *et al.* (1984). “Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS.” *Science* **224**: 500-503.

The identity of antigens used in HIV antibody tests is based on research published in 1983 by Montagnier and in 1984 by Gallo. Both scientists and their respective colleagues claimed to have isolated HIV from co-cultures of tissues of AIDS patients and achieved purification by passing supernatants of these cultures through a sucrose density gradient. The material which banded at a density of 1.16 gm/ml was claimed to be the “purified virus”, that is, purified HIV.

Although leading retrovirologists had agreed at least a decade earlier that electron micrographic confirmation of the existence and purity of retroviral-like particles is an essential component of retrovirus isolation, neither Montagnier nor Gallo published electron micrographs to justify their respective claims. Thus at the time HIV was discovered, and in fact for the next fourteen years, it was not possible to conclude that “purified HIV” contained any particles, be they retroviral, viral or of any other morphologies, pure or impure. The EMs that were published in the Montagnier and Gallo papers, not of “purified virus” but of unpurified cultures, revealed a few particles with the appearances of type-C particles. These were said to be HIV yet nowadays HIV is classified as different genus. That of a Lentivirus.

Regardless of the omission of electron micrographs, both groups designated certain proteins in the banded material as HIV in origin, that is, HIV specific. The proof for this claim is not extraction from retrovirus particles but that from the many proteins present in the 1.16 gm/ml band these were the few proteins that reacted with antisera from AIDS patients.

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HIV PROTEINS

“...analysis of the proteins
demands mass production
and purification”

Montagnier interview at Pasteur Institute July 1997

Continuum (1998) 5: 30-34. www.virusmyth.com/aids/data/dtinterviewlm.htm

In an interview conducted on July 18th 1997 at the Pasteur Institute, Montagnier stated that analysis of the HIV proteins demands mass production and purification of HIV, but...

Slide number 7 please

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MONTAGNIER DID NOT ISOLATE/PURIFY HIV

“I repeat, we did not purify”

Montagnier interview at Pasteur Institute July 1997
[Continuum \(1998\) 5: 30-34. www.virusmyth.com/aids/data/dtinterviewlm.htm](http://www.virusmyth.com/aids/data/dtinterviewlm.htm)

That he and his colleagues did not purify HIV.

Despite these obvious scientific difficulties, laboratory scientists used some of the many proteins banding at 1.16 gm/ml to develop antibody tests for proving HIV infection. The veracity of this procedure remains virtually unchallenged. Not even the discovery of HIV proteins in non-AIDS-related tissues, including tissues from healthy, no-risk individuals, led any HIV expert to question the validity of these tests. Certainly, the majority of clinicians appear unaware of these findings.

Slide number 8

HIV PROTEINS IN NORMAL HUMAN PLACENTA
p18/p24/p120

“Placentae from 25 normal term pregnancies were collected by vaginal delivery...Antigens gp120 and p17 were identified in normal chorionic villi...Antigen p24...in villous mesenchymal cells...localized to HLA-DR positive cells”

Faulk, WP *et al* (1991). “HIV proteins in normal human placentae.” [American Journal of Reproductive Immunology](#) **25**: 99-104.

From this abundant evidence here is an example we might consider germane to the present problem. Three of the most significant HIV proteins are present in normal placental tissue from healthy, non-HIV-infected women.

Slide number 9 please

THE “HIV” PROTEINS p41/p120/p160

Montagnier considers p41 to be cellular actin

p160, p120 in “HIV” WB are oligomers of p41

Pinter AW *et al* (1989). “Oligomeric structure of gp41, the transmembrane protein of human immunodeficiency virus type 1 Journal of Virology **63**: 2674-9.
Zolla-Pazner S *et al* (1989). Reinterpretation of Human Immunodeficiency virus Western Blot patterns. NEJM **320**:1280-1281.

And to continue this theme, from the very beginning and at present, Montagnier regards p41 not as an HIV protein but the ubiquitous cellular protein, actin.

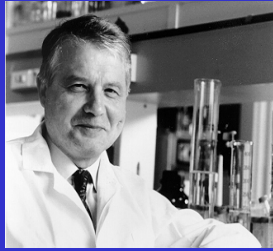
In 1989 Pinter and colleagues proved that the p120 and p160 proteins in the HIV Western blot are not distinct HIV proteins but oligomers of p41. That is, composed of an integral number of subunits of p41. In another paper researchers expressed concern about mistaken diagnoses based on the mistaken belief that p120 and p160 are individually distinct HIV proteins.

One should note that on this basis an African who has Western blot bands corresponding to the location of any two of the p41, p120 and p160 proteins, in reality has antibodies reactive with his own actin. Yet these are the criteria the WHO define as a positive Western blot in Africa.

Let us return briefly to the Montagnier interview. This was conducted by Djamel Tahj and the text was later published by the late Huw Christie in the English magazine *Continuum*. There are videotapes of this interview in circulation. Eleni Papadopoulos and I brought a copy to the Presidential AIDS Advisory Panel which we gave to Professor Mhlongo.

During the interview Professor Montagnier was asked why he did not publish electron micrographs of his “purified virus”.

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MONTAGNIER ON MONTAGNIER AND GALLO

No particles “typical of retroviruses” in “purified virus”

“Did Gallo purify?”

“Gallo?..I don’t know if he really purified.
I don’t believe so”



Montagnier interview at Pasteur Institute July 1997

[Continuum \(1998\) 5: 30-34. www.virusmyth.com/aids/data/dtinterviewlm.htm](http://www.virusmyth.com/aids/data/dtinterviewlm.htm)

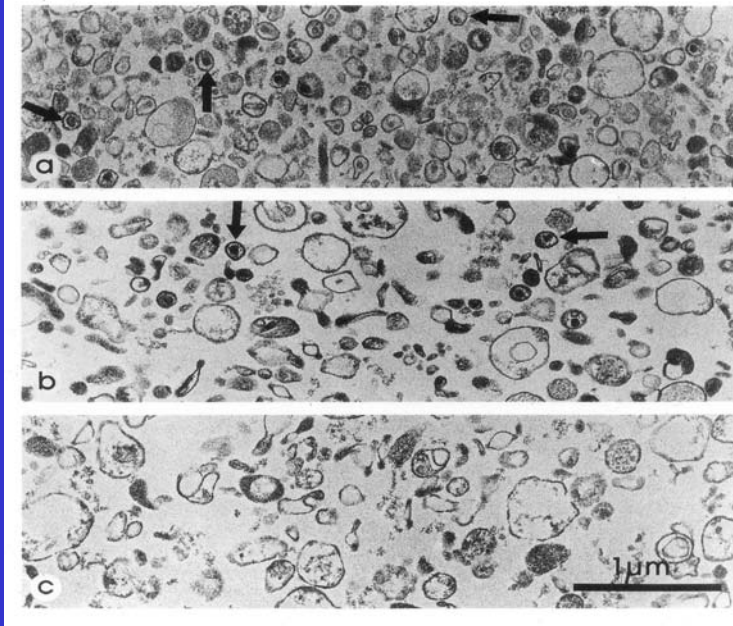
Montagnier’s response to this question is staggering. He replied that despite what he called a “Roman effort” no one at the Pasteur Institute could find particles in the just discovered “purified virus” that had the appearances of retroviral particles.

Pressed further he did not accept that Gallo’s laboratory had purified HIV.

In the same year two groups of researchers, one a European collaboration and the other American, provided the first electron micrographs of what has long been assumed to be “purified HIV”, as well as additional evidence that the HIV proteins have a cellular origin.

Slide number 11 please

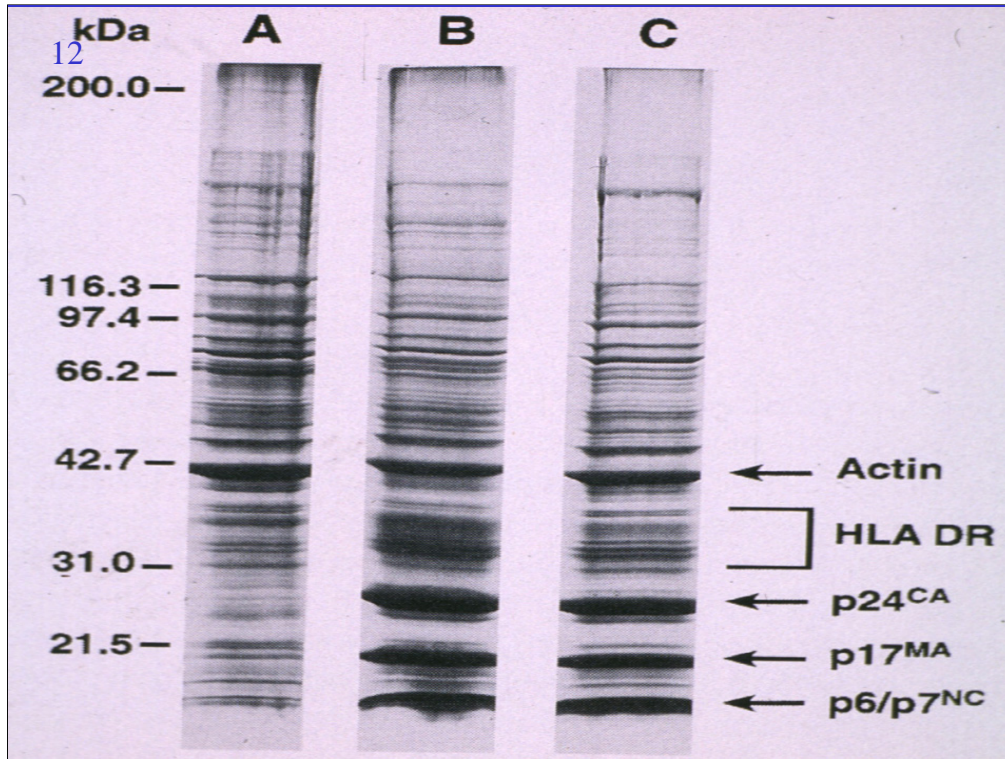
11



Gluschankof P *et al.* (1997). Cell membrane vesicles are a major contaminant of gradient-enriched human immunodeficiency virus type-1 preparations. *Virology* **230**: 125-133.

In the top two micrographs we see, and for the first time 14 years after its discovery, what purified HIV actually looks like. In other words, these are the first published electron micrographs of the 1.16 gm/ml sucrose density gradient, banded material from which proteins and nucleic acids are obtained for use as diagnostic reagents. These were published in *Virology* in March 1997 by a Franco/German consortium led by Pablo Gluschankoff. One does not need more than a glance, and one certainly does not need to be a scientist, to know that regardless of how this material is constituted, it is not pure. The authors themselves admit this and in fact labelled the top two pictures as “purified vesicles” and not purified HIV. Despite this, they still claimed that “purified vesicles” contain a few particles which are not vesicles but are HIV. However, these particles, indicated by the arrows, do not have the requisite morphology and two such particles are present towards the right in the lower picture, which is material similarly obtained from a non-HIV-infected culture.

Slide number 12 please



This slide is taken from the second, the US study, published by a group led by Dr. Julian Bess, under the auspices of the National Cancer Institute, which provides material for the US Vaccine program. It is a gel electrophoresis of the proteins in the 1.16 gm/ml band.

Lane A is the pattern obtained from a non-HIV-infected peripheral blood mononuclear cell preparation which, under the EM, reveals cellular material similar to the previous slide. Bess and his colleagues refer to this material as “cellular microvesicles”.

Lane B is an HIV-infected, malignant cell line, the H9 cell line, which under the EM, also consists of cellular microvesicles and other cellular debris including a number of particles with diameters twice the HIV particles in the previous European slide and twice the diameter of any known retrovirus particle, as well as lacking other morphological features of retrovirus particles. These are Bess and his co-workers’ “HIV”.

Lane C is an HIV-infected H9 clone with similar appearances.

As far as the protein patterns are concerned, there is only one pattern. There are no qualitative differences between the three strips. Although there are darker bands, that is, quantitative differences between the three, including differences between Lanes B and C, which are said to be infected with the same virus, the same protein bands exist across all three cultures. Significantly there is a prominent actin band present in all three cultures in the region where we would expect to find p41, which

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Bess et al
National Cancer Institute USA

“We agree that you can come to the conclusion from gel electrophoresis patterns that there are only quantitative differences between HIV and [cellular] microvesicles”

“We have been unsuccessful in separating microvesicles from HIV”

Bess, J. W., R. J. Gorelick, et al. (1997). Email correspondence August 2000 re Microvesicles are a source of contaminating cellular proteins found in purified HIV-1 preparations. *Virology* 230: 134-144

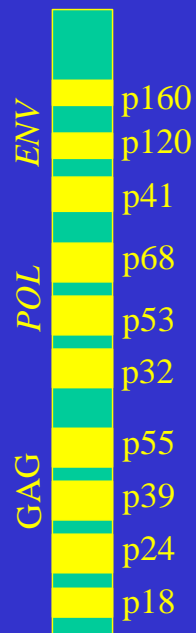
Dr. Bess agreed with us

He said “you can come to the conclusion from gel electrophoresis patterns that there are only quantitative differences between HIV and [cellular] microvesicles”, that is, between cellular proteins and HIV proteins”.

In conclusion, there is ample evidence that the antigens used in the HIV antibody tests are not proteins belonging to a unique retrovirus HIV but are in fact all cellular proteins.

Slide number 14

Western blot strip



Here are the proteins as they appear in the HIV Western blot strip. Although not in electrophoretic order. What we must consider is why patients may have or develop antibodies which react with these proteins, and why is there a correlation between these reactions and certain antediluvian diseases which, for the past two decades, have constituted a new syndrome defined as AIDS.

We also need to bear in mind why these antibody reactions should be so particularly prevalent in Africans compared to say Americans, and why almost equally in African women and men, but in American women and men.

Slide 15

15 AUTO-ANTIBODIES IN HIV/AIDS PATIENTS

Immune complexes, rheumatoid factor, anti-cardiolipin, anti-nuclear factor, anti-cellular, anti-platelet, anti-red cell, anti-actin, anti-DNA, anti-tubulin, anti-thyroglobulin, anti-albumin, anti-myosin, anti-thymosin, anti-lactoferrin, anti-TNF- α , anti-beta-2 glycoprotein I, anti-prothrombin, anti-neutrophil cytoplasmic, anti-ssDNA, anti-RNA, anti-histones, anti-nuclear antigen SS-A, anti-mitochondrial, anti-reticulin, anti-smooth muscle, anti-gut epithelial cell, anti-lymphocytic ganglioside, anti-Fab, anti-protein S, anti-brain proteins, anti-synthetic peptides of ubiquitinated histone H2A, anti-Sm-D antigen, anti-U1-A RNP antigen, anti-60 kD SSA/Ro antigen, anti-histone H1 and anti-histone H2B antibodies.

Anti-lymphocyte auto-antibodies in 87% of seropositives.

One possibility, for which there is abundant evidence, is that the antibodies are antibodies directed against cellular proteins. In other words, autoantibodies. This is a list of a few of the autoantibodies that have been found in the sera of AIDS patients. A MEDLINE search will reveal many more.

But there are also other reasons which have nothing to do with retroviruses to account for a positive Western blot.

Slide 16

ANTIBODY CROSS-REACTIVITY

- Hypergammaglobulinaemia (predicts seropositivity)*
- Antibodies directed against fungi and mycobacteria cross-react with HIV proteins
- Fungal and mycobacterial diseases are the indicator diseases present in 90% of AIDS patients
- Kashala *et al* 1995 advised caution using Western blot in high prevalence mycobacterial areas

*Brenner, B., S. Schwartz, et al. (1991). "The prevalence and interaction of human immunodeficiency virus and hepatitis B infections in Israeli hemophiliacs." Israel journal of medical sciences 27: 557-561.

Despite the acronym acquired immune deficiency, AIDS patients typically have high levels of all antibodies. That is, they have hypergammaglobulinaemia. Given that all antibodies have propensities for cross-reactivity, indeed this is the explanation AIDS experts provide to account for reactive but not positive ELISAs, as well as non-diagnostic or indeterminate Western blots, there is every reason to hypothesise the plethora of antibodies present in AIDS patients, with their attendant cross-reactivities, could account for many if not all positive Western blot tests, including those caused by autoantibodies. There is certainly no evidence to counter this possibility. In fact hypergammaglobulinaemia predicts HIV seropositivity.

AIDS patients are also infected with many infectious agents. For example, fungi and mycobacteria account for nearly 90% of all AIDS diagnoses. There is also plenty of evidence that antibodies directed against these agents react with the HIV antigens, both the so called envelope and internal proteins.

No doubt most are aware of the data published by Kashala from Uganda in 1995 which led to caution using the HIV ELISA and Western blot in mycobacterial prevalent areas. Significantly, in their paper Kashala and his coworkers published a series of Western blots from leprosy patients which would be reported positive anywhere else in the world including Australia, which has the most stringent criteria of all. Yet Kashala and his colleagues claimed these patients were not HIV infected because they did not have two glycoprotein bands, which by themselves are sufficient to diagnose an African HIV infected.

This explanation of antibody reactivity leads to the prediction that amongst individuals who are sick, that is, amongst those who have reasons for producing

No. OF SPECIMENS TESTED	No. HIV-1 POSITIVE	PERCENT HIV-1 POSITIVE*					
		ALL PATIENTS	NON-HISPANIC			MEN	WOMEN
			WHITE	BLACK	HISPANIC	25-44 YEARS OLD	25-44 YEARS OLD
17							
2897	225	7.8	1.6	10.1	4.0	21.7	7.4
4406	248	5.6	—	6.5	4.9	18.4	7.8
1968	63	3.2	3.3	3.9	2.7	13.3	3.5
1720	29	1.7	1.1	6.5	—	7.1	0.7
5380	48	0.9	0.6	1.9	—	3.2	0.8
3299	87	2.6	1.3	4.4	1.5	7.7	3.3
3823	73	1.9	1.8	2.2	—	1.8	2.4
4275	75	1.8	0.4	2.6	—	5.7	0.8
2698	70	2.6	2.5	3.5	1.5	9.2	1.3
2864	30	1.0	0.7	1.1	—	4.3	0.6
2989	18	0.6	0.3	0.8	—	1.8	0.6
5394	21	0.4	0.5	0.2	—	1.8	0.1
5272	15	0.3	0.2	0.2	—	0.9	0.0
5327	7	0.1	0.1	0.2	—	0.6	0.0
3364	4	0.1	0.1	0.0	—	0.7	0.0
2678	3	0.1	0.1	0.2	—	0.7	0.0

These are the results of a never followed up, never repeated, study from the US published in the *New England Journal of Medicine* in 1990.

HIV antibody tests including the Western blot were performed on 89,547 blood samples collected from patients at 26 US hospitals over a six month period. The patients were meticulously selected to avoid testing any patient in an AIDS risk group or with AIDS. Even patients with meagre risks such as gun shot and knife wounds were excluded. The HIV seropositive rate at some hospitals was impressive. Up to 21.7% of men and 7.8% of women aged 25-44 years were found positive.

In terms of retrovirus which in the US in 1990 was, and still largely is, restricted to certain identifiable groups, and predominantly men, these data make no sense. Why are the seroprevalence rates so high in no risk individuals and why are a third of positive tests in women?

In our view, these data represent the authentic explanation for a positive HIV test in Africa. That is, illness from a large variety of causes which are not retroviral. The only differences between the US and Africa is that in America diseases are not so prevalent while hospitals are.

Slide 18

HIV WESTERN BLOT STRIP		AFR	AUS	FDA	RCX	CDC 1	CDC 2	CON	GER	UK	FRA	MAC	
EMV	p160	ANY 2	ANY 1	ANY 1	ANY 1	p160/ p120 AND p41	p160/ p120 OR p41	p160/ p120 OR p41	ANY 1	ANY 1	ALL 3	3 WEAK BANDS OR ANY STRONG BAND	
	p120												
	p41												
POL	p68	NONE ESSENTIAL	ANY 3 GAG OR POL	p32	ANY 1	AND	AND	OR	p32	ANY 1 GAG OR POL	p32		ANY 1
	p53												
	p32												
p55													
p39													
p24													
GAG	p24	p24	ANY 1	AND	ANY 1	AND	AND	OR	p24	ANY 1 GAG OR POL	p24		ANY 1
	p18												

Even if we discount everything said so far, as physicians, how can we accept the assertion of the Centers for Disease Control, that the HIV Western blot possesses “extraordinary” specificity. How can we reconcile this statement when the criteria for a positive test vary so enormously between countries and institutions, and even between laboratories in the same city?

How can a man with two antibody bands be HIV infected in New York City but not in Sydney, Australia?

How can an African man be positive with a just a p41 and p120 band, while his brother or sister in Australia with the same bands, or even additional bands, for example, a p32 and p24 band, would not be positive?

This slide illustrates 11 different sets of criteria for diagnosing a positive Western blot. Can any of us imagine 11 sets of criteria for the diagnosis of myocardial infarction on an electrocardiogram? Or tuberculosis on a CXR? Is it possible to have a heart attack or TB in the UK but to have this negated merely by crossing the English channel?

How can doctors practice medicine under such circumstances? How can public health officials compare data? And most importantly, how can we subject mothers and babies to these tests and claim proof of heterosexual and mother to child transmission?

GOLD STANDARD

HIV ITSELF

HIV ISOLATION/PURIFICATION

This dilemma could have been solved many years ago if scientists had validated the antibody tests against a gold standard.

The only scientific gold standard for proving the specificity of an antibody test for HIV infection, is HIV itself. This means performing an experiment to compare the presence of absence of antibody reactivity with the presence of absence of what we wish to measure. That is, the virus, HIV, as determined by isolating it.

But there is no such evidence and at present could not be because no one has presented evidence for HIV isolation. Rather, when we analyse what HIV experts such as Montagnier and Gallo actually present as isolation, the data consist of a collection of non-specific findings, including antibody/antigen reactions, all of which have non-retroviral, non-viral and other non-microbial causes, and which have been reported from material which does not even contain retroviral-like particles.

Slide 20

“HIV” positive

What may a scientist conclude?

- Present or likely illness; similar to raised ESR or C-reactive protein
- No proof = HIV infection

What may a scientist conclude?

We agree with the HIV/AIDS experts that a positive HIV antibody test is a risk factor for the development of illness, at least in the AIDS risk groups. Our disagreement is the underlying cause of a positive test. We have argued the tests are non-specific and should be regarded in the same manner as an elevated erythrocyte sedimentation rate or C-reactive protein. Physicians find these to be extremely useful investigations. The ESR for example predicts many diseases and, like serial antibody titres, response to treatment. But no one imagines that diseases such as tuberculosis or osteomyelitis are caused by red cells clumping together.

In our view in the mid 1980s laboratory scientists serendipitously discovered an ESR-like test but in their haste to find the cause of a new syndrome, and in disregard for scientific principles, recommended its general use as a diagnostic agent for a retrovirus which was never isolated. And which in reality exists only because of this antibody test.

Slide 21

ANTIBODY DIAGNOSIS IN CHILDREN

Additional problem

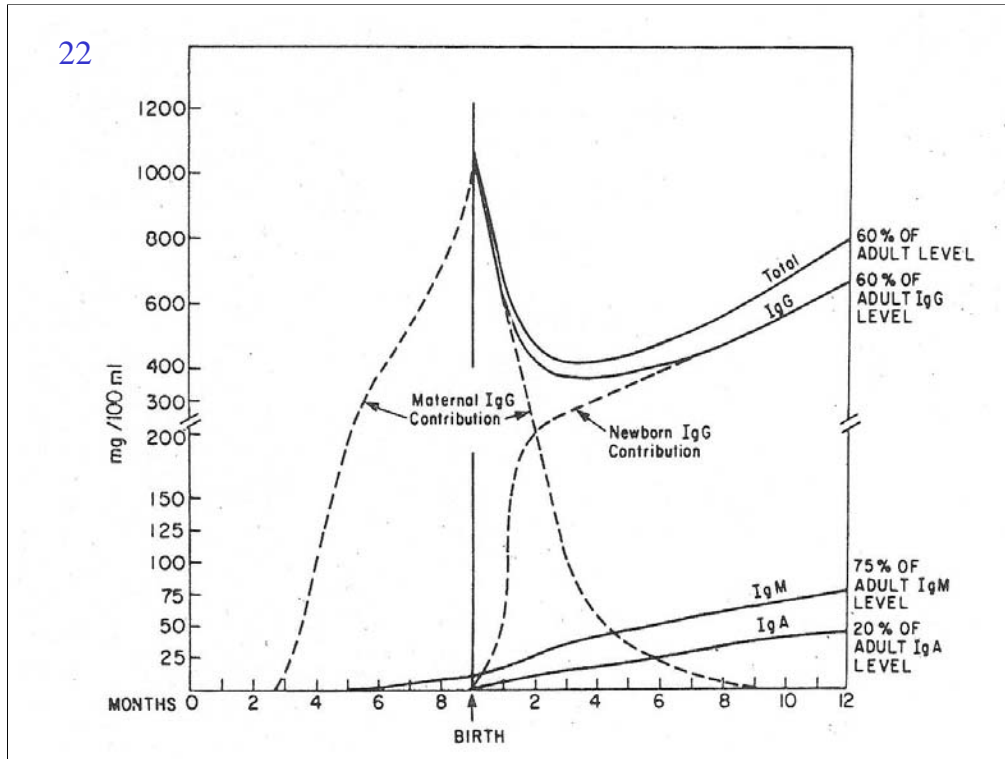
Persistent of maternal antibodies in infant

Regardless of how HIV antibody tests are interpreted in mothers, there is an additional problem in children.

Everyone accepts that maternal IgG immunoglobulin is transferred via the placenta from mother to infant and increasingly in the latter weeks of pregnancy.

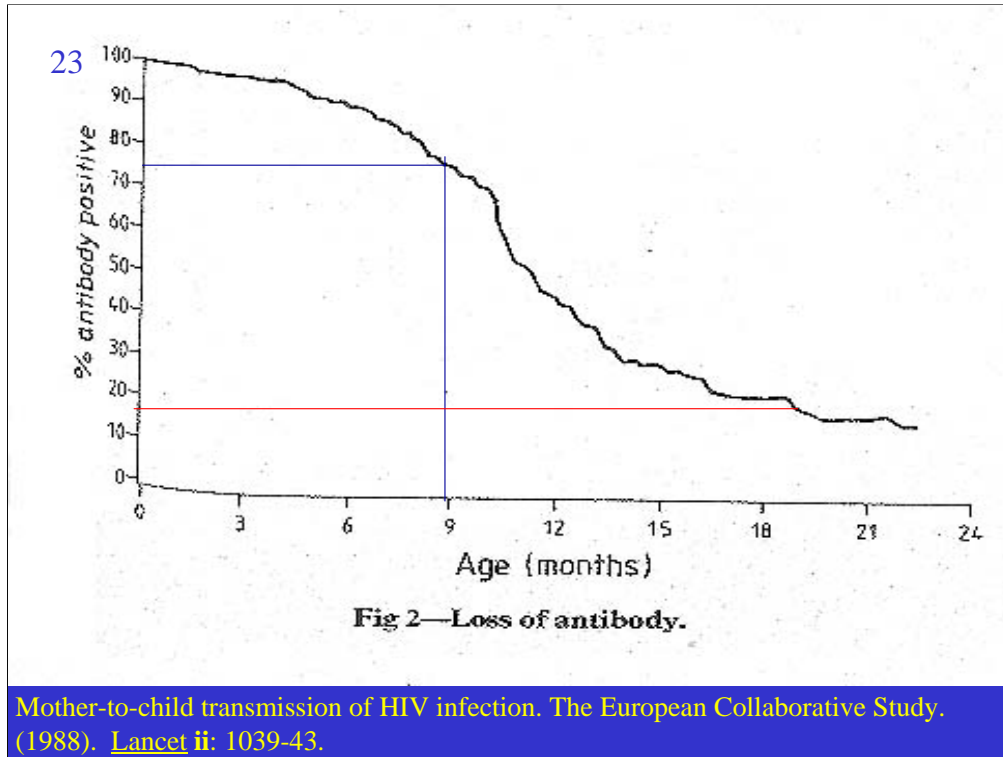
Slide 22

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In this slide the tent shaped, dashed line illustrates that at delivery, infant IgG antibody levels approximate maternal IgG levels and thereafter decline to zero over the next several months as maternal IgG is catabolised. The disappearance of the mother's IgG antibodies has an exponential decay with a half life of approximately 30 days. By 9 months of age the mother's antibodies have totally disappeared from her child's circulation.

Slide 23



This slide is from a study published in the *Lancet* in 1988 and is the only study to report the disappearance of infant HIV seropositivity over time. There were 271 children in this study, all born to mothers from 8 centres in Europe.

We see that because of the presence of maternal IgG, 100% of offspring of all HIV seropositive mothers are seropositive at birth.

By nine months of age approximately 25% of the children have seroreverted. The HIV experts attribute this to the disappearance of maternal HIV antibodies from the infant's circulation. By 21-22 months 15% have not seroreverted which the HIV experts explain as infant HIV antibodies representing the proportion of infants infected by their mothers.

In the scientific literature the only justification one can find for the prolonged persistence of maternal, IgG HIV antibodies over all others is that published by the Centers for Disease Control. In 1987 the CDC convened a panel of consultants representing the American Academy of Pediatrics and eight other disciplines to develop a classification system for HIV infection in children [1] At this conference “Most of the consultants *believed* that passively transferred maternal HIV antibody could sometimes persist for up to 15 months” but cited no evidence permitting identification and critical examination of the reasons for what all but the minority of experts “*believed*” (italics ours). Presumably the CDC was not concerned with the implications of the minority view.

This view of the CDC is even more bizarre given that in 1991 Parekh, who works at

ANTIBODY TESTS

WHO “Currently available HIV antibody tests are extraordinarily accurate, both in terms of sensitivity and specificity”

www.niaid.nih.gov/spotlight/hiv00/default.htm

Abbott Laboratories

“At present, there is no recognized standard for establishing the presence or absence of antibodies to HIV-1 and HIV-2 in human blood”

Packet Inserts Abbott AxSYM system (HIV-1/HIV-2). Abbott Laboratories, Diagnostics Division. 100 Abbott Park Rd. Abbott Park. Illinois, USA

When it comes to the antibody tests, how are we meant to reconcile statements by the World Health Organisation and Abbott Laboratories? If the tests are so extraordinarily accurate why do manufacturers repeatedly feel obliged to include caveats against their use in their packet inserts?

Slide 25

PROBLEMS WITH PCR

- Primers and probes not obtained from purified material
- No proof that particles in unpurified material are HIV or even RVPs
- No proof of specificity for HIV infection

HIV/AIDS experts have circumvented what they see as the ambiguity of maternal antibodies by recommending infants are diagnosed by detecting or measuring HIV RNA or DNA using the PCR.

A few of the many problems using this approach are listed on this and the next few slides.

We have already seen that as with the HIV proteins, nucleic acid primers and probes, said to be those of a unique retrovirus, are not obtained from purified retroviral particles.

In fact, the material from which nucleic acids are obtained is anything but pure but more importantly, it does not contain particles bearing the morphology typical of retroviruses.

Even if these particles were proven to be a retrovirus, there are no data demonstrating that the nucleic acids in question originate in these particles.

And regardless of their origin, there is no proof that positive tests which depend on these primers and probes, are specific for HIV infection.

REVIEW OF 379 STUDIES FROM 5698 PUBLICATIONS

"Our investigation produced two main findings. First, the false-positive and false-negative rates of PCR that we determined are too high to warrant a broader role for PCR in either routine screening or in the confirmation of diagnosis of HIV infection. This conclusion is true even for the results reported from more recent, high-quality studies that used commercially available, standardized PCR assays...We did not find evidence that the performance of PCR improved over time"

Owens DK *et al.* (1996). Polymerase chain reaction for the diagnosis of HIV infection in adults. A meta-analysis with recommendations for clinical practice and study design. *Annals of Internal Medicine* 124:803-15.

These problems of the HIV PCR can be summarised by a study published by Owens and his colleagues in 1996. This in-depth meta-analysis concluded that when the HIV PCR is compared against serology, not HIV isolation which should be the case, the false positive rates are QUOTE "too high to to warrant a broader role for PCR in either routine screening or in the confirmation of diagnosis of HIV infection. This conclusion is true even for the results reported from more recent, high-quality studies that used commercially available, standardized PCR assays...We did not find evidence that the performance of PCR improved over time" END OF QUOTE

Slide 27

PROBLEMS WITH HIV PCR

“Those laboratories which undertake HIV screening and confirmation assays understand fully the technical problems associated with PCR and other amplification assays and it is precisely for those reasons that PCR is NOT used as a confirmatory assay (as discussions with any competent virologist would have informed them)” (emphasis in original).

Chrystie IL. (1999). Screening of pregnant women: the case against. [The Practising Midwife](#) 2:38-39.

Virologists, such as Ian Christie from the UK Public Health Laboratories, lend further weight and strongly advise that PCR should NOT be used to confirm HIV infection.

Slide 28

CDC 2000 Revised AIDS Surveillance Definition

“This revised definition of HIV infection, which applies to any HIV (e.g., HIV-1 or HIV-2), is intended for public health surveillance only... This definition is **not** presented as a guide to clinical diagnosis” (emphasis in original).

Centers for Disease Control and Prevention. *Mortality and Morbidity Weekly Reports* 1999;48 (RR-13):1-27, 29-31

What the Centers for Disease Control in the United States assert in regard to HIV diagnosis in infants makes no scientific sense whatsoever. Firstly they assert that their original and four times revised AIDS definition does not apply to the diagnosis of HIV infection, as if there are two separate processes involved, one for counting the number of HIV/AIDS individuals for public health purposes and another for individual diagnosis. One would assume these statistics are identical.

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CDC 2000 Revised AIDS Surveillance Definition

“In adults, adolescents, and children infected by other than perinatal exposure, plasma viral RNA nucleic acid tests should NOT be used in lieu of licensed HIV screening tests (e.g., repeatedly reactive enzyme immunoassay)” (emphasis in original).

“HIV nucleic acid (DNA or **RNA**) detection tests are the virologic methods of choice to exclude infection in children aged <18 months” (“Positive results on **two separate specimens**) (emphasis added).

Centers for Disease Control and Prevention. *Mortality and Morbidity Weekly Reports* 1999;48 (RR-13):1-27, 29-31.

Second, the CDC forbids the use of RNA PCR to diagnose HIV infection in adults and adolescents and children infected by all other means except perinatally.

In other words, RNA cannot be used to prove infection of adults, or infants infected by blood transfusion, but it is the method of choice to prove infection transmitted via the mother to her baby.

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*Guidelines for the Use of Antiretroviral Agents in
Pediatric HIV Infection December 14, 2001 with
74 authors*

“...data are more limited regarding the sensitivity and specificity of HIV RNA assays compared with HIV DNA PCR for early diagnosis”.

www.hivatis.org/guidelines/Pediatric/Dec12_01/peddec.pdf

As recently as December 14th 2001, 74 experts in Pediatric HIV/AIDS, representing:
The Working Group on Antiretroviral Therapy, The National Pediatric and Family
HIV Resource Center,
The Health Resources and Services Administration and The National Institutes of
Health,

advised that the specificity of the HIV RNA PCR is unknown. Yet this is the test
used in many studies of mother to child transmission including the HIVNET 012
study.

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TABLE 1. *Effect of the HIV-1 clade on quantitation of HIV-1 RNA by RT-PCR, bDNA, and NASBA*

Subtype	HIV-1 strain	HIV-1 RNA copies per ml of HIV-seronegative plasma		
		RT-PCR ^a	bDNA	NASBA
A	DJ258	<400	111.500	100.000
A	DJ263	<400	79.800	60.000
B	SF2	225.500	38.000	240.000
B	III-B	54.000	17.000	360.000
C	ZAM18	78.300	70.000	66.000
C	ZAM20	178.800	125.800	420.000
D	UG270	179.800	29.200	170.000
D	UG274	320.000	41.400	32.300
E	CM241	18.800	72.800	35.000
E	CM235	4.700	52.000	15.000
F	163.3069	36.200	94.000	57.000
F	162.3070	2.800	78.100	26.000
G	G98	254.700	269.000	<400
G	LBV21	184.500	295.000	<400
H	VI557	950.000	587.000	125.000

Coste J *et al.* (1997). Effect of HIV-1 genetic diversity on HIV-1 RNA quantification in plasma: comparative evaluation of three commercial assays. [Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology](#) 15: 174.

If we dismiss every problem discussed so far, how much confidence can a physician or a patients place in a test when three different PCR techniques, the three columns on the right, carried out on the same quantity of virus, the two columns of the left, yield results varying almost a millionfold? If the RNA PCR had anything the recommend its use at least the minimum we would expect the numbers in the rightmost three columns all be of the same order.

There is no scientific proof of a retroviral origin for the PCR RNA reagents, we have scientists such as Owens and his colleagues warning that the PCR test parameters are extremely dubious, we have practising virologists recommending that the PCR is NOT to be used to confirm HIV infection, we have the CDC claiming a test not to be used in adults is perfectly acceptable in perinatally but not otherwise infected children to diagnose the same virus and finally,

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Roche Laboratories

“The Amplicor HIV-1 [RNA] Monitor test is not intended to be used as a screening test for HIV-1 or as a diagnostic test to confirm the presence of HIV-1 infection”

Roche Diagnostic Systems, 06/96, 13-08088-001. Packet Insert

we have Roche, the manufacturer of the only licensed PCR in the US, including a caveat against the use of their test in their packet insert.

Yet such tests are the *raison d'être* of mother to child transmission and underlie for example the recommendation that the South African Government provide nevirapine to all pregnant HIV positive women as well as their babies.

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EVIDENCE REQUIRED

- Proof of HIV infection of mothers and babies
- Proof of drug efficacy
- High benefit/risk profile

Let us now consider the data on nevirapine,

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PROOF OF DRUG EFFICACY

The most reliable evidence regarding the effects of a drug on a disease are obtained by conducting randomised, double blind, placebo controlled clinical trials.

“The placebo effect is assumed to occur in patients taking active drugs and therefore to account for some fraction of that drug’s total therapeutic effect”.*

“A placebo control group is important in drug trials because it allows researchers to determine that fraction of the overall treatment effect that is attributable to the drug’s specific, pharmacological activity”.*

*Barksy AJ et al. 2002. JAMA 287: 622-627.

We begin with drug efficacy.

The most reliable evidence regarding the effects of a drug on a disease are obtained by conducting randomised, double blind, placebo controlled clinical trials.

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THE HIVNET 006 STUDY

Musoke P *et al.* (1999). A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1-infected pregnant Ugandan women and their neonates (HIVNET 006). AIDS **13**:479-86.

Cohort 1: 8 women; 200mg NVP “when in active labour”

Cohort 2: 13 women; 200mg NVP
Infants 2mg/Kg “at 72 h of age”

The HIVNET 012 Ugandan study was preceded by a phase I, phase II trial called the HIVNET 006 study. The authors of this study are substantially the same authors of the HIVNET 012 study.

HIVNET 006 studied the safety and pharmacokinetics of nevirapine in 21 Ugandan women.

Cohort one consisted of 8 women who received 200 mg of nevirapine “when in active labour”.

Cohort two were 13 women similarly treated whose infants were given nevirapine, 2mg/Kg “at 72 h of age”.

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Musoke P *et al.* (1999). A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1-infected pregnant Ugandan women and their neonates (HIVNET 006). AIDS **13**:479-86.

OBJECTIVE: To determine the safety, pharmacokinetics, tolerance, antiretroviral activity, and infant HIV infection status after giving a single dose of nevirapine to HIV-1-infected pregnant women during labor and their newborns during the first week of life. **DESIGN:** An open label phase I/II study. **SETTING:** Tertiary care hospital, Kampala, Uganda. **PATIENTS AND INTERVENTIONS:** Nevirapine, 200 mg, was given as a single dose during labor to 21 HIV-1-infected

THE HIVNET 006 STUDY

Diagnosis

Women: ELISA and WB

Infants: Detectable RNA on 2 separate specimens

ELISA/WB at 18 months

Single RNA = “probable” infection

“Where possible” infant infection “confirmed” by culture

TRANSMISSION = 19% (4/21)

Musoke P, Guay LA, Jackson JB et al. (1999). “A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1-infected pregnant Ugandan women and their neonates (HIVNET 006).” *AIDS* 13: 479-86.

Mothers were diagnosed HIV infected on the basis of the ELISA and Western blot.

Infants were diagnosed HIV infected by RNA PCR on 2 separate specimens, or if they had a reactive ELISA and positive Western blot at 18 months, OR if the infant had a single positive PCR but died.

For reasons not explained by the authors, infant infection was “confirmed” by culture but no data were reported.

We should note that although the HIVNET 006 authors refer to a single RNA PCR in a child who died as “probable infection”, the CDC classify this as “not definitely diagnosed”.

This study reported a transmission rate of 19%

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HIVNET 012 STUDY

“Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial”.

Guay LA et al. (1999). Lancet **354**: 795-802.

The HIVNET 012 study was published in the same year.

The study compared AZT with nevirapine. The trial also commenced with a placebo but this was dropped after 49 women had enrolled and given birth. The placebo, which was not identified, was used in only 19 of the 645 patients. The study did not have a non-treatment arm, nor was it double blind, but it did claim to be randomised.

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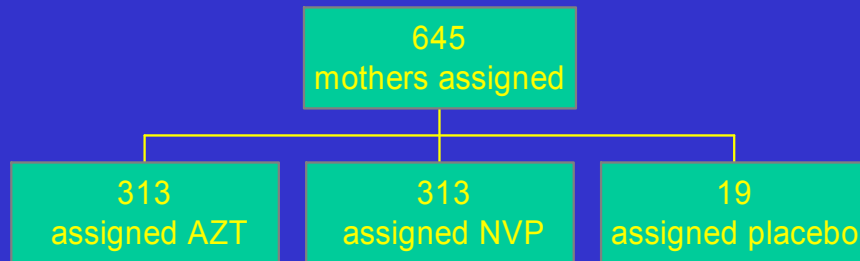
HIVNET 012 REGIME

Mothers: 200 mg NVP “at the onset of labour”

Infants: NVP 2mg/Kg within 72 hours of birth

The drug dosage regime was the same as the HIVNET 006. The timing of administration in the mothers was described as “at the onset of labour” and the children were given the drug “at 72 h after birth or at discharge from hospital, whichever occurred first”.

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HIVNET 012

There were 645 mothers assigned to the HIVNET 012 study of whom 313 were assigned to the AZT arm, 313 to the nevirapine arm and 19 placebo group.

One should note that this number fell well short of the 1500 mother child pairs that the authors considered necessary “to investigate the safety and efficacy of oral zidovudine and oral nevirapine for the prevention of vertical transmission of HIV-1 from pregnant women to neonates in Uganda”

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REPORTED TRANSMISSION HIVNET 012

	Birth	6-8 weeks	14-16 weeks
AZT	10.40%	21.30%	25.10%
NVP	8.20%	11.90%	13.10%
p value	0.354	0.0027	0.0006

Efficacy NCP vs AZT = $(25.1 - 13.1) / 25.1 = 48\%$

The study reported a transmission rate at 14-16 weeks for AZT of 25.1% *versus* 13.1% for nevirapine with a p value of 0.0006. This efficacy of nevirapine over AZT was calculated at 48%.

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CONSEQUENCES OF HIVNET 012 STUDY

In August 2000 12 international experts advised:

“At the present time the most practical, effective and safe antiretroviral intervention is nevirapine, one dose to the mother at the time of delivery and one dose to the newborn”

Furthermore:

“In high seroprevalence areas the drug intervention should be proposed to all seropositive pregnant women, to those who refuse testing, and possibly to those who lack access to testing”.

Akue, Babaki, Barre-Sinoussi, Charpak, de The, Rea, Huraux, Ndiaye, Pratomy, Samuel, Wilfert, Zetterstrom-Italy August 2000

As a result of this study, twelve international HIV experts including Barre-Sinoussi recommended this nevirapine regime as the most practical, effective and safe available for the prevention of mother to child transmission.

Its use was not only advised for HIV positive pregnant women and their babies but also for women who were not proven to be HIV positive but who lived in high seroprevalence areas, and in those women who did not have access to testing or those who refused to be tested.

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There are many scientific reasons to question the validity of this conclusion and these recommendations

It is our view that there are many scientific reasons to question the validity of this conclusion and these recommendations. Even more so when there are recommendations to give this drug to women whose HIV status is unknown.

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PROBLEMS WITH HIVNET 012 STUDY

#1. Diagnosis of infection

Diagnosis of HIV infection in infants:

1. One qualitative RNA “confirmed” by one quantitative RNA or culture on a second blood sample. (Data reported only for RNA PCR RNA, not culture)
2. “One positive RNA” + death

Test used Roche = AMPLICOR MONITOR

In HIVNET 012 the diagnosis of HIV infection in infants was made by one qualitative PCR confirmed by a second quantitative PCR, or culture. As in HIVNET 006, no data on culture were published and indeed, from reading the text, it appears no infections were confirmed by culture. And in contrast to HIVNET 006, a single RNA PCR followed by death, was elevated from “probable” to definite infection.

One must question why a test must be repeated to “confirm” infection in a live baby but not in a baby who dies. Especially when not all causes of death are given and not all deaths even in HIV infected children are caused by HIV.

Whether or not one agrees that the PCR is a valid method to diagnose HIV infection in a baby and hence mother to child transmission, at least it is objective.

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LABORATORY *versus* COMMITTEE

“HIV-1 infection was defined as a positive qualitative test for HIV-1 RNA assay confirmed by quantitative HIV-1 RNA assay or HIV-1 culture on a second blood sample”.

“In addition all available clinical, serological, and virological data were reviewed by the protocol chairperson, cochairpersons, biostatisticians, and the data manager to confirm HIV-1 infection”.

However, although the HIVNET 012 authors defined HIV infection using objective criteria, they appeared unable to confirm a child HIV infected without first having a multidisciplinary committee perform a review of the PCR and all their other data. This can only mean that, despite what they say about conducting serial PCRs to define HIV infection, the authors do not consider this sufficiently rigorous to confirm infection. Which means that they seem to place little weight on their objective PCR protocol and data and, in the final analysis, subjectively confirm infection and thus mother to child transmission.

Another criticism relates to the fact that in November 1998 the HIVNET authors changed their PCR.

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TWO ROCHE AMPLICOR RNA ASSAYS

Before November 1998 “with 1.0 version kit, with additional primers”

After November 1998 “with 1.5 version primers”.

Prior to November 1998 version 1.0 was used, with additional primers, and after November 1998 version 1.5. Although not statistically significant, the 1.5 version was more sensitive when used qualitatively. When used quantitatively it “yielded a significant increase in viral load for samples infected with subtypes A and E (greater than 1 log₁₀ HIV RNA copies/ml)”.

Since no mention is made whether the same number of children from the two groups were tested with each version, we have no way of excluding the introduction of a significant bias into the study groups.

Also of significance is that the PCR used to define HIV infection in the children was the Roche Amplicor

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Roche Laboratories Amplicor Monitor

“The Amplicor HIV-1 [RNA] Monitor test is not intended to be used as a screening test for HIV-1 or as a diagnostic test to confirm the presence of HIV-1 infection”

Roche Diagnostic Systems, 06/96, 13-08088-001. Packet Insert

Which manufacturer Roche asserts “is not intended to be used as a screening test for HIV-1 or as a diagnostic test to confirm the presence of HIV-1 infection” in anyone.

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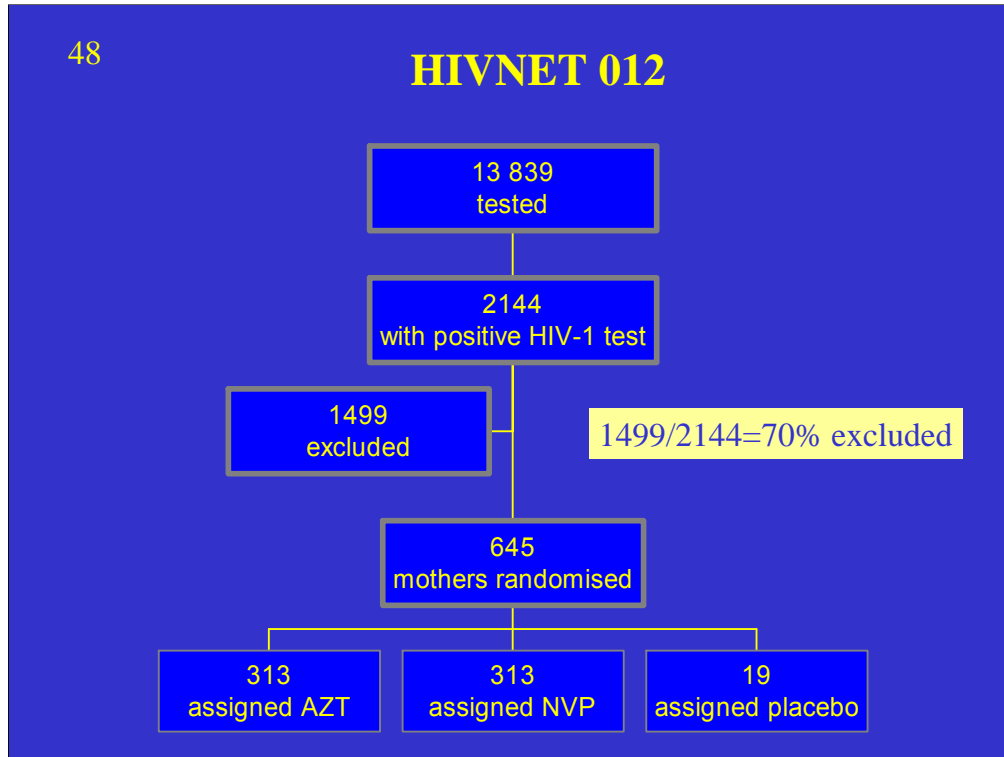
PROBLEMS WITH HIVNET 012 STUDY

#2. Randomisation

There are also problems in the manner in which the HIVNET 012 study was randomised.

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HIVNET 012



The mothers eligible for randomisation in this study were selected from 2144 women amongst 13, 839 women attending antenatal clinics at Mulago Hospital. The authors reported these 2144 women as having a “positive HIV-1 test”. Under “Methods” the authors stated:

“After receiving pretest counselling, women attending general antenatal clinics at Mulago Hospital in Kampala, Uganda, who consented were screened for HIV-1 infection by EIA [ELISA] antibody. If a woman tested positive, she received post-test counselling about her infection status and was informed about the opportunity to enroll in HIVNET 102”.

In another section of their paper they defined their HIV testing protocol for mothers as two ELISAs followed by a Western blot. A large proportion of the women with a positive test for HIV-1 were excluded from the study. In fact 70% of the women with a positive test were excluded.

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REASONS FOR EXCLUSION

“did not return for HIV-1 test results, did not want to give blood samples, were enrolled in other trials, delivered before they could be enrolled, or had an indeterminate or negative western blot”

The reasons given for excluding 1499 women included “an indeterminate or negative western blot”. The number of such women was not specified. These two exclusion criteria are extremely puzzling.

Since the HIVNET 012 study was investigating the effect of drugs on mother to child transmission of HIV one assumes that all 2144 women would not be eligible for randomisation unless were all HIV infected. Which leads to the question, what did the authors mean by a “positive HIV-1 test”?

Did they mean 2144 women with reactive ELISAs who had not had a Western blot? If so, then why were they included in the group eligible for randomisation? And did a woman in this group receive “post-test counselling about her infection status”? And why were the results of the ELISAs and Western blots not separately reported? The proportion of the 2144 mothers selected from all mothers HIV tested at the antenatal clinics was 15%, the same seroprevalence observed in Kampala during the study period. This confirms that the 2144 women had passed all steps of the author’s protocol, including the Western blot.

If this is the case then why did an undefined number of women have a second Western blot, if not further Western blots? And why did the authors not include this step in the description of their protocol and publish the results?

If an undefined number of 2144 women with a positive test for HIV-1 had an indeterminate or negative Western blot, how many of the 645 mothers randomised had a second or further Western blot and how many also had an indeterminate or

DIFFERENCES BETWEEN GROUPS

In table 1 differences between mothers and children in the two groups some of which are significant:

Duration of labour AZT 8.0 (5.3-12.8) vs NVP 9.3 (6.1-13.5) hours; $p=0.042$

Median birth weight AZT 3200 (2900-3500) vs NVP 3100 (2800-3400); $p=0.001$

Well known inverse relationship between risk of transmission and birth weight

There were also statistically significant differences in two of the characteristics making up the AZT and nevirapine groups.

Duration of labour was shorter in the AZT group and children born to mothers given nevirapine had lower birth weights.

Thus we must question the effectiveness of the randomisation procedure because a truly random selection would be free of such biases.

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PROBLEMS WITH HIVNET 012 STUDY

#3. Numerical inconsistencies

The HIVNET 012 study also had several numerical inconsistencies.

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Numerical inconsistencies

Figure 1 shows 302 (AZT) plus 307 (NCP) = 609 “assessable for HIV-1 infection” infants

HIV free survival measured at 14-16 weeks in 496/616 assessable infants. Thus 19% of assessable infants not assessed.

Discrepancy in numbers because 5 children in the AZT group and 2 in the NVP group died before they could be tested for HIV infection

In their Figure 1 the authors stated they had a total of 609 infants “assessable for HIV-1 infection”. Yet in the text the authors “measured directly HIV-1 free survival at age 14-16 weeks in 496 of the 616 assessable babies”.

The discrepancy in numbers is because 5 children in the AZT group and 2 in the nevirapine group died before they could be tested for HIV.

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12 sets of twins
1 set of triplets

“If all babies from multiple births were included, HIV-1-infection outcomes were concordant in all cases other than in three sets of twins”

Why exclude 14 additional infants? Are the outcomes of treatment not considered important in siblings?

Why not report their HIV status? Especially since 9 were in the nevirapine arm

Effect on results of study if concordant and infected

During the study 12 sets of twins and 1 set of triplets were born. These babies were tested for HIV but their status was not reported. Second and third born infants, 14 in all, were also excluded from the analysis.

Why was their individual HIV status not reported and why were they excluded from the analysis ? Are these infants not considered important in such a study, especially since 9 of these infants were in the nevirapine group. If all nine were either concordantly negative or positive this would produce considerable bearing on the outcome of the study.

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PROBLEMS WITH HIVNET 012 STUDY

#4. Not double blind

The HIVNET 012 study was not double blind or even single blind.

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NOT DOUBLE BLIND

“After randomisation, on-site study staff and investigators became aware of the treatment and infection status of the mother-baby pairs. Mothers also knew to what study group they had been assigned after randomisation and were told the infection status of their babies during the studies”.

The authors admitted that after randomisation everyone knew to which group mothers belonged and thus which drugs would be administered.

It is impossible to accept this could not influence the outcome of the study. Given the fear of infecting newborn children, and the hope and possible hype that surrounds any new treatment, mothers or others could have inadvertently adopted behaviours that amongst other things, altered the timing and dosing of the actual drugs themselves. One only has to recall the first trial of AZT in the USA where gay men were able to distinguish AZT from placebo and which led to drug sharing between the two groups.

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PROBLEMS WITH HIVNET 012

#5. No placebo

"No researcher can assess a drug's effectiveness with scientific certainty without testing it against a placebo. That's the only way we can know for sure if a short course of AZT or nevirapine is better than nothing"*.

J Brooks Jackson. Senior author of the HIVNET 012 study.

*1. Swingle AB. The pathologist who struck gold. *Hopkins Medical News* 2001;Spring/Summer 2001. www.hopkinsmedicine.org/hmn/S01/feature.html

Despite the fact that the HIVNET 012 was designed to be a randomised, placebo-controlled, double-blind, phase three trial of 1500 mother-infant pairs, the placebo group was dropped after results of another trial in Thailand were announced in February 1998.

Yet in 2001, Brooks Jackson, the senior author of the HIVNET 012 study, said:

"No researcher can assess a drug's effectiveness with scientific certainty without testing it against a placebo. That's the only way we can know for sure if a short course of AZT or nevirapine is better than nothing".

How can the senior author of this study claim "nevirapine is better than nothing" for the prevention of mother to child transmission? How can this study, with the claims it makes, even be published?

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PROBLEMS WITH HIVNET 012

Problem #5

NO PLACEBO

Without ARVs transmission rates vary considerably

15-20% in Europe; 16-30% in USA

25-40% in Africa; 13-48% Asia and SE Asia

By this time HIVNET 012 had enrolled only 49 women of which 19 women were assigned placebo.

This is a critical omission for any scientist wishing to prove a drug effect. Since no treatment or placebo may be associated with the benefit being sought, there is no possible means by which a scientist can claim a benefit over no or inactive treatment for the drug under investigation.

In the case of mother to child transmission of HIV this is not a trivial problem. Transmission rates vary widely between countries. For example, 15-20% in Europe; 16-30% in USA; 25-40% in Africa and 13-48% Asia and SE Asia. The authors themselves cite estimated transmission rates between 21-43%.

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NO PLACEBO

Among the reasons for large variations in MCT are “methodological differences between studies”.

Thorne C, Newell ML. (2000). Epidemiology of HIV infection in the newborn. Early human development, 58: 1-16

Experts themselves admit that methodological differences account for the large variations between studies.

One can only ask why has the large, double blind, properly randomised, placebo controlled drug trial become such a rarity during the AIDS era? Why design a trial containing all these elements and then abandon most? Are HIV positive mothers and their babies undeserving of scientific rigour?

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NO PLACEBO

Different hospitals of same study

TR Hospital A 14.3% vs Hospital B 23.7% (both placebo)

Different times during the same study

14.4% vs 23.5% before and after study mid-point

In the same hospitals A and B

TR placebo 18.6% vs no drug treatment placebo 24.2%

CDC (1998). "Administration of zidovudine during late pregnancy and delivery to prevent perinatal HIV transmission--Thailand, 1996-1998." *Morbidity and Mortality Weekly Reports* **47**: 151-4.

Shaffer, N., R. Chuachoowong, *et al.* (1999). "Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group." *Lancet* **353**: 773-80.

This slide documents three examples taken from studies with placebos to illustrate the unexpected, unpredictable and inexplicable variations in transmission which would otherwise remain hidden and lead to erroneous conclusions in the calculation of transmission rates. The examples are from two CDC studies conducted in Thailand.

The first is differences even between placebo transmission rates at two different hospitals within the same study. 14.3% *versus* 23.7%.

The second demonstrates how transmission rates may vary across the time span of a study, in this case according to the study midpoint.

The third that placebo can improve transmission in relation to no treatment. 18.6% *versus* 24.2%.

In relation to these data the authors commented that:

"The lower than expected background transmission rate highlights the importance of having included a randomised, concurrently enrolled, untreated control group. Had the test regimen been inactive, a transmission rate of 18.6% may have suggested some efficacy when compared with historical data".

NO PLACEBO

Transmission rate for nevirapine of 13.1% in HIVNET 012 is higher than the 12% transmission rate reported in a prospective study of 561 African women given no antiretroviral treatment

Ladner, J., V. Leroy, et al. (1998). Chorioamnionitis and pregnancy outcome in HIV-infected African women. Pregnancy and HIV Study Group. Journal of the Acquired Immune Deficiency Syndrome and Human Retrovirology **18**: 293-8.

Besides lacking a placebo group, the HIVNET 012 study did not study a non-treatment group. But in a prospective study reported in 1998, the transmission rate in 561 African women given no antiretroviral treatment was 12%, 1.1% less than the 13.1% reported for nevirapine in the HIVNET 012 study.

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PROBLEMS WITH HIVNET 012 STUDY

#6. Reporting of transmission rates

An additional problem is to do with the manner of reporting transmission rates.

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REPORTED INFECTION RATES

“Blood samples were collected at 24 h, 6 weeks, and 14 weeks after birth for all babies”

Infection rates estimated at 3 days, 8 weeks, and 16 weeks using KM method

Data used to calculate the efficacy of nevirapine

Why estimate infection rates?

Why not give the actual data without statistical manipulation?

The authors reported that “Blood samples were collected at 24 h, 6 weeks, and 14 weeks after birth for all babies”. The samples were frozen within 24 hours of collection and tested typically within a week.

This means that the authors had data as to the actual numbers of infants infected at these times.

But the results were presented as cumulative infection rates calculated from the Kaplan Meir method at times other than when the authors said they obtained the blood samples. In fact at day 3, 8 weeks, 16 weeks. These estimates were used to calculate the efficacy of nevirapine.

Nowhere in the paper are the infection rates reported at the times the infant blood samples were collected.

Why did the authors need to estimate infection rates? Why did they not report the actual data free from statistical manipulation?

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“The drug regimens in this trial were specifically designed to provide antiretroviral prophylaxis to the neonate during labour, delivery, and in the first week of life”.

YET

25 of the 37 children (68%) were “infected” between “Day 1-3” when the pharmacological effect of NVP was most pronounced

This fact alone casts serious doubt over the efficacy of nevirapine

According to the study authors “The drug regimens in this trial were specifically designed to provide antiretroviral prophylaxis to the neonate during labour, delivery, and in the first week of life”.

Yet the majority of 37 children were “infected” sometime in the first three days of life. This is at a time when the pharmacological effect of nevirapine was said to be at a maximum.

If 68% of the children were infected under these circumstances how can the authors claim this drug prevents mother to child transmission of HIV?

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**IS IT POSSIBLE FOR NEVIRAPINE
TO DECREASE THE RATE OF
MOTHER TO CHILD
TRANSMISSION OF HIV?**

Inevitably we must put the question “Is it possible for nevirapine to decrease the rate of mother to child transmission of HIV”.

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Viral Load and Transmission

“...elevated maternal viral load is a strong risk factor for both *in utero* and *intrapartum* transmission”. Mock PA et al. (1999). AIDS **13**:407-14.

“The most important maternal factor is viral load...maternal viral load has been found to predict vertical transmission” Thorne and Newell (2000) Early human development **58** 1-16.

“ 2.07-fold increase (1.57-2.72) [in risk of HIV transmission] for every \log_{10} increment in HIV-1 RNA copy number” (HIVNET 012)

All HIV experts agree that the level of maternal viral load predicts transmission to the infant.

The HIVNET 012 authors themselves reported a two fold increase in risk of transmission for every unit increment in \log_{10} maternal viral load before entry into the study.

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NECESSARY CONDITIONS TO REDUCE MTCT ACCORDING TO HIVNET AUTHORS

“...maternal viral load must be substantially decreased by the time of labour or the baby must have systemic concentrations of active drug present at the time of HIV-1 exposure to successfully lower risk of transmission”

In fact in their discussion, the authors set out two necessary conditions which must be fulfilled in order to reduce mother to child transmission. “...maternal viral load must be substantially decreased by the time of labour or the baby must have systemic concentrations of active drug present at the time of HIV-1 exposure to successfully lower risk of transmission”.

Let us consider their first condition

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HIVNET 012 and maternal viral load

“Quantitative plasma HIV-1 RNA measurements were done before entry, at delivery, and at 7 days and 6 weeks after delivery”

Reported only baseline value

“...nevirapine can reduce plasma HIV-1 RNA concentration by at least 1.3 log after a single dose¹³”

Reference 13 is the authors' HIVNET 006 study

In mothers the HIVNET 012 authors measured plasma HIV-1 viral load before entry, at delivery, and at 7 days and 6 weeks *post partum*.

But they reported only the baseline viral load.

Amongst the authors' pharmacological rationale for the choice of nevirapine was their claim that the drug reduces the plasma HIV-1 RNA concentration by at least 1.3 log after a single dose and cited a reference number 13.

Reference 13 is the authors' HIVNET 006 study, The phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-infected pregnant Ugandan women and their infants, published in AIDS in the same year as the 012 study.

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HIVNET 006 and viral load

19 women, median = 1.3 (95% CI; -1.46 -1.17) log reduction 7 days after single dose of nevirapine

2 had VLs of 556 and 672

Unspecified number < 400

Viral load < 400 is considered zero

At six weeks viral load same as baseline

In this study the authors measured RNA in 19 women and found a 1.3 log reduction 7 days after a single dose.

Two of the mothers had viral loads of 556 and 672 copies per ml at delivery and an unspecified number had a viral load less than 400 copies per ml.

We should note that a plasma RNA less than 400 copies per ml is considered a viral load of zero.

At six weeks viral load was the same as baseline.

These data invite two comments:

First, if a viral load < 400 copies per ml is considered zero, then viral loads of 556 and 672 are very close to zero. Especially on a log scale. If we consider these two mothers, as well as the unspecified number of mothers who had viral loads which were zero, then amongst a cohort of only 19 women we may ask how many mothers had a substantial viral load to reduce?

Second, the reduction in viral load reported by these authors is not confirmed by other researchers.

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HIVNET 006 RESULTS NOT REPRODUCIBLE

20 patients: NVP 200 mg daily 2 weeks; then 400 mg daily

“A mean decline of 0.46 ± 0.47 log RNA copy numbers was observed after 4 weeks of treatment, with a return to baseline values within 12 weeks of treatment”

de Jong, MD *et al.* (1997). “High-dose nevirapine in previously untreated human immunodeficiency virus type 1-infected persons does not result in sustained suppression of viral replication.” *Journal of Infectious Diseases* **175**: 966-70.

For example, de Jong and 22 colleagues, using a higher dose of nevirapine, observed an average reduction of 0.46 ± 0.47 log RNA copy numbers after 4 weeks of treatment, which returned to baseline 8 weeks later.

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HIVNET 006 and viral load

MOST IMPORTANTLY

“Maternal plasma HIV-1 RNA levels were also not significantly different at delivery from baseline”

Most importantly, and as one might anticipate from a median 1.3 log reduction measured 7 days after dosing, it is highly unlikely, within a few hours of administration, that is, at delivery, the HIV RNA viral load could have decreased at all.

Indeed, this is exactly what the authors observed.

“Maternal plasma HIV-1 RNA levels were also not significantly different at delivery from baseline”.

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CONCLUSION

“...maternal viral load must be substantially decreased by the time of labour”*

THUS

Nevirapine cannot “successfully lower risk of transmission”
“during labour and delivery”*

*Authors, HIVNET 012 study

Clearly these data contravene the author’s first condition. That maternal viral load must be substantially reduced by the time of labour.

Thus nevirapine cannot successfully lower the risk of transmission during labour and delivery by lowering the concentration of virus presented to the infant.

Where does this leave us in relation to the authors’ second condition? That the infant must have a systemic concentration of active drug at the time of HIV exposure?

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“...the baby must have systemic concentrations of active drug present at the time of HIV-1 exposure to successfully lower risk of transmission”*

Maternal blood and birth canal

Colostrum and breastmilk

*Authors, HIVNET 012 study

There are two sources of exposure to consider. The immediate source is the mother's blood and birth canal. And following this, the mother's colostrum and breastmilk.

There are two mechanisms by which nevirapine could act. The first is prophylactically in the infant following exposure to both sources mentioned, or by reducing the viral load in breastmilk and colostrum.

These lead to the question, what is a therapeutically effective plasma concentration of nevirapine?

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HIVNET 006 STUDY

“The target nevirapine plasma level in the infant one week after delivery was 100 ng/ml or higher. This target was chosen because it is 10 times greater than the nevirapine IC₅₀ for HIV-1”

IC₅₀ determined not by 006/012 authors

In vitro, not *in vivo*

Using synthetic template-primers, not HIV RNA.

Grob PM *et al.* (1992). Nonnucleoside inhibitors of HIV-1 reverse transcriptase: nevirapine as a prototype drug. [AIDS Research and Human Retroviruses](#) 8:145-52.

The HIVNET authors selected a target plasma concentration of nevirapine of 100 ng/ml which, according to the authors, is ten times the 50% inhibitory concentration.

The authors did not determine the IC₅₀ (50% inhibitory concentration) themselves.

The data cited in support of the authors IC₅₀ figure of 10 ng/ml were published by 13 authors from Boehringer Ingelheim Pharmaceuticals and 2 from the Department of Pediatrics and Medicine at the University of Massachusetts Medical School in December 1990.

Other authors, for example, Grob and his colleagues, also from Boehringer Ingelheim, report an IC₅₀ twice this concentration.

These and other studies reporting these data are obtained from *in vitro* experiments and measure inhibition of reverse transcription using not the HIV RNA but synthetic template-primers. They do not measure the concentration of nevirapine required to inhibit HIV replication in the cells of the living body.

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Infant pharmacokinetics
 200 mg nevirapine at “active labour”
 Infant 2mg/Kg

	PACTG 250	HIVNET 006	
Age (hrs)	53.3 (48-77.6)	72	
Pre-dose*	541 (141-768)	595 (77-1224)	
C_{max}*	1335 (644-1607)	1279 (736-2120)	
T_{max}	12 (2-24)	24.6 (22.0-38.3)	13
T_½	36.8 (27.3-49.5)	72.1 (36.6-81.6)	2
Conc 1 week*	215 (112-275)	383 (171-757)	

Mirochnick *et al* JID 1998; Musoke *et al* AIDS 1999

* ng/ml

This slide shows infant nevirapine pharmacokinetics from the PACTG 250 and HIVNET 006 studies.

PACTG 250 was an independent study conducted at seven hospitals in the USA and published a year earlier than HIVNET 006.

In the mothers both 250 and 006 used the same nevirapine regime as the HIVNET 012 study. In the infants the drug was administered at “between 48 and 72 h after birth” in 250 and “at 72 hours” in 006. In 012 nevirapine was given “at 72 h after birth or at discharge from hospital, whichever occurred first”. Also 012 included an unspecified number of children who were born at home or an outside hospital and who were given the drug “as soon as they arrived at the clinic if they presented within the first 7 days of life”.

One should note the pre-nevirapine dose differences, that is, the concentration which resulted from the mother’s nevirapine, the time of dosings, the range of C_{max} maximums, the 12.6 hour difference in the median T_{max} maximums, the range of T_{max} maximums and the twofold differences in half lives of the administered drug.

At one week there are differences between the median and maximum concentrations of over 70%.

In other words, similar to the viral load data, the HIVNET pharmacokinetic data are substantially different from those reported in other studies.

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CONCENTRATION REQUIRED *IN VIVO* FOR VIROLOGICAL RESPONSE

“4.7 µg/mL [17.7 µM]; range, 3.4-8 µg/mL”

Concentration required NVP = 4700 (3400-8000) ng/mL
 C_{\max} infants = 1279 (736-2120) ng/mL

In no child does C_{\max} reach the minimum concentration required for a virological response.

Time between mother’s first dose and delivery:
6.9 (3.0-13.2) hours

*Havlr, D., S. H. Cheeseman, et al. (1995). High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection. Journal of Infectious Diseases **171**: 537-45.

Not according to data published by Havlr and colleagues in the *Journal of Infectious Diseases* in 1995.

Here it was demonstrated that plasma trough levels of nevirapine required for an *in vivo* virological response range from 3.4 to 8 ug/ml with a median value of 4.7 ug/ml.

Expressed as nanograms per ml it can be seen that the C maximum in the infants does not reach the minimum concentration required for a virological response. Expressed as a mean it is about one quarter that considered necessary with a range 2-11 times too small.

Thus on this basis we conclude that the authors second condition, that is, achieving therapeutically active concentrations of nevirapine in the infant, is not fulfilled.

We must also note that the 294 mothers given NVP received it at a median time of 6.9 hours with a range of 3-0 to 13.2 hours. This means that an unknown number of infants may have delivered before sufficient time had passed to reach the target concentration based on exposure to their mothers’ NVP. This interval may have been days because the infant’s NVP was “given at 72 h after birth or at discharge from hospital, whichever occurred first”, or, in some cases “within the first 7 days of life” if born at home.

Could nevirapine reduce transmission via breastfeeding?

“...if nevirapine turns out to be efficacious in preventing vertical transmission at the time of delivery, it is unlikely to be caused by a reduction in maternal viral load. The decrease in viral load during colostrum feeding might, however, impact on postnatal transmission”.

“...findings from HIVNET 006 suggest maternal dose may primarily act by reducing early breastmilk transmission”*

*Hudson CP, Moodley J. University of Natal, Durban, South Africa (1999) [Lancet 354: 1817](#)

This brings us to breast feeding. For the sake of argument, let us give credence to the authors' own suggestion, expressed in the HIVNET 006 study, that “if nevirapine turns out to be efficacious in preventing vertical transmission at the time of delivery, it is unlikely to be caused by a reduction in maternal viral load. The decrease in viral load during colostrum feeding might, however, impact on postnatal transmission”.

Indeed, this is how Hudson and Moodley, from the University of Natal, interpreted the HIVNET 006 study data.

“...findings from HIVNET 006 suggest maternal dose may primarily act by reducing early breastmilk transmission”*

Could nevirapine reduce transmission by lowering maternal viral load during the time infants are breast fed ?

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REDUCTION VIA BREASTFEEDING

Even if the *in vivo* concentration for virological response is 100 ng/ml, since $T_{1/2}$ is 72 hours, the target will be sustained for a few weeks, at most.

Nevirapine could only reduce HIV transmission via breastmilk for a few weeks at most.

Even if the authors' target of 100 ng/ml is an effective *in vivo* concentration necessary reduce maternal breast milk viral load, we can see that because the half life is 72 hours at the most, the target concentration will be sustained for only a few weeks at most. Well short of the time mothers at least in this study, breastfed their babies. So any benefit from lowering breastmilk viral load will be transient. In fact it may be even worse, as James McIntyre expressed in the British Medical Journal on January 26th, 2002. That even after single dose, nevirapine may cause the the development of resistance to the drug. If, as Brooks Jackson and associates suggest, rebound after stopping antiretroviral treatment leads to higher viral loads, the HIVNET 012 regime may increase transmission via breastfeeding.

Regardless of what exposure the infant receives via breastfeeding, the previous argument applies. The concentration provided via the mother and the single dose given to the infant does not result in levels effective *in vivo*.

What then is the maximum possible lowering of mother to child transmission we might expect from nevirapine?

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Maximum possible lowering of MTCT by Nevirapine

According to the authors of 012, “a study in Malwai found a cumulative risk of HIV-1 infection associated with breast feeding of 7.0% at age 11 months and 10.3% at age 23 months”*

Assume:

NVP is 100% effective in preventing BF transmission up till 11 mo
Placebo = 26.2%

26.2% minus 7.0% = 19.2% = TR with NVP (vs AZT 25.1%)

Maximum efficacy NVP vs AZT = $(25.1 - 19.2) / 25.1 = 24\%$

*Miotti, P. G., T. E. Taha, *et al.* (1999). “HIV transmission through breastfeeding: a study in Malawi.” *Journal of the American Medical Association* **282**: 744-9.

Again, for the sake of argument, let us assume that nevirapine as administered in the HIVNET 012 study is 100% effective in preventing HIV infection via breastfeeding and that this effect lasts not for a few weeks but 11 months. We choose 11 months because the HIVNET authors cite a paper by Miotti and colleagues from Malawi which reported a 7% cumulative transmission risk due to breastfeeding at 11 months of age.

In HIVNET 012 the authors claimed nevirapine lowered the risk of HIV-1 infection by nearly 50% in a breastfeeding population. Therefore, let us assume that without treatment, or with a placebo, the transmission rate would have been twice their reported rate of 13.1%, that is, 26.2% This figure accords with data the authors quoted in the introduction to their paper.

If the placebo rate is 26.2%, and we subtract the 7% breastfeeding risk, we are left with 19.2%.

THIS REPRESENTS THE MINIMUM TRANSMISSION RATE WITH NEVIRAPINE

If we now compare the efficacy of nevirapine with AZT we arrive at a figure of 24%, approximately half that reported by the authors.

Furthermore,

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If placebo TR = 26.2% AND AZT TR = 25.1%

then AZT transmission rate = Placebo transmission rate

Yet the authors claimed that “short-course zidovudine may have had some benefit”

If the placebo transmission rate is 26.2% and the AZT transmission rate 25.1% then the AZT transmission rate is not significantly different from the placebo rate.

Yet the authors state their short course AZT may have had some benefit.

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DOES NEVIRAPINE PASS THE HIVNET 012 AUTHORS' TEST?

“Maternal viral load must be substantially decreased by the time of labour or the baby must have systemic concentrations of active drug present at the time of HIV-1 exposure to successfully lower risk of transmission”

- Does not reduce maternal viral load “during labour and delivery”
- Concentration in infant is less than that necessary for a virological response *in vivo*
- Cannot prevent transmission during pregnancy

Let us recount the conditions the authors stated were necessary for nevirapine to prevent mother to child transmission.

“Maternal viral load must be substantially decreased by the time of labour or the baby must have systemic concentrations of active drug present at the time of HIV-1 exposure to successfully lower risk of transmission”

But the authors demonstrated that nevirapine does not lower maternal viral load during labour and delivery.

We have demonstrated that the concentrations achieved *in vivo* cannot lead to a virological response.

And it goes without saying that nevirapine, as administered and recommended in this trial cannot effect transmission before the onset of labour, that is, during pregnancy.

Thus nevirapine does not pass the authors’ own set of criteria for the purpose proposed.

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CONCLUSION

“...CIs for their estimate of efficacy are wide, with a lower value of 20%. Further studies are needed, and are in progress, to confirm their findings”*

Where are these studies?

No study valid without manufacturers’ guarantees that tests are specific

*Hudson CP, Moodley J. University of Natal, Durban, South Africa
(1999) Lancet 354: 1817

In conclusion,

There are many questions regarding the design, execution, analysis and interpretation of the HIVNET 012 study. And as researchers from South Africa point out, just one factor, the wide confidence intervals reported for the efficacy of nevirapine over AZT, is sufficient to argue that the HIVNET data should be confirmed before this treatment becomes standard clinical practice.

“...CIs for their estimate of efficacy are wide, with a lower value of 20%. Further studies are needed, and are in progress, to confirm their findings”.

According to one of the best known European experts on MTCT, Marie Louise Newell, “A randomised, double blind placebo controlled trial of Nevirapine versus placebo in addition to routine anti-retroviral prophylaxis (ACTG316) is currently underway in the USA and Europe. The regimen under evaluation is as the HIVNET [012] trial...but is being studied in a very different population... Furthermore, women participating in ACTG316 are asked not to breastfeed their infants, It is expected that enrolment in this trial will be completed by mid 2000”.

The HIVNET 012 trial was published in 1999, five months after the completion of enrollment. On this time scale, dating from mid 2000, the 012 study could have been published four times over. We may well ask, why has the ACTG316 study and others, not been published. Including the SAINT study the initial findings of which were presented at the Durban AIDS Conference in July 2000? Now approaching two years ago.

EVIDENCE REQUIRED

- Proof of HIV infection of mothers and babies
- Proof of drug efficacy
- High benefit/risk profile

We conclude this presentation with a very brief look at deaths and adverse events in the two HIVNET trials as well as toxicity data.

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TOXICITIES IN CHILDREN

HIVNET 006

4/22 infants died (sepsis in one child, remainder not given)

12 “serious adverse events”

1 “possibly, but not likely, study drug related”.

In the HIVNET 006 study 4/22 infants died. The causes of death were not reported in three of these children.

There were also 12 serious adverse events of which one was thought possibly but not likely to be drug related.

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TOXICITIES IN CHILDRENHIVNET 012

38 babies died. 22 AZT vs 16 NVP.

Pneumonia, gastroenteritis, diarrhoea, dehydration, sepsis.

59 serious adverse events in the first 8 weeks of life

Sepsis, pneumonia, fever, congenital anomaly, asphyxia, dyspnoea.

4 in AZT, 2 in NVP “possibly, but unlikely to be, related to the study drug”.

No placebo: AZT and NVP have equal toxicities
Nevirapine reduces non-HIV deaths?

In HIVNET 012 adverse events in infants were uniformly recorded up to age 6 weeks, but after than only serious adverse events continued to be recorded at each visit up to age 18 months.

38 babies died. 22 in the AZT group and 16 in the nevirapine group.

Pneumonia, gastroenteritis, diarrhoea, dehydration and sepsis were given as the causes of death.

There were 59 serious adverse events in the first 8 weeks of life.

Those specified were sepsis, pneumonia, fever, congenital anomaly, asphyxia and dyspnoea.

Four adverse events in the AZT group and 2 in the nevirapine group were thought “possibly, but unlikely to be, related to the study drug”.

Overall there were 18 babies with maculopapular rash, 22 had anaemia.

In light of these data there are two claims in the HIVNET 012 study worthy of comment.

The first is that adverse events were “similar up to the 18-month visit”. Since the 012 study did not have a placebo all that can be claimed is that nevirapine and AZT have equal probabilities of adverse events. This may be because AZT and nevirapine are both toxic and equally so. These data do not prove that nevirapine or AZT

85 **Guidelines for the use of antiretroviral agents in pediatric HIV infection. CDC December 2001**

Major toxicities (continuous dosing, not single dose regimens)

More common: (similar to adults) Skin rash (some severe, requiring hospitalization, and life-threatening, including Stevens-Johnson syndrome, toxic epidermal necrolysis), fever, nausea, headache, and abnormal liver function tests.

Less common: Inflammation of the liver (hepatitis), which rarely may lead to severe and life threatening and in some cases fatal liver damage, and very rarely fatal liver failure and granulocytopenia.

Hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise and/or significant hepatic abnormalities).

www.hivatis.org/guidelines/Pediatric/Dec12_01/peddec.pdf

As far as drug toxicities are concerned, the recently published guidelines for the use of antiretroviral agents in children mention several. Some serious and some fatal.

Given these toxicities and the unproven benefit of nevirapine it would seem most unwise to recommend its use in children.

One should also remember that neonates, that is, children up to the age of four weeks, drug pharmacokinetics can differ markedly compared to adults and older children. In particular metabolism and excretion can be markedly reduced thus rendering them more susceptible to toxic insults. Especially when given drugs that are known to have marked toxic potential. The classic example is the "Gray Baby" syndrome caused by accumulation of chloramphenicol.

We should also note that although generations of medical students are taught the child is not a little man, there is still a sufficient nexus between the two to heed the toxicities that any drug may cause in adults.

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CDC

Nevirapine is toxic so much so that the CDC have advised doctors not to prescribe it for needlestick injuries, that is, healthy individuals. Toxicities may be “severe and life-threatening” and include Stevens Johnson syndrome, toxic epidermal necrolysis, hypersensitivity reactions and hepatotoxicities. Some fatal and at least one requiring liver transplantation. Gottlieb, BMJ (2001) 322: 126

EAEMP

European Agency for the Evaluation of Medicinal Products-only for combination therapy and only for “infected patients with advanced or progressive immunodeficiency” (2000)
www.emea.eu.int/pdfs/human/press/pus/1126000EN.pdf

The CDC warn that the toxicities of nevirapine are such that it should not be given prophylactically to healthy adults. Its use for this purpose, for example, after needle stick injuries, has resulted in severe and life threatening effects with at least one patient requiring a liver transplant for fulminant hepatitis. Many pregnant women are healthy adults.

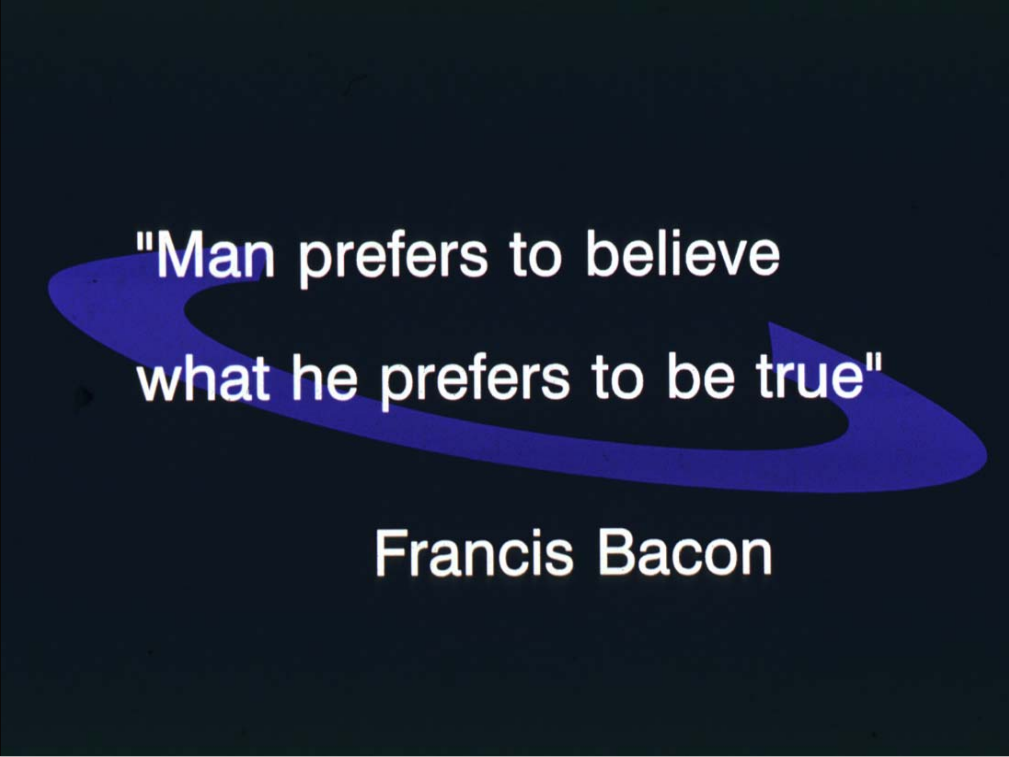
The European agency for the evaluation of medicinal products warns of the same toxicities and recommends the use of nevirapine only for advanced or progressive immunodeficiency.

Given these and all the preceding data, it is problematic to speak of nevirapine in terms of a benefit to risk ratio.

We conclude that doctors, institutions and governments must insist on further evidence before nevirapine can be advised for the prevention of mother to child transmission of HIV.

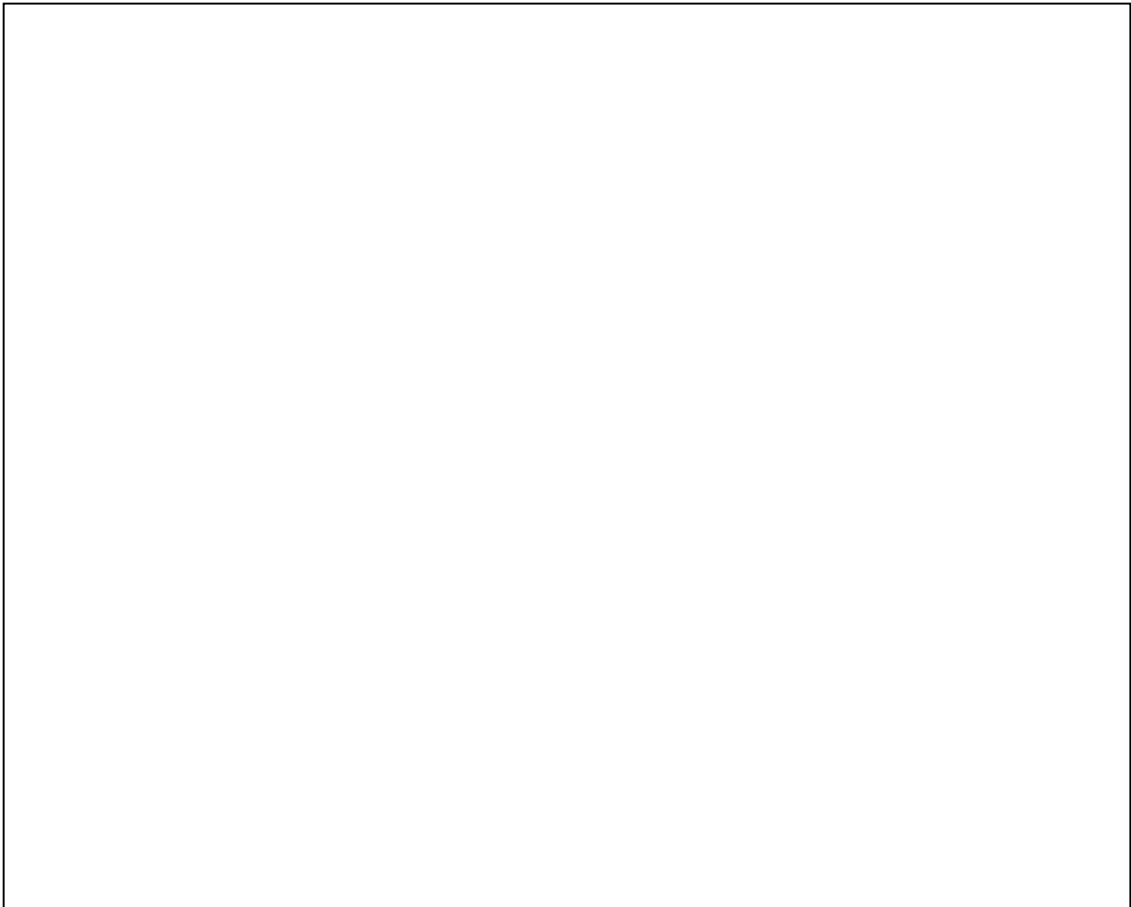
Thank you for your attention.

FIN



"Man prefers to believe
what he prefers to be true"

Francis Bacon



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